Facteurs de risque, dépistage et prévention des syndromes post-traumatiques à la suite d'un passage aux urgences

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Facteurs de risque, dépistage et prévention des syndromes post-traumatiques à la suite d'un passage aux urgences

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2. Résumé

Dans le monde entier, des dizaines de millions de personnes sont victimes de blessures mineures et beaucoup d'entre elles sont admises aux urgences. Cela représente chaque année environ 5 millions d'admissions aux urgences en France et près de 40 millions en Europe. Depuis plusieurs années, des études suggèrent que jusqu'à 20 % de ces patients souffriront pendant des mois de symptômes chroniques décrits initialement dans le traumatisme crânien léger (TCL) et appelés ainsi « Syndrome post-commotionnel » (SPC). Aujourd'hui, ces symptômes ont été identifié comme non spécifique du TCL et la plupart des auteurs utilise le terme de « Post-Concussion-Like Symptoms » (PCLS). Une telle combinaison de symptômes peut entraîner une détérioration importante de la qualité de vie sociale et familiale ou retarder le retour au travail ou à l'école. Rien qu'en France, si les résultats décrits dans la littérature sont représentatifs de l'ensemble de la population, jusqu'à un million de personnes pourraient être concernées par cette problématique, actuellement mal identifiée, de santé publique.
Les différents objectifs de ce travail de thèse étaient ainsi :

- Identifier les facteurs associés à l'apparition de « Post-Concussion like symptoms » à distance d'un passage aux urgences,
- Élaborer un outil d'évaluation du niveau de risque de développer ces symptômes pour les patients pris en charge aux urgences
- Identifier les interventions qui pourraient être proposer aux urgences comme moyen de prévention.
- Évaluer l'intérêt de la mise en place d'interventions au cours du passage aux urgences pour prévenir la survenue de ces symptômes.

Nous avons retrouvé dans SOFTER 1 que les PCLS à 4 mois sont associés au stress à la sortie des urgences. Puis grâce à l'élaboration d'un outil d'évaluation du niveau de risque, nous avons montré qu'il est possible de conduire des séances d'EMDR au cours du séjour dans les urgences. L'efficacité de cette intervention semblerait en revanche influencée par de nombreux facteurs comme le niveau socio-économique des patients, leur niveau de stress et l'expérience des psychologues.
Ainsi, les résultats actuellement disponibles suggèrent que les structures d'urgences pourraient être un lieu privilégié pour repérer et prendre en charge des patients fragiles, à risque de développer des PCLS. L'opportunité offerte par le passage aux urgences pourrait avoir un impact important en termes de santé publique et constituer un outil puissant de santé communautaire pour lutter contre les inégalités de santé.

Mots clefs :
Service d'urgence, EMDR, Trouble de stress post traumatique, syndrome post-commotionnel, symptômes équivalent à ceux du syndrome post-commotionnel.

3. Abstract

Worldwide, tens of millions of people suffer minor injuries and many are admitted to emergency departments (ED). This represents approximately 5 million ED admissions in France and nearly 40 million in Europe each year. For several years, studies have suggested that up to 20% of these patients will suffer for months from chronic symptoms initially described in mild traumatic brain injury (MTBI) and referred to as "post-concussion syndrome" (PCS). Today, these symptoms have been identified as non-specific to TCL and most authors use the term "Post-Concussion-Like Symptoms" (PCLS). Such a combination of symptoms can lead to a significant deterioration in the quality of social and family life or delay the return to work or school. In France, if the results described in the literature are representative of the entire population, up to one million people could be affected by this currently poorly identified public health problem.
The different objectives of this work were as follows:
- to identify the factors associated with the development of "Post-Concussion like symptoms" at a distance from an emergency room visit,
- to develop a tool to assess the level of risk of developing these symptoms for patients managed in emergency departments
- to identify interventions that could be offered to emergencies as a means of prevention.
- to assess the value of implementing interventions in the ED to prevent these symptoms from occurring.
We found in SOFTER 1 that PCLS were associated with stress at the ED discharge. Then, after creating a risk assessment tool, we showed that it is possible to conduct EMDR sessions during ED stay. The effectiveness of this intervention appeared to be influenced by many factors such as patients' socio-economic conditions, stress level and psychologists' experience.
Thus, results currently available suggested that ED could be a place to identify and manage fragile patients at risk of developing PCLS. The opportunity offered by ED visit could have a significant impact in terms of public health and could be a powerful community health tool to combat health inequalities.

Keywords :
Emergency department, EMDR, Post-traumatic Stress Disorder, Postconcussion syndrome, Postconcussion like symptoms

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5. Abréviations

CBT :	Cognitive Behavioral Therapy
CHU :	Centre Hospitalier Universitaire
CI :	Confidence Interval
CIM :	Classification Internationale des Maladies
CPP :	Comité de Protection des Personnes
DSM :	Diagnostic and Statistical Manual of Mental Disorders
DSMB :	Data Safety Monitoring Board
ED :	Emergency Department
EMDR :	Eye Movement Desenzitization and Reprocessing
ERP :	Emergency Response Protocol
ICD :	International Classification of Diseases
MTBI :	Mild Traumatic Brain Injury
OR :	Odds Ratio
PCL :	PTSD Check-List
PCLS :	Postconcussion like symptoms
PCS :	PostConcussion Syndrome
PHRC :	Programme Hospitalier de recherche Clinique
PRECI :	EMDR-protocol for recent critical incidents
PTSD :	Post-Traumatic Stress Disorder
RPQ :	Rivermead Postconcussion symptoms Questionnaire
RTEP :	Recent Traumatic Episode Protocol
SARSQ :	Stanford Acute Reaction Stress Questionnaire
SOFTER :	SymptOms Following Trauma Emergency Response

SPC : syndrome post commotionnel

SSMS : Shared Study Monitoring System

SUD : Subjective Unit of Disturbance

TC : Traumatisme crânien

TCC : Thérapie Cognitivo Comportementale

TCL : Traumatisme crânien léger

TSPT : Trouble de stress post-traumatique

6. Introduction

Dans le monde entier, des dizaines de millions de personnes sont victimes de blessures mineures et beaucoup d'entre elles sont admises aux urgences (1). Cela représente chaque année environ 5 millions d'admissions aux urgences en France et près de 40 millions en Europe (2). Plus de 90 % de ces patients légèrement blessés quitteront l'hôpital en quelques heures et n'auront pas besoin d'être hospitalisés (2). Ces patients sont tous d'origine et de culture très différentes et les pathologies qui les conduisent aux urgences ne sont pas moins variées. Les prises en charge diagnostiques sont ainsi parfois difficiles et nécessitent la réalisation d'examens complémentaires. Cette multiplicité de situations cliniques, les situations d'afflux de patients et les besoins d'exploration ne sont qu'une partie des éléments qui engendrent de longs délais d'attente au sein des services. Cela crée un environnement peu propice à une communication adaptée pour chaque patient.

Ainsi, en plus du stress causé par l'événement qui les a conduits aux urgences, les patients peuvent aussi y vivre des situations stressantes. Une étude récente portant sur 474 patients avait montré que la prise en charge aux urgences d'un événement cardiaque potentiellement mortel pouvait être associée à l'apparition de symptômes non spécifique dans les mois qui suivent (3). En revanche, les études ayant évalué les conséquences du stress demeurent rares. Pourtant, depuis plusieurs années, des études suggèrent que jusqu'à 20 % de ces patients souffriront de symptômes chroniques non spécifiques, regroupés initialement sous l'appellation «Syndrome post-commotionnel» (SPC) (Post-concussion syndrome pour les anglo-saxon) pendant des mois (4–8). Il peut s'agir de maux de tête, de difficultés de concentration, de perte de mémoire, d'intolérance au stress, d'un changement de personnalité, d'irritabilité...(9).

Une telle combinaison de symptômes peut entraîner une détérioration importante de la qualité de vie sociale et familiale ou retarder le retour au travail ou à l'école. Ainsi, un simple antécédent de Traumatisme Crânien Léger (TCL) peut avoir de lourdes conséquences sur la qualité de vie quotidienne des patients (10,11). Notamment, des auteurs ont retrouvé une association entre les scores bas concernant la qualité de vie et la présence d'un Syndrome Post-Commotionnel (SPC) (11). Pour autant, ces scores ne sont pas forcément liés à la sévérité du traumatisme (12).

En France, si les résultats décrits dans la littérature sont représentatifs de l'ensemble de la population, jusqu'à un million de personnes pourrait être concernées par cette problématique actuellement mal identifiée de santé publique.

Les différents objectifs de ce travail de thèse étaient :

- Identifier les facteurs associés à l'apparition, à distance d'un passage aux urgences, des symptômes équivalents à ceux du SPC.
- Évaluer le niveau de risque de développer ces symptômes pour les patients pris en charge aux urgences pour permettre une sélection de ceux qui pourraient bénéficier d'une intervention
- Évaluer l'intérêt de la mise en place d'interventions au cours du passage aux urgences pour prévenir la survenue de ces symptômes à distance.

Ce travail de thèse correspondait aux premières étapes du Projet SOFTER, Symptoms Following Trauma Emergency Response, initié par l'équipe pour mettre en place des outils permettant aux patients de « mieux vivre les urgences ».

7. La genèse du projet SOFTER

Le projet SOFTER fait suite à l'étude PERICLES. Celle-ci avait été conduite par notre équipe aux urgences de l'hôpital Pellegrin du CHU de Bordeaux. Elle s'était intéressée au syndrome post-commotionnel et avait inclus des patients victimes de traumatismes, crâniens ou non crâniens. Il avait été montré que dans les suites d'un traumatisme ayant conduit les patients aux urgences, entre 20 et 25% d'entre eux souffrait 3 mois plus tard de symptômes correspondant à ceux du SPC (9,13). Par ailleurs, les symptômes du SPC ont une part de chevauchement avec ceux du trouble de stress post-traumatique dans ses dimensions hyperéveil et engourdissement. La santé physique et psychique du patient avant son admission ainsi que le mécanisme de survenue du traumatisme sont des éléments qui chacun jouent un rôle dans le développement d'un SPC (14). Ainsi, ces symptômes étaient plus fréquents chez les individus qui percevaient leur état de santé altéré ou qui prenaient des traitements anxiolytiques. De la même façon, les patients pris en charge à la suite d'une agression étaient plus à risque de présenter des symptômes du SPC à 3 mois que ceux ayant subi une chute ou un accident de la circulation. En revanche, quelques soit la localisation ou le mécanisme du traumatisme, la gravité du diagnostic posé n'était pas associée aux symptômes étudiés.

Ces différentes publications ont, ainsi, soulevé plusieurs problématiques :

- La population concernée par le SPC s'étend probablement au-delà des patients traumatisés crâniens : il s'agirait plutôt d'un syndrome post-traumatique au sens psychologique du terme.
- Le lien entre SPC et trouble de stress post-traumatique reste à comprendre
- Le possible lien entre le stress lié à une situation et la survenue d'un SPC reste à démontrer

- Il reste enfin à identifier la meilleure prise en charge préventive pour ces patients à risque

7.1. De « Post-concussion syndrome » à « Post-concussion-like symptoms »

Ces symptômes ont d'abord été décrits dans les suites d'un traumatisme crânien léger (TCL) et identifiés ainsi comme syndrome post-commotionnel (SPC) (15,16). Les symptômes constituant le SPC sont très hétérogènes. Avec une part somatique, cognitive et émotionnelle, le SPC reste difficile à diagnostiquer.

Actuellement, il existe différents outils diagnostics du SPC dont les plus utilisés sont :

- La quatrième et la cinquième version du Manuel Diagnostic et Statistique des troubles Mentaux (15,17),
- La Classification internationale des maladies (16),
- Le « Rivermead Post-Concussion Symptoms Questionnaire » (RPQ) (18).

Les symptômes utilisés dans chacune des classifications ne sont pas totalement superposables même s'il est vrai qu'ils sont assez proches. Les critères diagnostiques de chacun de ces outils sont présentés dans le tableau 1.

Tableau 1 : Liste des symptômes inclus dans les trois principaux outils de diagnostic du SPC

Symptômes	RPQ	CIM-10	DSM IV
Maux de tête	+	+	+
Vertiges	+	+	+
Nausées/Vomissements	+		
Sensibilité exacerbée au bruit	+		
Troubles du sommeil	+	+	+
Fatigue	+	+	+
Irritabilité, se met davantage en colère	+	+	+
Dépression	+		+
Anxiété			+
Diminution de la tolérance au stress		+	
Sentiment de frustration, d'impatience	+		
Troubles de la mémoire	+	+	
Difficulté à se concentrer	+	+	
Lenteur de la réflexion	+		
Vision floue	+		
Vision double	+		
Sensibilité à la lumière	+		

Impression de ne pas trouver le repos	+
Changement de personnalité	+

CIM 10 : Classification internationale des maladies 10ème édition ; DSM IV : 4ème Edition du Manuel Diagnostic et Statistique des troubles Mentaux ; RPQ : Questionnaire des symptômes post commotionnels du Rivermead.

Le diagnostic de SPC est posé lorsqu'au moins 3 symptômes sont présents pour chaque échelle. Le DSM-IV et la CIM-10 ne recherchent que la présence ou l'absence de chaque symptôme alors que le RPQ tient compte de la gêne occasionnée par chaque symptôme. Il mesure ainsi par une échelle de Likert à cinq niveau la gravité du symptôme :

0. Aucun
1. Symptôme présent avant l'accident et inchangé depuis
2. Symptôme léger
3. Symptôme modéré
4. Symptôme important

La publication princeps de King et al. (18) proposait de retenir le diagnostic de SPC à partir de trois symptômes considérés « modérés » ou « important ».

D'autres différences notables existent entre ces outils diagnostiques. Dans la CIM-10 la présence d'une perte de connaissance lors du TCL est nécessaire pour pouvoir affirmer le diagnostic. La durée des symptômes avant le diagnostic n'est également pas la même, elle est d'un mois pour la CIM-10 contre trois pour la DSM-IV. Plusieurs autres éléments n'apparaissent également que dans le DSM-IV : les symptômes retrouvés peuvent préexister, les troubles cognitifs doivent être objectivés par des test psychotechniques et les symptômes doivent avoir un retentissement social ou professionnel. Un quatrième critère est la nécessité de troubles cognitifs objectivés par des tests psychométriques dans la DSM-IV.

Le choix de l'outil diagnostic est un élément important car il peut entrainer de grandes différences dans la prévalence du SPC. Boake et al. (19) ont ainsi comparé la CIM-10 et le DSM-IV. Chez les mêmes patients et lors de la même consultation, la proportion de SPC retrouvée était ainsi de 64 % avec la CIM-10 contre 11 % avec le DSM-IV. Cet exemple, même s'il est

caricatural, met en évidence le manque de spécificité de ces deux classifications et la nécessité de réévaluer ces deux outils diagnostics. Le débat existe également au sujet du RPQ. En effet, des études récentes sur le RPQ ont remis en question la validité interne de cet outil (20,21). Cependant, il reste actuellement l'outil le plus utilisé et celui qui est recommandé par plusieurs sociétés savantes et notamment américaine et anglaise (22,23).

Cependant, même s'ils ont d'abord été identifiés au décours d'un traumatisme crânien, plusieurs études ont suggéré que l'ensemble des symptômes inclus dans ce syndrome ne sont pas spécifiques aux TCL. En effet, ils ont été observés à la suite d'un événement traumatique quelconque (14,24,25) dans des proportions équivalentes. Une autre caractéristique frappante de ces symptômes était qu'ils semblaient être plus fréquents lorsque l'événement traumatique était stressant. Certains de des auteurs des études portant sur le sujet avaient également observé que les troubles affectifs et l'anxiété dans l'année précédant l'événement étaient des facteurs prédictifs de la survenue d'un SPC (26).

Cependant, huit symptômes ont parfois été décrit comme plus spécifique du TCL (9): maux de tête, vertiges, diminution de la tolérance au stress, troubles de la mémoire, difficulté à se concentrer, lenteur dans la réflexion, vision floue et changement de personnalité.

Ces différents travaux montraient la diversité des situations cliniques pouvant conduire à l'apparition de ces symptômes initialement décrits au décours d'un traumatisme crânien. C'est ce manque de spécificité qui a probablement entrainé sa disparition du DSM-V (17). Ainsi, les auteurs qui continuent à s'intéresser à cette entité nosologique utilisent aujourd'hui le terme de « post-concussion like symptoms » (PCLS) ou « concussion-like symptoms » pour symptômes équivalent à ceux du syndrome post-commotionnel (24,25,27–42).

Contrairement au PCS historique, cette nouvelle dénomination même si elle n'a, pour l'instant ni support organique identifié (28,43–46), ni nomenclature attribuée, semble être celle qui s'approche le plus de la réalité pour les patients.

7.2. Post-concussion like symptoms et trouble de stress post-traumatique

Le trouble de stress post-traumatique (TSPT) est un ensemble de symptômes qui se développent suite à l'exposition à un ou des événements traumatiques. Il a été initialement décrit dans une population militaire et a fait l'objet de nombreuses études notamment lors des conflits en Irak et en Afghanistan (47–51). L'exposition à un traumatisme comme facteur prédictif de survenue d'un TSPT a été largement étudiée. La survenue d'un TSPT est favorisée par l'exposition au combat ou à un traumatisme (52–54) dont le plus fréquent était le TC (55–58). De nombreux auteurs ont pu ainsi montrer que le TCL majorait la prévalence d'un TSPT (37). Celle-ci varie beaucoup en fonction des études et peut aller de 0 à 50% pour une moyenne de 13% à trois mois (59,60).

Le TSPT est également très présent dans la population civile, notamment dans ce même contexte de TCL. Dans cette population, les résultats sont très proches de ceux des militaires. Plusieurs études ont ainsi montré que le TCL était un fort prédicteur de la déclaration d'un TSPT (14,61–63). Paradoxalement, l'association entre TSPT et TCL apparait être plus importante que celle entre PCLS et TCL. C'est ainsi que le stress semble avoir un rôle plus important dans la survenue de symptômes à long terme que le mécanisme traumatique en lui-même (14). Certains auteurs pensent même qu'un TCL n'est pas prédicteur d'un PCLS à trois mois contrairement à l'existence préalable d'un TSPT ou d'autres troubles psychiatriques comme l'anxiété (59).

Comme nous l'avons dit plus haut, plusieurs des symptômes du PCLS (troubles du sommeil, irritabilité, troubles de la concentration) font également partie des dimensions hyperéveil et

engourdissement du trouble de stress post-traumatique (TSPT) du DSM-IV-TR et du DSM-V (3,14,15,17).

Il existe donc probablement un lien fort en TSPT et PCLS mais celui-ci reste encore à déterminer plus précisément. Il est ainsi difficilement envisageable de ne s'intéresser qu'à l'une de ses entités nosologiques quand on évalue les conséquences d'un traumatisme.

7.3. Outils diagnostique du TSPT

La majorité des études portant sur le TSPT s'appuient sur les critères de la quatrième édition du manuel diagnostique et statistique des troubles mentaux (DSM-IV-TR) publiée par l'Association Psychiatrique Américaine (APA) (15). Ce manuel a été révisé en 2013 en une cinquième édition (17). La nouvelle édition du DSM apporte quelques modifications :

- Le TSPT appartient désormais à une nouvelle catégorie appelée « troubles consécutifs au traumatisme et au stress »
- L'exposition au traumatisme n'est pas obligatoirement directe, mais peut-être liée à la proximité émotionnelle avec une victime (famille ou amis proche) ou l'exposition répétée.

Le diagnostic de TSPT peut ainsi être posé au moyen des critères du DSM-V (17) où en utilisant des échelles d'orientation diagnostique comme la PCL-5 (PTSD Checklist 5ème version)(64,65). Ces échelles permettent une évaluation plus simple des patients en créant un score offrant la possibilité de suivre l'évolution du trouble et de son intensité, par exemple à l'issue d'une prise en charge thérapeutique.

8. Association entre « Post-concussion like symptoms » et Stress

La relation entre la survenue d'un SPC et la dépression, l'anxiété, le TSPT et le stress a fait l'objet de nombreux travaux. Ces différentes entités pathologiques ont été souvent décrites

comme des facteurs prédictifs majeurs du SPC, que ce soit en présence ou en l'absence d'un TCL (59,66).

Concernant la dépression, beaucoup d'études ont décrit une forte relation entre la présence d'une dépression au cours de l'année précédent un traumatisme et la survenue d'un SPC chez des patients sans TCL (67,68). L'évaluation psychiatrique est donc très importante avant de poser le diagnostic de SPC. En effet, les modalités de prise en charge thérapeutique sont très différentes entre ces deux entités.

Depuis 1992, des auteurs évoquent l'influence du stress chez des patients traumatisés crânien et non traumatisés crânien sur la survenue de PCLS (69) remarquant l'association entre le stress quotidien et la survenue, l'intensité et la durée des PCLS. Ces résultats ont été confirmés dans une étude plus expérimentale (70) dans laquelle des patients victimes de TCL ou non traumatisés avaient été soumis à des situations de stress ou à des séances de relaxation. A l'aide de tests psychométriques, les auteurs de ces travaux ont mis en évidence un lien entre PCLS et traumatisme. Il existait également une sensibilité importante aux variations d'intensité du stress chez les individus ayant présenté un TCL.

Edmed et al. en 2012 ont également décrit au cours d'une étude transversale portant sur 72 étudiants sans antécédent de traumatisme crânien que la présence de stress et d'anxiété, associés ou non à une dépression, majore le risque de survenue d'un SPC. Ils font partie des premiers à avoir suggéré que le stress était un facteur prédictif important dans la survenue d'un SPC (33).

8.1. Mesurer le stress aux urgences

Les études, conduites au cours de ce travail doctoral portaient donc sur l'influence du stress aigu, une notion encore mal définie et pour laquelle des outils de mesures reproductibles et fiables restent à développer. Aussi, a-t-il fallu pour les besoins de nos enquêtes créer un outil

ad-hoc permettant d'estimer les niveaux de stress entre l'admission et la sortie des urgences. Il devait correspondre à deux critères :

- Être applicable à la phase aiguë
- Être suffisamment sensible pour détecter une variation sur une période aussi courte que celle du séjour aux urgences (< 12h)

Des échelles d'évaluation d'une réaction de stress existent mais aucun de ces outils n'est validé à un moment aussi aigu d'un traumatisme. Par exemple, le *Stanford Acute Stress Reaction Questionnaire* (71) peut être utilisé pour un évènement aigu mais il s'effectue dans les 3 à 5 jours suivant l'évènement stressant.

Un outil pouvant correspondre a déjà été utilisé (72), il s'agissait d'une échelle de Likert à cinq niveaux avec laquelle une seule mesure était réalisée. Cependant, cet outil n'a pas eu de validation dans la littérature et le faible nombre de niveaux nous a paru insuffisant pour bien identifier les variations au cours du séjour aux urgences. Nous avons donc finalement utilisé une échelle numérique à 10 niveaux entre 0 « pas du tout » et 10 « pire stress imaginable ».

9. Présentation du travail de thèse

Les « Post-Concussion-Like Symptoms » sont ainsi un problème qui peut concerner une large partie de la population des adultes pris en charge dans les services d'urgence. En effet, la plupart des situations qui justifient leur admission sont des problèmes aigus qui sont une source de stress importante pour les patients. L'enjeu de ce travail de thèse sera de mieux comprendre la nature et la cause de ses symptômes, d'identifier les patients les plus à risque et de proposer des interventions permettant d'agir. Pour cela nous avons mené plusieurs études qui ont chacune apportée des éléments de réponse mais ont également soulevé des questions qui ont permis de façonner l'étude suivante.

L'étude SOFTER 1 avait pour objectif d'évaluer le rôle du stress ressenti aux urgences sur l'apparition à distance de PCLS. Il s'agissait d'une étude de cohorte observationnelle prospective où nous avons mesuré le stress des patients à l'entrée et à la sortie et rechercher le lien qui pouvait exister avec l'existence à 4 mois de PCLS.

Convaincus que le stress jouait un rôle important, nous avons ensuite conduit une revue de la littérature pour identifier les interventions qui pouvait être proposées pour intervenir dès les urgences sur les patients. Les travaux conduits sur le syndrome de stress post traumatique nous ont conduit à sélectionner une prise en charge psychothérapeutique appelée EMDR et à la tester grâce à l'essai pilote SOFTER 2. La cohorte de traumatisés crâniens PERICLES, précédemment conduite par notre équipe, nous a permis de créer un score de prédiction du niveau de risque de PCLS utilisé pour cet essai pilote SOFTER 2 qui avait donc pour objectif d'évaluer la faisabilité de l'EMDR aux urgences. Les résultats encourageant de ce premier essai a conduit à la mise en place d'un nouvel essai, SOFTER 3, bi-centrique (Lyon et Bordeaux) celui-là, dont l'objectif était d'évaluer l'efficacité de l'EMDR pratiqué aux urgences dans la prévention des PCLS à trois mois. Nous verrons que les résultats de SOFTER 3 ont apportés plus de questions que de réponse. Un nouvel essai (SOFTER 4) reste ainsi à réaliser pour y répondre. Nous en présentons le protocole. Il sera conduit en 2020 dans le cadre de l'appel à projet « Programme Hospitalier de Recherche Clinique » National 2018.

10. L'étude SOFTER 1

La littérature récente s'intéressant au syndrome post-commotionnel a mis en évidence plusieurs notions importantes :

- Le syndrome post-commotionnel est probablement plutôt un « syndrome post-traumatique » au sens plutôt psychologique du terme « traumatisme » et il peut ainsi

concerner de nombreux patients présentant des pathologies variées. Il convient ainsi dorénavant de lui préférer le terme de « post-concussion-like symptoms »

- Les situations stressantes jouent un rôle majeur dans l'apparition d'un syndrome post-commotionnel chez les patients traumatisés qu'il s'agisse d'un TCL ou non.
- Il existe un lien fort entre TSPT et PCLS

Les objectifs de l'étude SOFTER 1 était ainsi d'étudier le rôle du stress dans l'apparition, à distance d'un traumatisme mineur ayant nécessité un passage aux urgences, d'un PCLS en premier lieu, mais aussi d'un TSPT.

10.1. Résumé de l'étude SOFTER 1

Contexte : Selon des recherches récentes, jusqu'à 20 % des patients souffrant de traumatismes mineurs admis aux urgences souffriront de symptômes chroniques non spécifiques au cours des quelques mois suivants. Ainsi, la présente étude a évalué l'association entre ces symptômes et les niveaux de stress autodéclarés à l'admission et à la sortie de l'urgence.

Méthode : Cette étude était une étude d'observation prospective menée aux urgences de l'hôpital universitaire de Bordeaux auprès de patients admis pour traumatisme mineur. Tous les participants ont été contactés par téléphone quatre mois après leur présentation aux urgences afin d'évaluer l'apparition de symptômes équivalents à ceux du syndrome post-Commotionnel (PCLS).

Résultats : Au total, 193 patients ont été recontacté à 4 mois ; 5,2 % des participants souffraient d'un trouble de stress post-traumatique (TSPT) et 24,5 % du PCLS. Une analyse multivariée a révélé une association entre les PCLS et le niveau de stress à la sortie des urgences (rapports de côtes [RC] : 2,85, intervalle de confiance à 95 %[IC] : 1,10-7,40).

Conclusions : Le risque de PCLS 4 mois après une visite aux urgences pour un traumatisme mineur augmentait avec un niveau de stress élevé à la sortie des urgences. Ces résultats pourraient améliorer la qualité de vie des millions de patients qui subissent chaque année des blessures stressantes.

10.2. Article SOFTER 1 – In Press – International Emergency Nursing (Annexe 1)

Stress and lasting symptoms following injury: results from a 4-month cohort of trauma patients recruited at the emergency department.

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Abstract

Background: Recent research suggests that up to 20% of minor trauma patients admitted to the emergency department (ED) will suffer from non-specific chronic conditions over the subsequent several months. Thus, the present study assessed the correlates of symptoms that persisted at 4 months after an ED visit and, in particular, evaluated the associations between these symptoms and self-reported stress levels at ED admission and discharge.

Method: This study was a prospective observational investigation conducted in the ED of Bordeaux University Hospital that included patients admitted for minor trauma. All participants were contacted by phone 4 months after presentation at the ED to assess the occurrence of post-concussion-like symptoms (PCLS).

Results: A total of 193 patients completed the follow-up assessment at 4 months; 5.2% of the participants suffered from post-traumatic stress disorder (PTSD) and 24.5% suffered from

PCLS. A multivariate analysis revealed an association between PCLS and stress level at discharge from the ED (odds ratios [OR]: 2.85, 95% confidence interval [CI]: 1.10-7.40).

Conclusions: The risk of PCLS at 4 months after an ED visit for a minor injury increased in association with the level of stress at discharge from the ED. These results may improve the quality of life for the millions of patients who experience a stressful injury event every year.

Introduction

Tens of millions of people worldwide suffer from minor injuries and many of these individuals are admitted to an emergency department (ED) (1). Each year, this represents approximately 5 million ED admissions in France and nearly 40 million across Europe (2). More than 90% of patients who present at an ER for a minor injury will be discharged within a few hours and do not require hospitalization (2). However, recent research suggests that up to 20% of such patients will suffer from non-specific chronic conditions for the subsequent several months (4–8). These conditions can include symptoms such as headache, concentration difficulties, memory loss, intolerance of stress, change in personality, and irritability (9), which, in combination, often lead to significant impairments in quality of life, fewer social and family activities, and delayed return to work or to school. If the available results are representative of an entire population, then up to 1 million people in France alone have been affected by this significant and unrecognized public health burden.

In particular, these symptoms co-occur in the context of mild traumatic brain injury (MTBI), which has been identified as post-concussion syndrome (PCS) (15). However, several studies have suggested that the symptoms encompassed by this syndrome are not specific to MTBI and may manifest as a consequence of any type of traumatic event (14). Another striking characteristic of these symptoms is that they appear to be more frequent when the traumatic

event was stressful. For example, several of these symptoms (e.g., sleeping disorders, irritability, and trouble concentrating) are also listed as components of the hyperarousal and numbing dimensions of post-traumatic stress disorder (PTSD) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V)[DSM-V; 10]. Moreover, in addition to the stress associated with the MTBI event itself, patients may experience stressful events during their ED stay. For example, a recent study of 474 patients found that the evaluation of a potentially life-threatening cardiac event in the ED is associated with subsequent post-traumatic stress symptoms (3). However, data supporting the effects of non-specific stress-related consequences remain scarce.

Thus, the present longitudinal observational study of patients who were admitted to the ED of Bordeaux University Hospital for a minor injury was conducted to determine the correlates of symptoms that persisted at 4 months after the ED visit and, in particular, to evaluate the associations of these symptoms with self-reported stress levels at ED admission and discharge.

Methods

Study design and settings

This prospective observational study evaluated patients who presented at the ED of Bordeaux University Hospital, which serves both rural and urban areas that include a total of 1.4 million inhabitants, for a minor injury over 3 weeks from February 24th to March 15th, 2015. Clinicians interviewed patients who had recently been admitted for a minor trauma prior to their medical examination and recorded the general health conditions and current stress levels of each patient. At the end of the ED stay, the same physician interviewed the patient again. Approximately 4 months after the ED stay, a physician contacted each participant by phone to assess the occurrence of symptoms that are listed as components of PCS according to the definitions of the International Classification of Diseases, 10th Revision (ICD-10) (73),

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) (15), and Rivermead Post-concussion Symptoms Questionnaire (18) as well as symptoms listed as part of PTSD according to the DSM-IV-TR.

Participants

The present study included all patients ≥ 18 years of age who were able to answer the interviewer (Glasgow Coma Score = 15 when interviewed) and had been admitted in the first 24 hours after an injury. Patients who required medical attention in the operating room or the critical care unit were excluded.

Data collected

Using a numerical scale ranging from 0-10, all participants were asked to describe their stress levels, expectation for recovery, and whether they felt overwhelmed by the events at the ED both at admission and at discharge. In the admission questionnaire, the participants were also asked to rate their overall health condition just prior to the event and in the previous 1 year using a 5-point Likert scale. The participants were also asked whether they had experienced any concentration problems, sleeping disorders, loss of energy, or need for anxiolytics in the past 12 months. These four items were selected because they are predictive of symptoms listed as components of post-concussion-like symptoms (PCLS) [8]. Upon discharge, the participants were also asked to rate their level of satisfaction with the ED care they were provided.

The third quartile of the self-reported stress scale distribution was used to define the 'stressed' population at each stage of the study (admission and discharge). Subsequently, these two variables were used to classify further the participants into three categories: those who were never stressed, those who were stressed at admission only, and those who were stressed at discharge irrespective of their stress status at admission. Several attempts were

made to contact all participants by phone 4 months after ED admission using the phone number provided by the patient to assess the following nine symptoms based on the DSM-IV-TR definition for PCLS (15): headache, dizziness, personality change, sleeping disorders, tiredness, irritability, depression, anxiety, and lack of spontaneity. PCLS was defined as the presence of at least three of these symptoms and the same definition was applied to all participants, including those with non-head injuries. Thus, the term 'PCLS' will be applied hereafter to patients even when the injury was not a head injury.

The following 14 symptoms included in the DSM-IV-TR definition for PTSD were also selected for assessment (15): intrusion symptoms (reliving the event through upsetting thoughts, nightmares, or flashbacks and/or having very strong mental and physical reactions when reminded of the event), avoidance (avoiding activities, thoughts, feelings, or conversations that remind the person of the event; feeling numb to one's surroundings; and/or being unable to remember details of the event), negative alterations in cognition and mood (loss of interest in important activities, feeling alone, being unable to have normal emotions, or feeling that there is nothing to look forward to in the future), alterations in arousal and reactivity (feeling that one can never relax and must be on guard all the time to protect oneself, trouble sleeping, feeling irritable, overreacting when startled, angry outbursts, or trouble concentrating), and functional significance and exclusion. A diagnosis of PTSD required that one or more symptoms from each of these categories be present for at least 1 month and that the symptom or symptoms seriously interfered with leading a normal life.

Statistical analysis

Univariate analyses were performed to evaluate the associations between PCLS and the risk factors using Student's t-tests for continuous variables and Chi-square tests for categorical variables. Variables with a p-value < 0.20 were selected for the multivariate logistic analysis.

Subsequently, all significant variables ($p < 0.05$) and confounders (variation of $\beta > 20\%$) were selected using a manual step-by-step backwards selection process and then the odds ratios (OR) and 95% confidence intervals (95% CI) were estimated. Then, interactions between independent variables that were kept in the final model were tested. Additionally, sensitivity analyses were performed by changing the cut-off for the stress definition and stratifying the analysis according to location of the injured body part. All data were analyzed using SAS Software (v9.4, SAS Institute Inc©; North Carolina, USA)

Results

Of the 296 ED patients who provided self-assessments of stress at both admission and discharge, 103 could not be contacted at 4 months and, therefore, the present study included a total of 193 patients. Patients who were lost to follow-up did not differ from the patients who were contacted in terms of sex, age, injury location, stress levels, or health condition. The only significant difference between these two groups was in terms of satisfaction such that patients lost to follow-up were more likely to be unsatisfied ($p = 0.03$).

The third quartile of the stress scale distribution provided a threshold of '4' as a definition for the status of 'stressed' for the present study. Accordingly, 28.0% and 17.6% of ED patients were stressed at admission and discharge, respectively. Additionally, 25.9% and 19.2% of patients reported being overwhelmed by events at admission and discharge, respectively. These two variables were highly associated with self-reported stress levels beyond the first quartile threshold ($p < 0.001$ at admission and at discharge).

Overall, 24.5% of the participants had PCLS at 4 months. The proportions of PCLS and PTSD are presented according to patient characteristics (Tables 2 and 3), ED stay experience, and stress levels (Table 4 for questions asked during ED stay and Table 5 for questions asked at 4 months). A multivariate analysis (Table 6) revealed an association between PCLS and stress at

discharge from the ED (OR: 2.85, 95% CI: 1.10 – 7.40). Additionally, patients who expected a good chance of recovery and reported no loss of energy in the past 12 months were significantly more likely to report PCLS 4 months later. The impact of stress level at discharge on the risk of PTSD was the only correlate, albeit a very strong correlate, of PTSD (OR: 32.58, 95% CI: 3.65-290.90). A sensitivity analysis (Table 7) did not reveal any significant variations in these estimates when potential confounders, including sex, age, self-estimated chance of recovery, body part of the injury, injury type, and stress at admission, were introduced to the models.

Discussion

Main findings

The present longitudinal observational study evaluated patients who presented to the ED for a minor injury and were then contacted 4 months later for a self-assessment of their health status. The present results showed that the risks of PCLS and PTSD at 4 months post-injury increased with the level of stress at discharge but not at admission.

Strengths and weaknesses

To the best of our knowledge, this study is the first to investigate the impact of self-reported stress throughout one's stay at the ED on symptoms related to PCLS and PTSD at 4 months post-injury. Based on the typical attendance statistics of the ED at Bordeaux University Hospital, approximately 75% of eligible patients were included in this study. However, this should be considered a rough estimate because it was not possible to collect data from all potentially eligible patients due to the complex patient-flow times and spatial environment. Of the recruited patients, 35% were lost to follow-up but exhibited the same characteristics as the patients who were contacted 4 months later, except for satisfaction regarding their stay

at the ED. However, it is unlikely that this difference biased the present results as there was no association between self-reported stress levels and satisfaction.

Although several tools have been designed and validated for the assessment of chronic cumulative stress, no such instruments for measuring acute stress at a given timepoint are currently available. The Stanford Acute Reaction Stress Questionnaire (SARSQ) (71) is one of the few instruments that is focused on acute stress but this measure must be administered 3-5 days after the event and, therefore, could not be used in the present study. A previous study has validated the use of a 5-point Likert scale for this purpose (72) but it was assumed for the present study that this number of levels would be insufficient to identify variations in stress over such a short period of time. Consequently, the patients were asked to describe their current level of stress using a 10-point numerical scale at both admission and discharge. The difference in the number of levels on the scale is likely not to have influenced the validity of this tool. In fact, there was a strong and consistent association between this measure and responses regarding whether the patients felt overwhelmed by the current events.

Recent studies, including one that assessed 1361 injury patients, have suggested that PCLS may not be specific to MTBI (10). However, even though the present authors believe that this syndrome should be renamed with no reference to the location of the injured body part, the DSM-IV-TR definition of PCLS was used in the present study so as to be consistent with previous studies. The self-reported stress levels of the ED patients were likely to have depended on several factors, including injury severity, the mental health and anxiety levels of each patient, ED affluence (stress contamination between patients), context of care delivery, duration of stay, and quality of attention provided by caregivers. Although several of these factors were accounted for in the present analyses (e.g., mental vulnerability and injury

severity), it was not possible to isolate all, if any, of the components of the stress triggers that may have influenced the potential long-term consequences of the participants.

Interpretation

The present study identified strong associations between self-reported stress at discharge and PCLS and PTSD at 4 months post-injury, which is interesting because these findings indicate that the early management of stress may prevent, at least in part, a very significant component of the public health burden. A multivariate analysis also revealed that loss of energy and treatment for anxiety in the year prior to ED admittance were associated with PCLS. This finding suggests that people with anxiety and mood disorders may have an increased risk of long-lasting post-traumatic symptoms, which has been previously observed in cases of military-related MTBI (67) and in trauma patients admitted to the ED (24). The prevalence of PCLS in the present study was similar to that reported in previous MTBI studies [8,10,17–21]. This indicates that these symptoms, which are described in the DSM-IV-TR as PCLS (15), are likely to be related to all injury events, as previously suggested by several authors (14,42,79), as well as other stressful non-injury medical events.

The screening of individuals who are most at-risk for PCLS using tools such as the Whittaker prediction model (80) or lists of simple symptoms (81,82) has been proposed for brain injury patients. The present results suggest that this proposal could be extended to non-head injury patients and that self-assessed stress levels should be included in the scoring systems of screening tools. However, the actual predictive performance of these tools and symptoms remains to be tested. The present results also suggest that stress during an ED stay may play a causal role in the risks of PCLS and PTSD. However, further studies will be necessary to determine whether addressing stress levels in the early stages after an event could impact long-term health. Interventions proposed for the prevention of PTSD (83–85), such as eye

movement desensitization and reprocessing (EMDR) and cortisol treatments, should be tested as ED-based early prevention tools. Based on the present findings, our research group conducted a pilot study that successfully assessed the impact of an early EMDR session on PCLS after an ED visit (86) and designed a larger bicentric randomized controlled trial that has recently ended (87). Screening tools that can aid in the selection of candidates for these interventions can be designed based on the available results of prospective cohorts of injured patients, such as the cohort built for the present study.

Conclusions

Minor injuries constitute the basis of a significant number of ED visits. The present study found that the risks of PCLS and PTSD at 4 months post-injury increased with the level of self-reported stress at discharge but not at admission. These results suggest that early interventions in the ED have the potential to improve the quality of life of patients who may be at a high risk of PCLS and PTSD several months later. The next step will be to identify the best interventions for lowering stress and arousal levels in the ED and then conduct a randomized controlled trial to evaluate the feasibility and efficacy of these interventions on symptoms at 4 months after the injury.

Table 2. Patient characteristics and PTSD and PCLS at 4 months.

	N	PTSD (%)	p value	PCLS (%)	P value
All	193	5.2		24.5	
Sex			< 0.05		< 0.05
Male	131	3.0		19.1	
Female	62	9.7		35.5	
Age			NS		NS
15-29	109	3.7		19.3	
30+	84	7.1		30.9	
Cause of admission					
Road traffic crash	30	16.7	$< 10^{-2}$	30.0	NS
Sport	47	2.1		12,8	< 0.05
Violence	11	0.0		18.2	NS
Fall	53	5.7		34.0	0.056
Work injury	49	10.2		30.6	NS
Domestic injury	16	12.5	NS	37.5	NS
School injury	3	33.3		33.3	NS
Leisure injury	13	7.7		7.7	NS
Other	14	21.4		35.7	NS
Injury type			NS		NS
Head	26	0.0		15.4	
Bruise	83	6.0		25.3	
Wound	11	0.0		27.3	
Sprain	54	3.7		24.1	
Dislocation	2	0.0		0.0	
Fracture	5	20.0		20.0	
Body part			NS		$< 10^{-2}$
Head	29	0.0		17.2	
Upper limb	33	0.0		24.2	
Spine/Thorax	19	10.5		57.9	
Lower limb	92	6.5		18.5	
Multiple	8	0.0		12.5	

Table 3. Patient health prior to the injury event and PTSD and PCLS at 4 months

	N	PTSD (%)	P value	PCLS (%)	P value
Difficulty with concentration in the past 12 months			< 0.05		$< 10^{-2}$
No	147	2.7		19.1	
Yes	34	14.7		44.1	
Restlessness in the past 12 months			NS		$< 10^{-4}$
No	126	3.2		15.1	
Yes	59	8.5		42.4	
Loss of energy in the past 12 months			NS		$< 10^{-4}$
No	127	3.9		14.2	
Yes	60	8.3		45.0	
Medicine consumption for anxiety in the past 12 months			NS		$< 10^{-4}$
No	163	4.3		19.6	
Yes	19	10.5		57.9	
Health condition before the event			NS		NS
Excellent	62	3.2		6.5	
Very good	64	5.7		25.0	
Good	37	2.7		35.1	
Fair	22	9.1		40.9	
Bad	6	33.3		83.3	
Health condition as compared to 1 year ago			NS		NS
Much better	28	7.1		21.4	
Better	30	13.3		43.3	
Identical	121	2.5		19.0	
Worse	9	0.0		33.3	
Much worse	3	0.0		33.3	
Have relatives at home that can help			NS		NS
No	15	0.0		33.3	
Yes, occasionally	36	0.0		30.6	
Yes, if necessary	137	6.6		21.9	

Table 4. Patient ED experiences and PTSD and PCLS at 4 months.

	N	PTSD (%)	p value	PCLS (%)	P value
Self-estimated chances of recovery at admission			< 0.05		$< 10^{-2}$
≥ 9	142	2.8		19.0	
< 9	49	10.2		38.8	
Self-estimated chances of recovery at discharge			NS		NS
≥ 9	149	4.0		22.2	
< 9	42	9.5		30.9	
Overwhelmed by events as reported at admission			$< 10^{-2}$		$< 10^{-2}$
< 4	142	1.4		19.0	
≥ 4	48	14.5		39.6	
Overwhelmed by events as reported at discharge			$< 10^{-4}$		$< 10^{-3}$
< 4	155	0.7		18.7	
≥ 4	37	21.6		47.4	
Stress at admission			$< 10^{-2}$		$< 10^{-2}$
< 4	138	1.5		18.1	
≥ 4	54	13.0		37.0	
Stress at discharge			$< 10^{-4}$		$< 10^{-4}$
< 4	159	1.3		18.9	
≥ 4	34	23.5		50.0	
Time since admission			NS		NS
< 100 min	57	7.0		28.1	
100 to 149 min	49	6.1		20.4	
150 to 199 min	34	0.0		17.6	
200 min	53	5.7		28.3	
Satisfied by ED stay			NS*		NS*
No	23	8.7		21.7	
Yes	170	4.7		24.7	

Table 5. Questions asked at 4 months and PTSD and PCLS at 4 months.

	N	PTSD (%)	p value	PCLS (%)	P value
4-month variables					
Is there anything that you can't do anymore because of the symptoms following your accident?			$< 10^{-4}$		$< 10^{-4}$
No	123	1.6		16.3	
Yes	37	21.6		70.3	
No symptoms	33	0.0		0.0	
Work stoppage			NS		NS
No	95	4.2		22.1	
Yes	78	6.4		29.5	
No occupation	20	5.0		15.0	
Health condition as compared to before the event			$< 10^{-2}$		NS
Much better	21	0.0		14.3	
Better	30	6.7		26.7	
Almost identical	98	2.0		19.4	
Worse	36	8.3		33.3	
Much worse	8	37.5		50.0	
Satisfied by ED stay			NS		NS
No	34	11.8		29.4	
Yes	159	3.7		23.3	

Table 6. Multivariate logistic models of the predictors of PTSD and PCLS at 4 months.

	PTSD*		PCLS*	
	OR	95% CI	OR	95% CI
Self-estimated chances of recovery at admission				
No	Ref.		Ref.	
Yes	0.55	(0.12 – 2.46)	0.28	(0.12 – 0.68)
Loss of energy in the past 12 months				
No			Ref.	
Yes			4.46	(1.98 – 10.03)
Medicine consumption for anxiety in the past 12 months				
No			Ref.	
Yes			8.22	(2.60 – 25.96)
Stress at discharge				
No	Ref.		Ref.	
Yes	41.43	(4.83 – 355.39)	3.19	(1.25 – 8.10)

Table 7. Multivariate analysis of the factors associated with PTSD and PCLS: Results from a logistic regression adjusted for potential confounders and the sensitivity analysis.

	PTSD		PCLS	
	OR	95% CI	OR	95% CI
Model 1				
Stress at discharge	32.58	(3.64 – 290.90)	2.85	(1.10 – 7.40)
Model 2				
Stress at discharge	40.18	(4.64 – 347.75)	3.08	(1.20 – 7.90)
Model 3				
Stress at discharge	30.84	(3.38 – 288.45)	3.10	(1.06 – 9.05)
Model 4				
Stress at discharge	32.09	(3.57 – 355.39)	2.50	(0.91 – 6.83)
Model 5				
Stress at discharge	56.43	(3.78 – 842.74)	3.53	(1.05 – 7.04)

Model 1: adjusted for sex and self-estimated chances of recovery at admission
Model 2: adjusted for age and self-estimated chances of recovery at admission
Model 3: adjusted for body part and self-estimated chances of recovery at admission
Model 4: adjusted for injury type and self-estimated chances of recovery at admission
Model 5: adjusted for stress at admission and self-estimated chances of recovery at admission

10.3. Complément de réflexion sur SOFTER 1 :

Les deux messages principaux de l'étude SOFTER 1 sont :

- Le PCLS peut se développer à la suite de tout traumatisme
- L'apparition d'un PCLS quatre mois après un traumatisme minime est associée au stress des patients à la sortie des urgences.

Cette première étude comporte plusieurs limites méthodologiques relativement importantes mais elle permet d'ouvrir des perspectives pour la suite.

Le critère de jugement principal était initialement la présence d'un PCLS à 3 mois mais pour des problèmes d'organisation le rappel n'a pu s'effectuer qu'à 4 mois. Cela pose le problème de la comparabilité par rapport à la plupart des études qui évalue habituellement ces symptômes ou ceux du TSPT 3 mois après un évènement.

Un autre problème important est la mesure de notre variable d'exposition principale à savoir le stress ressenti par le patient à l'admission et à la sortie. L'outil utilisé présente clairement plusieurs limites. D'une part, il n'a jamais été validé voir même utilisé comme tel auparavant (l'échelle de Likert à cinq niveaux déjà utilisée (72) manque de précision.). D'autre part, la catégorisation d'une variable continue comporte toujours une part d'arbitraire (88,89) . Nous avons basé notre choix sur deux éléments :

- La distribution de la variable en choisissant de dichotomiser au niveau du troisième quartile.
- Le sens clinique donné aux différents niveaux de l'échelle, en s'appuyant notamment sur la limite qui a été définie dans le cadre de l'évaluation et de la prise en charge de la douleur (90).

Nous aurions dû réaliser au préalable un calcul du nombre de sujets nécessaires pour cette étude exploratoire, ce qui nous aurait permis d'affiner la réflexion et de mieux évaluer le réel

impact des différemment éléments inhérents aux patients et à leur pathologie. Une rapide estimation du nombre de sujets nécessaire aurait pu être faite en se basant sur 20 à 30 évènements par variable d'intérêt (91,92). Ainsi, en considérant 10 variables d'intérêt indépendantes il aurait fallu 200 ou 300 évènements dont l'incidence attendue dans la population est de 20 à 25 % dans la littérature. Selon la méthode de calcul choisie, cette étude aurait finalement plutôt nécessité 800 à 1500 patients. D'autres auteurs considèrent qu'un minimum de 100 à 200 évènement est suffisant (93), ce qui aurait représenté ici plus de 800 patients.

L'anxiété et les troubles de l'humeur liés à la prise d'anxiolytiques dans les 12 derniers mois sont largement décrits dans la littérature comme majorant la survenue du PCLS (14,33). Il est intéressant de voir que nous retrouvons dans cette étude ces mêmes résultats.

La conclusion principale de cette étude était qu'au terme de leur prise en charge aux urgences pour un traumatisme minime, les patients qui se déclaraient stressés avaient un risque plus important de développer quatre mois plus tard un PCLS. Cette influence du stress à la sortie des urgences nous permet d'envisager d'intervenir dès les urgences pour diminuer ce stress et espérer réduire ainsi l'incidence des PCLS parmi les patients qui consultent aux urgences pour un traumatisme.

11. Agir sur le stress des patients aux urgences : quelles options ?

Les résultats de la littérature et des études PERICLES et SOFTER 1 nous ont conduit à envisager la mise en place d'intervention précoce dès les urgences pour diminuer l'incidence des PCLS à distance d'un passage aux urgences. Nous avons donc initié une recherche documentaire afin d'identifier les solutions qui pourraient permettre de réduire le niveau de stress pendant un séjour aux urgences.

11.1. Connaissances actuelles sur la prise en charge des PCLS

Il y a relativement peu d'études sur la prévention et le traitement des PCLS (94–96). Ces études concernent essentiellement les patients qui ont été victime d'un traumatisme crânien et correspondent donc plutôt à la définition princeps du syndrome post-commotionnel. Une revue systématique publiée en 2010 (95) a suggéré que la thérapie cognitivo-comportementale (TCC) pourrait être efficace dans le traitement des SPC. Cependant, les auteurs n'y avaient identifié aucune étude de qualité et appelaient à conduire des essais plus rigoureux permettant de connaitre l'intérêt réel de la thérapie cognitivo-comportementale dans la prise en charge des PCLS. D'autres stratégies évoquées comprennent l'information, l'éducation et la réassurance (97–99). D'autres auteurs suggèrent que la relaxation permettrait de diminuer la survenue d'un SPC chez les traumatisés crânien légers (70) mais les niveaux de preuve à l'appui de ces affirmations restent très faible.

Un nombre croissant d'études suggèrent un possible impact du niveau des attentes des patients d'une part et d'autre sur les facultés d'adaptation et de coping sur l'installation de maladies chroniques à la suite d'un traumatisme, en particulier chez les patients souffrant d'entorse cervicale (100,101) et de lombalgie (102). On a constaté que le réconfort fourni dans

le contexte du cancer (103), des douleurs lombaires (104) et des traumatismes crâniens légers (99) aide les patients dans leur processus de rétablissement. Il est donc possible qu'au moins un sous-groupe de patients ayant subi un évènement traumatique puisse bénéficier d'interventions de cette nature. Par ailleurs, la littérature concernant les thérapeutiques qui permettent de réduire les PCLS reste relativement pauvre.

Le paysage reste donc relativement pauvre. C'est la raison pour laquelle nous avons exploré également les interventions évaluées dans le contexte de la prévention et du traitement du TSPT, profitant du chevauchement existant entre cette entité et le TSPT.

11.2. Traitements médicamenteux du TSPT

Plusieurs substances pharmacologiques ont été testées dans l'espoir de prévenir le TSPT. Il s'agit notamment du propranolol, de la morphine, de la kétamine et de l'hydrocortisone (105,106). Seule cette dernière a jusqu'à présent démontré un effet bénéfique significatif (risk ratio : 0.17; Intervalle de confiance à 95% 0.05 à 0.56) (94,105).

11.3. Interventions psychologiques du Trouble de Stress Post-Traumatique

11.3.1. Psychological débriefing

L'une des premières idées proposées aux patients ayant vécu un événement stressant a été d'initier une procédure de gestion du stress avant la consolidation des souvenirs stressants. C'est en partie pour cette raison que le débriefing psychologique, qui consiste en des séances menées 2 à 10 jours après l'évènement, a été largement diffusé. Cependant, plusieurs critiques (107) et une revue de la Cochrane (108) ont conclu que cette forme d'intervention entraînait une augmentation du taux de TSPT et devait donc être proscrite.

11.3.2. Exposition précoce

Plus prometteuse, la thérapie d'exposition précoce, basée sur l'extinction de la peur, semble être un traitement efficace du TSPT (109,110). Le TSPT est considéré par certains comme un échec de la guérison, lié à l'échec de l'extinction du traumatisme (111). Les recherches menées sur l'animal montrent que l'extinction précoce peut modifier la consolidation de la mémoire de la peur d'origine (112,113). Rothbaum et al. ont recruté pour la première fois en 2012 un échantillon de 137 patients randomisés en trois groupes. Ils ont démontré l'efficacité d'une intervention de type extinction (exposition prolongée) débutant aux urgences dans la prévention du TSPT (114). Il est à noter que l'intervention comprenait également deux autres séances une et deux semaines plus tard. Les mêmes auteurs ont montré 2 ans plus tard qu'une telle intervention pourrait également permettre de réduire le risque de TSPT chez les patients qui présentent des gènes reconnus pour être associés à la réponse au stress (111).

11.3.3. Thérapie cognitivo-comportementales.

La thérapie cognitivo-comportementale (TCC) axée sur les traumatismes peut être utilisée dans les semaines suivant un événement potentiellement traumatisant pour les personnes présentant des signes de détresse. La TCC a longtemps été la thérapeutique la plus utilisée dans le traitement du stress aigu, des symptômes précoces ou dans la prévention du TSPT(115–118). Parmi ces thérapies cognitivo-comportementales l'intervention psychothérapeutique EMDR (Eye movement desensitization and reprocessing) occupe une place particulière que nous décrivons ci-après.

11.3.4. Eye Movement Desensitization and Reprocessing

Inventé par Francine Shapiro (119), l'EMDR (Eye movement desensitization and reprocessing) est une approche psychothérapeutique largement utilisée qui permet de traiter rapidement et de manière adaptative des expériences perturbatrices à l'aide de mouvements oculaires ou

d'autres formes de stimulation bilatérale. Plusieurs méta-analyses et une revue de la Cochrane ont montré qu'il s'agit d'un des traitements les plus efficaces contre le TSPT (120–122). Le traitement peut commencer peu de temps après le traumatisme, mais il est le plus souvent mis en place après une plainte du patient qui souffre déjà de symptômes de TSPT. Plus récemment, une étude de Cyril Tarquinio de l'Université de Lorraine, France, a démontré l'efficacité d'une intervention EMDR initiée dans les premières 48 heures. dans la prévention du TSPT chez des travailleurs ayant subi des violences professionnelles (agressions, vols, etc.) (123).

Une étude menée en Israël a montré des résultats très prometteurs avec une seule séance d'EMDR précoce (le protocole est adapté à cette temporalité) en milieu hospitalier général et en ambulatoire pour 86 patients souffrant d'un trouble de stress aigu suite à des accidents et des attentats terroristes (124). La moitié des patients ont décrit une atténuation immédiate des symptômes intrusifs et un soulagement général de la détresse, 27 % ont décrit un soulagement partiel de leurs symptômes et de leur détresse, tandis que 23 % n'ont signalé aucune amélioration. Après un suivi de 4 semaines et de 6 mois, les patients répondeurs dès la prise en charge initiale ne présentaient toujours aucun symptôme, tandis que les non-répondeurs présentaient davantage de facteurs de risque de développer un TSPT. Ces résultats appuient d'autres études anecdotiques sur les effets rapides d'une intervention EMDR brève sur des symptômes intrusifs dans des cas post-traumatiques précoces non compliqués (125).

Après la reconnaissance de l'échec du « psychological debriefing » (108), la question de la prise en charge des patients présentant des niveaux élevés de stress ou de dissociation restaient posée. Ce dernier point était d'autant plus critique que l'on savait que la dissociation au moment du début de la thérapie d'exposition était associée à une réponse plus faible (125).

En réponse au nombre croissant de patients ayant besoin de soins après des catastrophes telles que les attentats, des procédures EMDR modifiés et adaptés pour une intervention précoce ont été développés pour aider les victimes. Les deux protocoles proposés pour une mise en œuvre peu après un traumatisme sont l' « Emergency Response Protocol »(ERP)(126) et le « Recent Traumatic Episode Protocol » (R-TEP)(127,128).

L'ERP est une procédure courte décrite pour la première en 2013 par Martin Luber (129). L'ERP est mis en œuvre selon des procédures conçues et testées dans des contextes d'urgence, y compris dans les services d'urgences (130).

L'efficacité maximale de l'ERP est attendue pour les patients très agités, correspondant à un score de 7-10 sur 10 sur l'échelle des unités subjectives de perturbation (« Subjective Unit of Disturbance » : SUD où 0 = aucune perturbation et 10 = la perturbation la plus élevée possible) par rapport à ceux qui sont passés dans une "terreur silencieuse" (SUD 10/10). Il parait ainsi intéressant pour les patients des urgences mais il est classiquement utilisé au-delà de 48h après un traumatisme.

Le protocole R-TEP peut être pratiqué plus tôt. Il s'agit d'une intervention précoce de l'EMDR axée sur les traumatismes actuels qui incorpore et prolonge les concepts principaux originaux du protocole pour les évènements récents de Francine Shapiro (131). Il a été décrit pour la première fois par Elan Shapiro et Brurit Laub en 2008 (127).

12. Le choix pour la suite de SOFTER

Nos réflexions basées sur les données disponibles dans la littérature nous ont amenés à choisir l'EMDR R-TEP. En résumé, ce choix s'est fondé sur les considérations suivantes :

- L'absence de documentation suffisante sur les interventions préventives en matière de PCLS

- Le chevauchement partiel entre le PCLS et le TSPT
- Les résultats de nos études préliminaires suggérant fortement le rôle majeur du stress dans la PCLS
- Le consensus en faveur de l'utilisation de l'EMDR dans la prévention précoce du TSPT
- L'existence de plus en plus évidente d'une composante psychologique importante dans les plaintes persistantes.
- L'échec du débriefing psychologique précoce pour prévenir le TSPT

13. Évaluer le niveau de risque pour définir les patients devant bénéficier d'une intervention

Plusieurs auteurs se sont déjà intéressés aux facteurs associés au SPC. L'âge, le sexe (66,132) ainsi que l'existence de problèmes physiques ou psychologiques (59) avant l'accident sont autant de variables associées à l'existence d'un SPC 3 mois plus tard. Dans une étude qui a inclus à la fois des patients traumatisés crânien et non-crânien (14), ces même facteurs sont mis en évidence. Ainsi, un âge plus élevé et le sexe masculin sont des facteurs protecteurs alors qu'une dépendance à l'alcool, une gêne dans la vie de tous les jours et l'existence de symptômes avant l'évènement traumatique sont des facteurs de risque de PCLS. Cette étude met également en évidence l'absence de facteurs de risques propres aux TCL. Comme nous l'avons vu plus haut, les études récentes ont mis en évidence qu'une vulnérabilité psychologique et le stress vécu au moment et après l'accident sont deux des éléments les plus prédicteurs de ces symptômes (27,39,133,134).

L'identification de ces facteurs de risques, retrouvés de manière répétée dans la littérature, nous permet d'envisager la création d'un outil d'évaluation du niveau de risque. Pour la mise en œuvre d'études interventionnelle la conception d'un tel outil est nécessaire pour au moins

eux raisons. D'une part, la durée d'une séance d'EMDR est d'environ une heure et il n'est donc pas envisageable de prendre en charge l'ensemble des patients se présentant aux urgences. D'autre part, certains auteurs ont déjà décrit que l'efficacité d'une intervention peut-être liée à sa population cible et qu'il serait plus pertinent de s'intéresser aux populations les plus à risque (135).

13.1. Création d'un outil d'évaluation du niveau de risque individuel de PCLS.

L'objectif pour cette analyse secondaire de la cohorte PERICLES est ainsi de construire un score d'évaluation du niveau de risque d'un individu de développer à 3 mois un PCLS. L'idée de ce score est d'être capable d'identifier un groupe d'individu dont le risque de développer des symptômes invalidants est particulièrement élevé.

13.2. Résumé

Introduction : Les traumatismes de la vie quotidienne sont un motif fréquent d'admission aux urgences avec près de 5 millions de visites en France. Des études récentes ont montré que 10 à 20 % des patients traumatisés présentent un ensemble de symptômes (équivalents au syndrome post-commotionnel et au trouble de stress post-traumatique) qui peuvent persister pendant plusieurs semaines ou mois après l'événement traumatique. Ils peuvent induire un changement dans la qualité de la vie sociale, professionnelle ou familiale de ces patients. Il s'agit d'une question de santé publique importante. La conception de cette entité pathologique et l'existence d'une thérapie abondent dans la recherche d'un outil de dépistage.

Matériau et méthode : L'objectif de ce travail est de développer un score pour mieux identifier les patients les plus à risque de présenter ces symptômes lors d'un traumatisme lors de leur visite à l'urgence. Ce score a été élaboré à partir des résultats de la cohorte prospective PERICLES. La population sélectionnée pour le score est composée de patients Traumatisé crânien léger (TCL) et de patients témoins traumatisés non crâniens qui ont rempli les questionnaires M0 et M3 et en

particulier les données SPC et TSPT. Nous avons randomisé les patients avec une partie pour la construction des scores (2/3 des patients) et l'autre partie pour les tests (1/3 des patients). Analyses univariées et multivariées pour l'étude des facteurs prédictifs de la SCP et du TSPT, suivies d'une sélection de variables pas à pas descendante. Pour la construction du score, le poids de chacune des variables a été défini à partir des valeurs des coefficients bêta (β) résultant de ces analyses. La capacité diagnostique de chacun des scores a été modélisée à l'aide d'une courbe ROC. Pour chaque seuil de notation, les caractéristiques intrinsèques et extrinsèques ont été calculées.

Résultats : La note choisie était la suivante : Du sexe féminin : +1 ; Impression, perception de l'état de santé avant l'épisode : Excellent, Très bon 0, Bon +1, Moyen +2, Mauvais +3 ; Prise de traitements calmants (anxiolytiques, antidépresseurs) : +2 ; score maximum total : 6

Conclusion : Les caractéristiques et les capacités diagnostiques de cet outil de dépistage sont similaires en termes de dépistage des patients à risque de présenter des symptômes équivalents à ceux du SSPT et du SSPT.

13.3. Article

Article actuellement soumis à Journal of psychiatric research

Creation and validation of a tool to assess individual risk of post-concussion like symptoms 3 months after ED visit.

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Abstract

Introduction: Trauma in everyday life is a frequent reason for attending emergency department with nearly 5 million visits in France. Recent studies have shown that 10 to 20% of trauma patients will have a set of symptoms (equivalent to post-concussion syndrome and post-traumatic stress disorder) that may persist for several weeks or months after the traumatic event. They can induce a change in the quality of social, professional or family life of these patients. This is an important public health issue. The conception of this pathological entity and the existence of a therapy abound in the search for a screening tool.

Material and method: The objective of this work is to develop a Score to better identify the patients most at risk of presenting these symptoms during a trauma during their visit to the emergency room. This score was developed using the results of the prospective Pericles cohort. The population selected for the score is composed of MTBI and control patients who have completed the M0 and M3 questionnaires and in particular the PCS and PTSD data. Randomization of patients with one part for score construction (2/3 of patients) and the other part for testing (1/3 of patients). Univariate and multivariate analyses for the study of PCS and PTSD predictive factors, followed by selection of step-by-step downward variables. For the construction of the score, the weight of each of the variables was defined from the values of

the Beta coefficients (β) resulting from these analyses. The diagnostic capacity of each of the scores was modelled using an ROC curve. For each score threshold, intrinsic and extrinsic characteristics were calculated.

Results: The selected Score was as follows: Female sex: +1; Impression, a feeling of discomfort in everyday life regarding one's health: +2; Taking calming treatments (anxiolytics, antidepressants): +2; Maximum score total: 5

Conclusion: The characteristics and diagnostic capabilities of this screening tool are similar in terms of screening patients at risk of presenting symptoms equivalent to those of PCS and PTSD.

Introduction

In the emergency department (ED), patients are admitted for a wide variety of diseases, from life-threatening pathologies to particularly benign problems. Among them, about 20% will suffer in the following months from non-specific but invalidating symptoms (9,14). Previously grouped as the Post-Concussion Syndrome (PCS) (136), these symptoms were described as the consequence of head trauma, and particularly mild traumatic brain injury (MTBI) (9,39,79,134). Another non-negligible part of patients that attended an ED (about 5%) suffer from Post-Traumatic stress disorders (PTSD) (137), a conditions that regroups another set of invalidating symptoms, some of them being also listed as part of the PCS. Some studies have questioned whether MTBI have a causal role in these two syndromes (9,13,14). In fact, authors found that incidence of PCS after head trauma or non-head trauma were not different (14).Thus, PCS is unspecific of MTBI and it is probably more accurate to refer to these symptoms as Post-Concussion Like Symptoms (PCLS) (27). Those studies also suggested that emergency cares play a major role in the onset of these symptoms, whether patient was

admitted after a trauma or not (3,79). Moreover, recent works, conducted in the context of emergency, underlined that the stress felt during ED visit and especially at discharge is strongly associated with both PCLS and PTSD (69,70). It suggested that interventions could be provided in the ED to prevent the occurrence of those invalidating symptoms by acting on ED stress. Several drugs including betablockers and anxiolytics have already been tested to prevent PTSD with very contrasted results (106,108,122). Recently, psychotherapeutic approach such as Eye Movement Desensitization and Reprocessing (86,123), showed remarkable efficacy in the treatment of patients with PTSD (83,124,138,139) and PCLS However, it is impossible to achieve an EMDR sessions for all patients attending the ED, hence the need for a tool that would allow for the selection of the most at risk patients. In literature, such a tool does not currently exist. In addition, one study suggested that this kind of research have to focus on the most inconvenienced patients (135).

Thus, the aim of this study was to create and validate a risk assessment tool of PCLS occurrence 3-months after attending the ED in order to focus on the most at-risk patient in further clinical trials.

Methods

Study design and settings

We designed the study as an ancillary study of the PERICLES Cohort Study (9,13,14,78) to construct a risk assessment score. The PERICLES cohort was originally designed to assess the incidence of PCS and PTSD 3 months after ED discharge among head and non-head injured patients. We randomly assigned patients in a creation and a validation cohort in a ratio 2:1.

Participants

All patients of the PERICLES cohort, legally of age, admitted in the ED after a trauma, head or non-head, with 3 months follow-up, were eligible for study inclusion.

Data collected

Patients answered a standardized questionnaire during their ED stay with an interviewer and 3 months later by phone. ED questionnaire assessed demographics, anamnestic and clinical data. At 3 months, patients were assessed for PTSD and PCS symptoms.

Post-traumatic stress disorder and Post-Concussion Syndrome

Symptoms selected as part of the PCS were those listed in the ICD-10 (140): headache, dizziness, personality change, sleeping disorders, tiredness, irritability, depression, anxiety, lack of spontaneity. PCS was defined as the report of at least 3 of these symptoms. We applied the same definition to all participants, including those who did not experience a head injury; we refer below to the name PCS even when the injury was not a head injury.

The 14 symptoms of the DSM-IV-R definition for PTSD were also selected (ref). These include intrusion symptoms (reliving the event through upsetting thoughts, nightmares or flashbacks, or having very strong mental and physical reactions if something reminds the person of the event), avoidance symptoms (avoiding activities, thoughts, feelings or conversations that remind the person of the event; feeling numb to one's surroundings; or being unable to remember details of the event), symptoms related to negative alteration in cognition and mood (loss of interest in important activities, feeling all alone, being unable to have normal emotions or feeling that there is nothing to look forward to in the future may also be experienced), symptoms related to alterations in arousal and reactivity (feeling that one can never relax and must be on guard all the time to protect oneself, trouble sleeping, feeling irritable, overreacting when startled, angry outbursts or trouble concentrating), social disturbance and exclusion. The diagnosis of PTSD requires that one or more symptoms of each of these categories be present for at least a month and that symptom(s) seriously interfere with normal life.

Statistical Analysis

Univariate analysis was conducted to compare the score generation and validation cohort. In the generation cohort, univariate analyses were performed to investigate the association between PCS and risk factors using Wilcoxon Test for continuous variables and the Fisher test for categorical variables. Variables with a p value lower than 0.20 were selected for logistic multivariate regression. All significant variables ($p < 0.05$) and all confounders (variation of $\beta > 20\%$) were selected by a manual step-by-step backwards selection process and odd-ratios (OR) and 95% confidence intervals (95% CI) were estimated. We tested interactions between independent variables kept in the final model. We used integer numbers for scoring to obtain an easy way to assess the risk level. They were obtained regarding betas estimators of the multivariate analysis model. Firstly, lower betas were set to 1 and then we used proportional integer numbers. were tested on the validation cohort to assess diagnostic performance. ROC curves were computed and compared with Delong test.

Ethical

The protocol was approved by the French data protection authority and the regional ethics committee. All participants gave informed consent.

Results

A total of 2,597 patients were included in the PERICLES study. Among them, 1,963 were contacted at 3 months by a phone call and were randomly assigned to either the generation set (1,295 patients) or the validation set (668 patients) (figure 1).

Patients characteristics and comparison between generation and validation sets are presented in table 8. We found no significant difference between the two groups. There was also no difference between generation and validation sets along all components of the accident (place, reason, activity and type of accident) and the medical history.

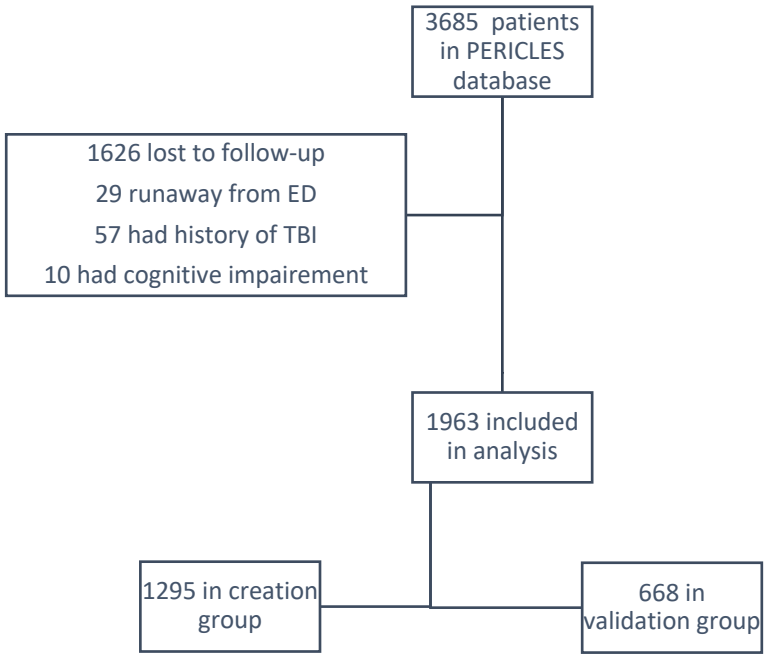


Figure 1. Study flow chart

Table 8. Univariate comparison between generation and validation sets

		Population	Creation		Validation		*p value*
		N	n	%	n	%	
		1963	1295		668		
Age							0.95
	15-39 years	982	645	49.8	337	50.4	
	40-69 years	611	406	31.4	205	30.7	
	>69 years	370	244	18.8	126	18.9	
Sex							0.84
	Women	844	555	42.9	289	43.3	
Reason for coming							
	Medicine	160	113	70.6	47	29.4	0.62
	Neurology	22	14	63.6	8	36.4	
	Surgery	3	2	66.7	1	33.3	
	Trauma	1743	1145	65.7	598	34.3	

Type of trauma							
	Road crash	417	265	63.5	152	36.5	0.83
	Home accident	863	573	66.4	290	33.6	
	assault	130	85	65.4	45	34.6	
	Work accident	271	178	65.6	93	34.4	
	Other	142	97	68.3	45	31.7	
Symptoms before admission							
Loss of consciouness							
	No	548	355	64.8	193	35.2	0.78
	Yes	408	260	63.7	148	36.3	
seizure							
	No	746	480	64.3	266	35.7	1
	Yes	20	13	65.0	7	35.0	
amnesia							
	No	505	322	63.8	183	36.2	1
	Yes	326	208	63.8	118	36.2	
headache							
	No	550	350	63.6	200	36.4	0.65
	Yes	210	133	63.3	77	36.7	
	Don’t know	26	19	73.0	7	27.0	
confusion							
	No	752	475	63.1	277	36.9	0.73
	Yes	79	54	68.3	25	31.7	
	Don’t know	3	2		1		
vomiting							
	No	768	491	64.0	277	36.0	0.81
	Yes	45	31	68.9	14	31.1	
	Don’t know	13	9	69.2	4	30.8	
Symptoms at admission							
vomiting							
	No	875	556	63.5	319	36.5	0.40
	Yes	59	41	69.4	18	30.6	
sleepiness							
	No	454	293	64.5	161	35.5	0.86
	Yes	37	23	62.1	14	37.9	
diziness							
	No	468	301	64.3	167	35.7	0.50
	Yes	22	16	72.7	6	27.3	
anxiety							
	No	435	283	65.0	152	35.0	0.35
	Yes	50	29	58.0	21	42.0	
headache							
	No	636	401	63.0	235	27.0	0.51
	Yes	297	194	65.3	103	34.7	
Labour disruption							
	No	175	116	66.3	59	33.7	0.44
	Yes	183	114	62.3	69	37.3	
Marital Status							
	in a relationship	1058	698	66.0	360	34.0	1
	Alone	905	597	66.0	308	34.0	
Children							
	No	827	532	64.3	295	35.7	0.19
	Yes	1095	736	67.2	359	32.8	
Professionnal status							
	unemployed	965	647	67,0	318	33,0	0,32
	Employed	993	644	65,0	349	35,0	
Previous consultation for trauma in the ED							0.07
	Yes	1001	642	49.6	359	53.7	
Health condition at admission							0.25

	Excellent	270	173	13.4	94	14.1	
	Very good	475	314	24.3	161	24.2	
	Good	1003	655	50.7	348	52.2	
	Poor	174	127	9.8	47	7.1	
	Bad	38	22	1.7	16	2.4	
Inconvenience in everyday life							0.24
	Yes	927	599	46.3	328	49.1	
Anxiolytics use in the past 12 months							0.53
	Yes	333	225	18.8	108	16.2	
Pain medication in the past 12 months							0.42
	Yes	518	334	25.8	184	27.5	
Tobacco use							0.28
	Yes	734	473	36.5	261	39.2	

Table 9 – Univariate comparison between patients with and without post-concussion like symptoms

Variable		**Population**	**SPC+**		**SPC-**		***P***
		N	n	%	n	%	
Age							
	15-39 years	644	156	24.2	488	75.8	<0.01
	40-69 years	402	134	33.3	268	66.6	
	>69 years	236	79	33.5	157	66.5	
Sex		1282					
	Men	738	167	22.6	571	77.4	$<10^{-7}$
	Women	544	202	37.1	342	62.8	
Reason for admission	1261						
	Medicine	110	35	31.8	75	68.2	0.20
	Neuro med.	14	7	50.0	7	50.0	
	Surgery	2	1	50.0	1	50.0	
	Trauma	1135	322	28.4	813	71.6	
Traumatic event		827					
	Road traffic crash	264	81	30.7	183	69.3	<0.01
	Domestic	563	174	30.9	389	69.1	
	Assault	85	26	30.6	59	69.4	
	Accident at work	178	47	26.4	131	73.6	
	Others (sport, school, suicide attempt)	97	13	13.4	84	86.6	
Symptoms before admission							
Loss of consciouness							
	No	349	104	29.8	245	70.2	0.86
	Yes	259	75	29.0	184	71.0	
seizure							
	No	474	139	29.3	335	70.7	0.35
	Yes	12	5	41.7	7	58.3	
amnesia							
	No	318	95	29.9	223	70.1	1
	Yes	205	61	29.8	144	70.2	
headache							
	No	347	94	27.1	253	72.9	0.08
	Yes	130	48	37.0	82	63.0	
	Don't know	19	4	21.0	15	79.0	
confusion							
	No	469	137	29.2	332	70.8	0.23
	Yes	53	21	39.6	32	60.4	
	Don't know	2	0	0	2	100	
vomiting							

	No	485	149	30.7	336	69.3	0.55
	Yes	30	9	30.0	21	70.0	
	Don't know	9	1	11.1	8	88.9	
Symptoms at admission							
vomiting							
	No	550	172	31.3	378	68.7	0.48
	Yes	40	10	25.0	30	75.0	
sleepiness							
	No	293	95	32.4	198	67.6	0.82
	Yes	23	8	34.8	15	65.2	
diziness							
	No	301	98	32.6	203	67.4	0.78
	Yes	16	6	37.5	10	62.5	
Anxiety							
	No	283	92	32.5	191	67.5	0.41
	Yes	29	12	41.4	17	58.6	
headache							
	No	398	116	29.1	282	70.9	0.07
	Yes	191	70	36.6	121	63.4	
Neuropsychological disorders		1282					
	Non	1253	351	28.0	902	72.0	$<10^{-3}$
	Oui	29	18	62.0	11	38.0	
thrombotis treatment							
	Non	1032	279	27.0	753	73.0	<0.01
	Oui	136	55	40.4	81	59.6	
Medical leave							
	Non	115	30	26.0	85	74.0	0.38
	Oui	114	36	31.6	78	68.4	
Marital Status							
	in a relationship	693	207	29.9	486	70.1	0.35
	Alone	589	162	27.5	427	72.5	
Children							
	No	531	130	24.5	401	75.5	<0.01
	Yes	724	234	32.3	490	67.7	
Professionnal status							
	unemployed	635	198	31.2	437	68.8	0.07
	Employed	643	171	26.6	472	73.4	
Previous consultation for trauma in the ED							
	Yes	647	199	30.8	448	69.2	0.12
Health condition at admission		635	170	26.8	465	73.2	
	Excellent						
	Very good	176	32	18.2	144	81.8	$<10^{-3}$
	Good	312	60	19.2	252	80.8	
	Poor	648	200	30.9	448	69.1	
	Bad	126	64	50.8	62	49.2	
Previous consultation for trauma in the ED		20	13	65.0	7	35.0	
Gène							
	No	693	132	19.0	561	81.0	$<10^{-15}$
	Yes	589	237	40.2	352	59.8	
Anxiolytics use in the past 12 months							
	No	1061	260	24.5	801	75.5	$<10^{-12}$
	Yes	221	109	49.3	112	50.7	
Pain medication in the past 12 months							
	No	954	223	23.4	731	76.6	$<10^{-11}$
	Yes	328	146	44.5	182	55.5	
Tobacco use							
	No	810	225	27.8	585	72.2	0.37
	Yes	470	142	30.2	328	69.8	

The results of the univariate analysis in the generation set are presented in Table 9. Sex and age group were significantly different between the PCLS group and the non-PCLS group (respectively $p < 10^{-5}$ and $p < 0.01$).

In medical history, we found only one difference for psychiatric disorders ($p < 10^{-3}$), use of anxiolytics ($p < 10^{-5}$) and preadmission health conditions ($p < 10^{-3}$). No significant association was found with symptoms before and at the time admission in the ED.

The beta coefficients from five multivariable models are presented in Table 10. Their weighted integer contributions to each corresponding score are presented in Table 11. Figure 2 shows the ROC curves, AUC and 95 %confidence interval for the six scores we proposed. Delong Test for ROC curves comparison did not reveal any statistical differences between each score. For example, we have chosen to present in Table 12 and 13 the performance of the risk level assessment derived from score 1.

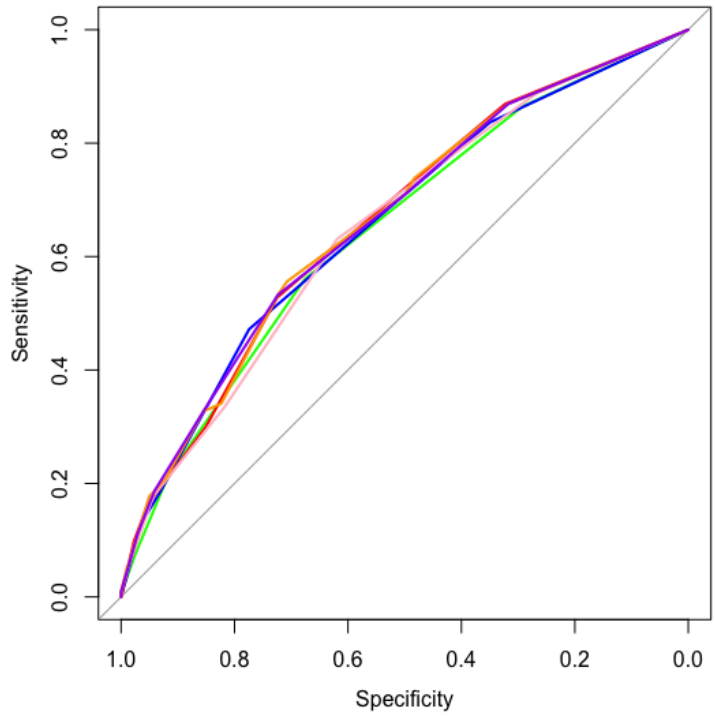
Table 10: Results of multivariable logistic regression for variables associated with Post Concussion Like Symptoms: β coefficients obtained for different models computed.

		Beta coefficients				
		Mode 1	Model 2	Model 3	Model 4	Modem 5
Gender	**female**	0,50***	0,43**	0,36**	0,42**	0,37**
Self-Assesment of Health condition at admission						
	Good or better	0,51*	-	-	0,43*	0,26
	Poor	1,20***	-	-	1,10***	0,75**
	Bad	1,63**	-	-	1,47**	1,11*
Disturbance in everyday life						
	Yes	-	0,90***	0,80***	-	0,68***
Anxiolytics use	**Yes**	0,70***	0,82***	0,72***	0,60***	0,59***
Pain killers use	**Yes**	-	-	0,46**	0,53***	0,38*

* : p value <0,05 ; ** : p value <0,01 ; *** : p value <0,001

Table 11: Entire number weighting of beta coefficients from multivariate logistic regression models

		Score					
Variable		**1**	**2**	**3**	**4**	**5***	**6***
Gender	**Female**	+1	+1	+1	+1	+2	+1
Self assessment of Health condition at admission							
	Excellent very good	0	-	-	0	-	-
	Good	+1	-	-	+1	-	-
	Poor	+2	-	-	+2	+4	+2
	Bad	+3	-	-	+3	+6	+3
Disturbance in every day life							
	Yes	-	+2	+2	-	+4	+2
Anxiolytics use	**Yes**	+1	+2	+2	+1	+3	+1
Pain killers use	**Yes**	-	-	+1	+1	+2	+1
Total. Max		**5**	**5**	**6**	**6**	**17**	**8**



Score	AUC	IC 95 %
1	0,648	0,605-0,691
2	0,658	0,615-0,702
3	0,663	0,619-0,706
4	0,653	0,610-0,696
5	0,644	0,621-0,708
6	0,644	0,621-0,708

Figure 2: ROC curves of the different scores for screening patients at risk of PCLS

Table 12: Score 1 properties according to the threshold used for screening patients at risk of PCLS.

Score properties	**Screening threshold**					
	0	**1**	**2**	**3**	**4**	**5**
Se	1,0	0,86	0,56	0,21	0,07	0,02
Spe	0,0	0,29	0,68	0,91	0,98	0,99
PPV	0,33	0,37	0,46	0,56	0,68	0,68
NPV	-	0,82	0,76	0,70	0,59	0,67

Sen: Sensitivity ; Spe: Specificity ; PPV: Positive Predictive Value ; NOV : Negative Predictive Value

Table 13: Table of Score 1 properties according to the threshold used for screening patients at risk of PTSD.

Score properties	**Screening threshold**					
	0	**1**	**2**	**3**	**4**	**5**
Se	1,0	0,80	0,74	0,58	0,14	0,08
Spe	0,0	0,29	0,48	0,73	0,90	0,94
PPV	0,08	0,09	0,11	0,15	0,11	0,10
NPV	-	0,95	0,96	0,95	0,92	0,92

Sen : Sensitivity ; Spe : Specificity ; PPV : Positive Predictive Value ; NPV : Negative Predictive Value

Discussion

Main findings of the study

This secondary analysis of the PERICLES Cohort database showed that the relevance of constructing a score-based risk assessment tool designed to identify patients with at high risk of PCLS 3 months after admission to the ED for a trauma. Such a score could usefully be used to identify patients requiring special preventive management.

Strengths and weaknesses

Although many studies have been conducted to describe the epidemiology of PTSD, and, to a lesser extent, PCLS (9,39,79,81,134), no study have considered so far the creation of a risk assessment tool. We are therefore proposing for the first time a tool that can be used in ED to identify patients most at risk. This score could be used for research purposes but also for immediate patient care.

The construction of this score was not foreseen by the original study protocol, which can be considered as a weakness of the study. However, analysis performed in this study are also based on risk factors assessment.

Other limitations of this study had been detailed in previous publication related to PERICLES project (9,13,14). We present below those that may have affected our score building process. The PERICLES study was conducted in the ED, a hospital service with a high level of activity and uncontrollable clinical priorities that may hinder the systematic collection of epidemiological data. This particular context can lead to an unusually high rate of missing data, difficulties in contacting patients three months after their visit to the ED, but also interruptions in efforts to include an uninterrupted flow of consecutive patients. Patients lost to follow-up at 3-months represented 25% (n=634) of the sample firstly assessed in the ED. This may have introduced selection bias. Patients who were lost to follow-up were older, more likely to

report pre injury symptoms and more likely to have experienced head injury than patients who had completed the study.

Another limitation of the study stems from the sample which by design included a similar number of head and non-head injury patients, a distribution that do not prepresent the proportion of mild traumatic brain injury in an ED population As the aim of this study was to create a score, the betas did not have had significantly modified. A dedicated study protocol should still be conducted to accurately re-evaluate the variable to be included in this score.

The final model did not take into account age of patients. The “age” variable did not significantly modify the coefficient resulting from the multivariate logistic regression and did not provide additional information for the score we calculated.

Interpretation

The diagnostic performances of the risk assessment tool we proposed were similar for PCLS and PTSD. It is consistent with current literature data that indicate an overlap in symptoms between these two entities. Indeed, the symptoms and the mechanism of occurrence are similar. According to literature, it is probably related to the stress and mental and physical health status of the patients before the trauma.

The intrinsic and extrinsic characteristics of this score appear to limit its use in clinical practice to emergencies. Indeed, using the lowest threshold to screen patients increases the sensitivity of the test and therefore the number of patients selected, but selects too many patients who may not have these symptoms at three months. Conversely, the use of the higher threshold will lead to a better specificity of the test, leading to a decrease in the size of the selected population and therefore to a high proportion of non-selected patients who will be at risk of presenting these symptoms at 3 months.

It could be used to select patients for studies to evaluate the effectiveness of early therapeutic and preventive management in emergency departments, their impact on the incidence of these symptoms and their relevance to patients' health and the cost to public health.

Such a detection tool is only interesting if it is possible to offer an effective early management or referral. As recently showed, EMDR is a recognized psychotherapeutic technique in the treatment of PTSD (141–143). Some studies support the value of early implementation (<48h) of this approach in an attempt to reduce the incidence of PTSD among trauma patients (114,123).

With regard to the PCLS, literature generally supports the use of psychotherapeutic intervention such as reinsurance or cognitive behavioural therapy (CBT) (95). We recently tested the usefulness of a short psychotherapeutic session of Eye Movement Desensitization and Reprocessing (EMDR) in the ED setting (86). In this pilot randomized study, we showed that EMDR was both feasible in the ED and effective in preventing the development of PCLS. Moreover, the control group allowed us to confirm the capabilities of the risk assessment tool. The incidence of PCLS 3 months after discharge from the emergency department was similar to the rates predicted by the score. It is interesting to note that the same rates have also been observed in “medical patients”. There is a need to confirm the effectiveness of this score for all ED patients in a prospective diagnostic implementation study. This could also help to improve the accuracy of the tool.

Conclusion

We computed, from data of a cohort of trauma patients recruited at the ED, a risk assessment tool in order to detect patients with high risk of PCLS 3-months after discharge. Replication studies are still needed in other patient populations presenting to the emergency room. If successful, such a score will be very useful to offer a targeted population preventive

management of a group of symptoms that remains frequent and can contribute to an important decrease in quality of life.

13.4. Interprétation et implication pour la création d'un outil d'évaluation du niveau de risque de développer un PCLS après un passage aux urgences.

L'objectif de cette analyse secondaire était de créer un outil nous permettant d'identifier le niveau de risque des patients de présenter trois mois après leur passage aux urgences des symptômes équivalent à ceux du syndrome post-commotionnel (PCLS).

Pour la suite du programme SOFTER, nous avons choisi finalement d'utiliser le score 1. Il présentait l'avantage d'être simple mais aussi de mieux prendre en considération l'état de santé perçu par le patient qui est déjà largement décrit comme un facteur de risque de PCLS (14).

En préparant l'étude interventionnelle pilote SOFTER 2 à laquelle nous consacrons le chapitre suivant, nous avions identifié qu'une psychologue serait en mesure de réaliser entre 3 à 5 séances d'EMDR sur ses horaires de présence. Sur ces mêmes horaires, le nombre moyen de patients admis dans le service était lui estimé à 60 environ. Parmi eux les patients venant pour un épisode aigu de moins de 24 h représentaient environ 40 patients. Nous avons donc choisi de fixer la limite du score à 3, ce qui nous permettait d'avoir environ 20% de patients éligibles soit 8 par jour avec un taux attendu de PCLS de 65%.

Grâce à cet outil d'évaluation du niveau de risque nous devrions donc être en mesure de sélectionner les patients les plus à risque. Cependant, l'étude PERICLES n'a pas été conçue pour la création d'un score. Ce score pose la question de sa validité externe et de son utilisabilité. Nous avons donc testé le score sur la cohorte créée à l'occasion de l'étude SOFTER 1 qui est donc une cohorte indépendante de celle de la création du score. Nous avons obtenu des performances diagnostiques similaires à celles obtenues lors de la phase de création et de validation intrinsèque.

Nous avons donc utilisé ce score dans le cadre de l'étude SOFTER 2 pour identifier les patients les plus à risque qui pourraient bénéficier d'une prise en charge par un psychologue.

14. Essais cliniques

14.1. Etude SOFTER 2

14.1.1. Protocole d'étude

Le protocole de l'étude a été enregistré sur le site Clinical Trial sous le numéro : NCT03194386. Il s'agissait d'une étude pilote dont l'objectif principal était d'évaluer la faisabilité d'une séance d'EMDR chez des patients identifiés comme à risque de développer un PCLS 3 mois après le passage aux urgences.

14.1.2. Résumé

Jusqu'à 20 % des patients qui se présentent aux urgences après un événement stressant souffriront pendant plusieurs mois de symptômes très divers et d'une altération importante de leur qualité de vie, souvent décrits comme des "Post-Concussion-Like Symptoms » (PCLS). Les objectifs de notre étude ouverte randomisée monocentrique étaient d'évaluer la faisabilité d'interventions conduite par des psychologues dans le contexte de l'urgence et de comparer l'effet de l'EMDR, à celui 'une séance de réassurance ou aux soins courants. Réalisée aux urgences de l'hôpital universitaire de Bordeaux, l'étude comprenait des patients présentant un risque élevé de PCLS randomisés en trois groupes : une séance de réassurance de 15 minutes, une séance de 60 minutes d'EMDR et les soins habituels. Les critères de jugements principaux et secondaire étaient respectivement la proportion d'interventions qui pouvaient être réalisées et la prévalence du PCSL et trois mois après le passage aux urgences.

Cent trente patients présentant un risque élevé de PCLS ont été randomisés. Aucun problème logistique ou refus du patient n'a été observé. Dans les groupes EMDR, rassurant et témoin, les

proportions de patients atteints de PCLS à trois mois étaient de 18 %, 37 % et 65 % respectivement. Le rapport de risque pour le PCLS ajusté pour le type d'événement (blessure, absence de blessure) pour la comparaison entre les groupes EMDR et témoin était de 0,36 [IC à 95 % : 0,20-0,66].

Il s'agit du premier essai contrôlé randomisé qui démontre qu'une intervention EMDR de courte durée est faisable et potentiellement efficace dans le contexte de l'urgence.

L'étude a été enregistrée sur ClinicalTrials.gov (NCT03194386).

14.1.3. Article – Publié – Journal of psychiatric Research (Annexe 2)

Emergency room intervention to prevent post concussion-like symptoms and post-traumatic stress disorder. A pilot randomized controlled study of a brief eye movement desensitization and reprocessing intervention versus reassurance or usual care.

Running title: Early Eyes Movement Desensitization and Reprocessing in the Emergency Department.

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Abstract

Up to 20% of patients presenting at an emergency room (ER) after a stressful event will for several months suffer from very diverse long-lasting symptoms and a potentially significant decline in quality of life, often described as post concussion-like symptoms (PCLS). The objectives of our randomized open-label single-center study were to assess the feasibility of psychologist-led interventions in the context of the ER and to compare the effect of eye movement desensitization and reprocessing (EMDR) with reassurance and usual care. Conducted in the ER of Bordeaux University Hospital, the study included patients with a high risk of PCLS randomized in three groups: a 15-minute reassurance session, a 60-minute session of EMDR, and usual care. Main outcomes were the proportion of interventions that could be carried out and the prevalence of PCSL and post-traumatic stress disorder (PTSD) three months after the ER visit.

One hundred and thirty patients with a high risk of PCLS were randomized. No logistic problem or patient refusal was observed. In the EMDR, reassurance and control groups, proportions of patients with PCLS at three months were 18%, 37% and 65% and those with PTSD were 3%, 16% and 19% respectively. The risk ratio for PCLS adjusted for the type of event (injury, non-injury) for the comparison between EMDR and control was 0.36 [95% CI 0.20-0.66].

This is the first randomized controlled trial that shows that a short EMDR intervention is feasible and potentially effective in the context of the ER.

The study was registered at ClinicalTrials.gov (NCT03194386).

Introduction

According to a 2012 national survey in France, 10.6 million people came or were taken to the emergency room (ER), several times in some cases, accounting for 18 million visits recorded that year (144). About half of these visits are the consequence of injury and more than 90% of patients will leave the service within hours, without hospitalization (145). Consistent recent studies (5–8) reveal that 10 to 20% of these injured patients for several months after the event will suffer from very diverse symptoms often associated with a potentially significant decline in quality of life, delay in return to school or work activities and change in social and family relationships. Extrapolating these figures to the annual number of ER visits in France led us think that at least one million people each year could be concerned by varying degrees of difficulty in the months following an ER visit. The potential link with the initial event, often unidentified, is all the more difficult to make as these symptoms are non-specific: headaches, concentration disorders, memory problems, stress intolerance, personality change, irritability. They have been described for more than 50 years, in the context of head injury, and thus referred to as the post-concussion syndrome (PCS). Recent studies suggest that these symptoms are not specific to brain injuries and can occur for all types of trauma (7,9,14,146), greatly expanding the size of the population concerned. They are henceforth now frequently described as post concussion-like symptoms (PCLS) (33).

Further, the results of a study we conducted among injured patients admitted to the ER (14) reinforced the hypothesis that concussion-like symptoms included ones that were very similar to those of the hyperactivation and numbing dimensions of post-traumatic stress disorder (PTSD) (17). This led us, with other authors (33), to raise the hypothesis that PCS and PTSD partly share a causal pathway in which stress plays a key role. Another interesting result of our previous study (14) was that a small set of measurable factors were associated with the risk of PCS and PTSD, paving the way to the development of simple assessment tools to

identify a subset of high-risk patients. Consistently, several studies conducted in the past five years noted that patients' psychological vulnerability and stress experienced during and in the aftermath of the event that led to ER admission were the two most predictive elements of these long-lasting symptoms (39,41,133,134,147). These result prompted us to consider testing the feasibility and the effectiveness of stress management interventions during ER stay, with the hope of improving outcomes of injured patients, but also of all patients presenting at the ER and who experience stress either related to an event (accident or medical condition) or to the ER stay. While no result is available in the literature concerning the prevention of PCLS, studies evaluating interventions for PTSD prevention are sufficient in number and quality to identify credible modes of intervention. We identified eye movement desensitization and reprocessing (EMDR) (148) as an intervention both promising and potentially suitable for use in the ER:, for which . Because of (i) the strong overlap between PTSD and PCLS, (ii) the importance of stress as reported in the ER in the sustained PCLS three months later, and (iii) the availability of a shortened adapted protocol (126,128,149), we decided to define a first comparison group of the trial with patients recieving the EMDR intervention by trained psychologists. We selected reassurance as a second comparison group as a small number of study reports suggest a preventive potential of reassuring patients about recovery and persistent symptoms (103,104,150,151). This second intervention group will allow us to compare the impact of EMDR with a shorter interaction by the same trained psychologists.

We conducted a pilot randomized controlled study to assess the feasibility of psychologist-led interventions in the context of the ER and to compare the 3-month rate of PTSD and PCLS among patients presenting at the ER, assessed as being at high risk for these two syndromes

and randomized in three groups: a 15-minute reassurance session, a single 60-minute session of EMDR, compared with usual care

Patients and Method

Study design

Between October 1st and December 31st 2016, we conducted a randomized open-label single-center study in the ER of Bordeaux University Hospital, one of the main ERs in the region of Nouvelle-Aquitaine, accounting for more than 52 000 admissions per year. Patients were then contacted at 3 months by phone, to assess the prevalence of PCLS and PTSD symptoms.

Participants

All patients aged 18 years or more, admitted to the ER were assessed for study inclusion using a scoring tool designed to select patients with a high risk of PCLS. The score items were selected using data from a previous study we conducted among more than 1 963 injured patients presenting to the ER (14) and split into a training sample (2/3) and a testing sample (1/3). Items included gender (+1 point for Female), self-assessment of health conditions before admission (0 for Excellent to +3 for Poor), and history of anxiolytic use (+1). The assessment tool developed in the training sample was validated in the testing sample, and yielded an sample an area under the curve of 0.67, a positive predictive value of 51%, and a negative predictive value of 74% for a score threshold of 2. Patients with a score strictly higher than 2 therefore had a PCLS prevalence at 3 months of 51%, as compared with 29%. Exclusion criteria were altered consciousness (defined as Glasgow coma scale score less than 14), cognitive impairment, confusion according to the attending ER physician, not speaking French, unable to be contacted by phone, requiring admission to the operating room or critical care unit. Patients admitted to the ER for an injury were excluded if the event had occurred more than 24 hours before. People admitted to the ER for a medical disorder were excluded if the

problem had already been assessed or discovered during a previous ER visit. All participants provided written informed consent to participate.

Recruitment and randomization

The identification and recruitment of potential study participants were carried out between 8 am and 6 pm by the ER staff, under the supervision of the project manager, as soon as the patient's condition permitted, always after the initial clinical evaluation conducted as part of usual care. Included patients were randomized into one of three groups: (i) care as usual; (ii) 15-minute reassurance session; (iii) 60-minute EMDR session (using the EMDR recent traumatic episode protocol as described below).

The randomization plan was established before the study began. The study protocol was open-label, but the randomization group allocation was masked to the personnel in charge of calling the participants at 3 months and to the statistician in charge of the analysis.

Interventions

Care as usual

Patients in this control group were medically and psychologically attended to by ER staff with no intervention of the study psychologist.

Reassurance

During the 15-minute reassurance intervention, participants were educated regarding the response to stressful medical events. The therapist also identified, discussed, and challenged any cognitive distortions such as unrealistic beliefs about being responsible for their injury or medical event.

The EMDR recent traumatic episode protocol (R-TEP)

Due to the situation and conditions in the ER, a brief EMDR intervention, utilizing the *R-TEP protocol,* was chosen (128). This protocol is specially designed for victims of recent traumatic

events based on Francine Shapiro's early EMDR intervention protocols (131). It takes into account the fragmented, unconsolidated nature of recent traumatic memories and the need for safety and containment. After identification, disturbing fragments are processed using a current trauma focus. Sessions were carried out by two trained psychologists from a team specialized in the management of patients with psychological trauma (Centre d'Accueil SPEcialisé dans le Repérage et le Traitement des Traumatismes psychiques (CASPERTT) of the Cadillac hospital center (Gironde, France)).

One of the two psychologists was present every day of the study and performed either an EMDR or reassurance session. No specific room was allocated to the study. The intervention sessions could be performed in any available closed treatment room, at the bedside. The psychologist had to make sure that no specific care was needed in the following hour (15 minutes for reassurance) before starting the intervention.

Data collection during ER stay

Participants were asked at ER admission and discharge to describe, using 0-to-10 numerical rating scales, their stress level, acute pain intensity, and their expectation for recovery. In the admission questionnaire, patients were asked to rate on a 5-item scale their overall health condition just before the event, and one year earlier. Finally, they were asked in the discharge questionnaire to rate their satisfaction with the ER stay using a 0-to-10 numeric rating scale.

Measure of primary outcome: EMDR completion rates

Feasibility was assessed by the completion rate of the intervention in the EMDR group defined by the proportion of patients randomized in the EMDR group who received the intervention before leaving the ER. The reasons for noncompletion were also recorded (patient refusal, logistic problems).

Measurement of secondary outcomes: PCLS and PTSD at 3 months.

Patients were contacted by phone 3 months after the ER visit using the phone number provided by the patient during ER recruitment. Whenever needed, several attempts were made; attempts to contact a patient were interrupted when the time since admission exceeded 3 months plus one week. Symptoms were assessed with a standardized questionnaire administered by one of the investigators, none of whom were aware of the randomization group of the interviewee. PCSL was defined using the ICD-10 definition of PCS (16). PCLS was defined as reporting at least 3 symptoms among the following: headache, dizziness, sleeping disorders, fatigue, irritability, decreased stress tolerance, memory trouble and concentration disorders. Further, questions related to symptoms listed in the DSM-IV-TR definition of PCS and Rivermead Post-concussion Symptoms questionnaire (18) were added to the 3-month questionnaire in order to test the sensitivity of our results to the definition of PCS.

As regard to PTSD, because the risk assessment score was developed from a previous study we conducted using the fourth version of the diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR) (15), it was assessed using the PTSD checklist – civilian version based on DSM-IV-TR (152). PTSD was defined as follows: Criterion A: all patients were supposed to have been exposed to a traumatic event; Criterion B: at least one of the re-experiencing symptoms (reliving the event through upsetting thoughts, nightmares or flashbacks, or having very strong mental or physical reactions if something reminds the person of the event); Criterion C: at least three of the avoidance and numbing symptoms (avoiding activities, thoughts, feelings, conversations, people, or places that remind the person of the event; having markedly diminished interest or participation in significant activities; feeling of detachment or estrangement from others; having restricted range of affect; having sense of foreshortened future; or being unable to recall important aspects of the event); Criterion D:

at least two alterations in arousal and reactivity (feeling that one can never relax and must be on guard all the time to protect oneself; trouble sleeping; feeling irritable or angry outbursts; overreacting when startled; or trouble concentrating), functional significance and exclusion; Criterion E: the duration of disturbance was more than 1 month; Criterion F: reported symptoms interfere seriously with leading a normal life.

Sample size

The sample size was planned to be able to evidence a 40% decrease in PCLS in the EMDR group as compared with the "care as usual" control group. With a 20% prevalence of PCLS in the general population as estimated from our previous study (14), of 70% in the high-risk population, an alpha risk of 5% and a power of 80%, we needed 32 patients in each group. Anticipating a 10% rate of loss to follow-up, the protocol aimed to include 36 patients per group.

Statistical analysis

Primary outcome analysis simply consisted in observing the proportion of patients randomized to the EMDR group who successfully received the intervention. Secondary outcome analyses were performed using the chi-square test to compare the of 3-months prevalence of PCLS and PTSD among the three treatment groups. Because the phone number was only collected at the end of the ER stay (discharge questionnaire), it was not possible to contact participants who were randomized but did not go on to receive the intervention they were allocated to. Consequently, only a per-protocol analysis could be performed.

A Mantel-Haenszel estimates of the risk ratio for the association between PCLS and treatment group stratified on the cause of ER admission (injury or non-injury) was performed. Complementary analyses were performed using DSM-IV-TR and Rivermead PCS definitions instead of ICD-10. A worst-case scenario was also analyzed in which all participants who were

randomized in an intervention group but who did not complete the protocol and could therefore not be contacted 3 months later were recorded as having PCLS.

Role of the funding source, administrative and ethical clearance

The study was approved by the local institutional ethics committee (Comité de protection des personnes Sud-Ouest Outre-Mer III).

The study was registered at ClinicalTrials.gov (NCT03194386).

Results

Recruitment, follow-up and EMDR R-TEP feasibility

Of 933 patients assessed for inclusion, 13 declined and 447 were excluded either because the event occurred more than 24 hours before ER admission or because the cause of ER admission was a non-injury condition that was already known (Figure 3). Finally, we included 343 patients with a low risk of PCLS and 130 with a high risk of PCLS. Patients of the latter group were randomized. There were no differences in the characteristics of the three treatment groups except for a lower proportion of injury events in the control group (Table 15). The numbers of patients who declined participation did not differ between groups (3, 2 and 2 patients in the control, reassurance, and EMDR groups, respectively). No exclusion due to clinical state worsening or early discharge was recorded in the control group, while respectively 3 and 5 patients were excluded for these reasons in the EMRD and reassurance groups. At 3 months, the number of patients lost to follow-up was low, with 1 patient who could not be contacted and 1 patient who died in each group (overall follow-up proportion was 95%). The patient in the control group was a 78-year-old man admitted to the ER following a hemorrhagic stroke. He was diagnosed with metastatic lung cancer and transferred to the intensive care unit where he died from massive hemoptysis 7 days later. The patient in the reassurance group was a 62-year-old man admitted to the ER because of anemia. He received a blood transfusion and

returned home after 24 hours. The patient died before the three-month follow-up call. The patient in the EMDR group was a 67-year-old man who attempted to commit suicide by poisoning 5 days after the intervention. He was admitted to the intensive care unit and then transferred to the psychiatric hospital where he committed suicide by hanging the following day. The patient had been diagnosed 2 months before participating in the study with relapsed glioblastoma. The case was reviewed by an independent psychiatrist who looked for any potential link between the intervention and the suicide attempt. The review concluded that the study participation was unrelated to the suicide attempt.

All but 2 patients were contacted within 86 to 93 days after recruitment; the two remaining patients were interviewed at day 84 and day 95. As regards the feasibility of the EMDR R-TEP procedure (primary outcome of the study), no logistic problem or patient refusal related to the intervention was observed.

Intervention outcomes

Figure 4 shows the proportion of patients with PCLS (according to the ICD-10 definition of PCS) and PTSD (according to the DSM-IV-TR definition of PTSD) in the three randomization groups. In the control, reassurance and EMDR groups, the proportions of patients with PCLS were 65%, 37% and 18% and the proportions of patients with PTSD were 19%, 16% and 3% respectively. According to the DSM-IV-TR definition of PCS, the proportions of PCLS at 3 months were 65%, 50% and 15% respectively. According to the Rivermead definition of PCS, the proportions of PCLS at 3 months were 62%, 42%, and 18%, respectively.

Because of the imbalance observed between groups as regards the type of event (63 patients with a medical event and 46 patients with injury), a complementary analysis was performed adjusting for the type of event. The risk ratio for the comparison between EMDR and control was 0.41 [95% CI 0.25-0.68] and was 0.36 [95% CI 0.20-0.66] when adjusted for the type of

event (injury, non-injury). Regarding the rest of comparisons, reassurance vs control groups risk ratio were 0.56 [95% CI 0.38-0.82] and 0.52 [95% CI 0.33-0.82] when adjusted for the type of event and respectively 0.73 [95% CI 0.41-1.32] and 0.75 [95% CI 0.43-1.34] for EMDR vs reassurance groups.

In the worst-case scenario, in which patients who abandoned the protocol after randomization for reasons related to clinical worsening or early discharge were designated as having PCLS at 3 months, the proportions of PCLS (according to DSM-IV-TR definition of PCS) in the control, reassurance, and EMDR groups were 65%, 44%, and 24%, respectively. The prevalence of PCLS in the EMDR group remained significantly lower than in the control group (Fisher test p = 0.001).

Discussion

This pilot study suggests that a single session of EMDR R-TEP psychotherapy performed at the ER in the first hours following a traumatic event is feasible and has the potential to significantly reduce the rate of both PCLS and PTSD symptoms 3 months after ER admission.

These results provide several new insights and prospects for care. While EMDR psychotherapy has been shown to help in PTSD prevention and treatment (131,148,153), similar work has not been performed for PCLS. As discussed above, while the two conditions partly overlap, PCLS is much more frequent than PTSD (10-20% versus 5% for a population attending an ER). The use of EMDR in a high-risk population therefore carries a great potential of benefit in terms of public health and savings to society as both PTSD and PCLS are associated with costs due to treatment and to dysfunctions impacting work, education, and health care (154). To our knowledge, only one early single-session EMDR intervention (EMDR-recent Event) has been evaluated so far in a controlled comparative study and showed promising results for victims of workplace violence: none of the 19 patients who received the EMDR intervention reported

PTSD symptoms after 3 months (123). In this study, however, the treatment was provided 48 hours after the traumatic event and lasted between 1.5 and 2 hours, a protocol incompatible with the ER context. No such attempt has yet been made for PCLS. Price et al. (125) compared PTSD symptoms 4- and 12-months after trauma among 68 patients using a Prolonged Exposure Therapy protocol, with the first session initiated at the ER, and 69 controls. Dissociation at the time of the traumatic event was associated with poorer response to treatment. It will therefore be important to verify in a larger studywhether EMDR R-TEP is suitable for this small subset of patients. Assessment of the impact of an EMDR intervention over a longer time-period (12 months) will also be needed.

No difference in prevalence of PCLS between EMDR group and reassurance group can be explained by a lack of power of the study. Indeed, the gap between the two rates suggests that the benefit of the EMDR intervention might not stem solely from the interaction with a psychologist, even if the shorter duration (15 minutes) of the reassurance session should be stressed here. The reason for the short duration of the reassurance treatment was to assure that interaction does not include elements of psychological debriefing, which has been identified as potentially harmful for the patient (108).

No exclusion due to clinical state worsening or early discharge was recorded in the control group while 3 (EMDR) and 5 (Reassurance) patients were in this situation in the two intervention groups. This may be partly related to the fact that, on average, the latter patients had to stay longer in the ER to receive the intervention than patients of the control group. To make sure this potential source of bias did not compromise our results, we performed a worse-case scenario analysis assuming that patients excluded at this stage all had PCLS. Even in this extreme situation, the 3-month prevalence of CSL remained significantly lower in the EMDR group than in controls.

The number of patients included in the study was low and replications with a larger sample size, in several other ERs, are needed before reaching a definitive conclusion. In particular, the imbalance between medical and injury patients prevented us from reaching any definitive conclusion as regards the impact in the latter group. In spite of the fact that we used no block randomization, there was no major between-group imbalance in sample size.

Individual factors used for the assessment of the risk of PCLS were selected from the literature and from the results of a prospective study we conducted among 534 patients with head injury and 927 patients with other nonhead injuries presenting at the ER (14), with no patients with non-injury reason for ER admission. It was therefore significant that 74% of the 24 non-injury patients in the control group had PCLS. Among the 10 injury patients in the control group, 4 had PCLS at 3 months.

As mentioned in the method section, we assessed PTSD prevalence at three months using the PTSD checklist – civilian version. Because criterion A in the DSM IV version refers to "threat to physical integrity of self or others", we assumed this was the case for all patients attending the ER. However, the required extra criterion related to person's response involving "intense fear" was clearly not met for all study participants. Consequently, the prevalence of PTSD at 3 months should probably be considered as exaggerated.

EMDR is a psychotherapy first developed by Francine Shapiro in 1987 (131), has subsequently been adapted for use for recent trauma: recent event protocol (REP) (128), recent traumatic episode protocol (R-TEP) (149) and EMDR-protocol for recent critical incidents (PRECI) (150). REP and PRECI were designed to be used between two days and six months after trauma and their suitability for intervention in the first few hours after trauma, directly in the ER, was not documented. By contrast, EMDR R-TEP was designed to be used even hours after a trauma.

As regards the procedure itself, the mechanism by which EMDR impacts memory processing is poorly understood. While not unusual for psychotherapy, knowledge in this matter will be helpful in improving its efficacy and adapting it to different contexts. For example, there is an ongoing debate on whether eye movements are a necessary part of the EMDR protocol (155). Sack et al. suggested that eye movements have no advantage compared with visually fixating on a nonmoving hand (153), and Lyaduraye and colleagues suggested that an early trauma memory reminder cue plus playing Tetris for 20 minutes in the 6 hours following a road traffic crash was associated with fewer intrusive memories in the following weeks (156). These observations support the "working memory" hypothesis that stipulates that benefits occur when patients divides their attention between traumatic memory and another competing task (157,158). It has been suggested that eye movements may be more effective because they include visual and spatial components (155). Another neurobiological model stipulates that EMDR enhances episodic retrieval through increased interhemispheric connectivity caused by eye movements (159) but this hypothesis has yet to be supported by conclusive studies. Here again, we reviewed results obtained in PTSD and no such work is available for PCLS, a condition that has yet to be properly characterized before being acknowledge as a frequent and debilitating condition.

Observed self-assessed levels of stress as recorded at admission and at discharge support our hypothesis that early stress and hyperarousal management have a large potential for proper recovery after a traumatic event. One strength of our results is the feasibility of the intervention in a place where a significant number of patients with a risk of PCLS and PTSD are concentrated, despite a limited time for assessment and treatment. The dissemination of this intervention depends, however, on the availability of trained psychologists in the ER, with additional costs that need further medical economics studies to quantify the overall

cost/saving balance of such an amendment to the ER care system. In this respect, testing shortened treatment options in non-inferiority studies would certainly contribute to the future generalization of an intervention that may have the potential to ease the life of several hundred thousands people in France each year.

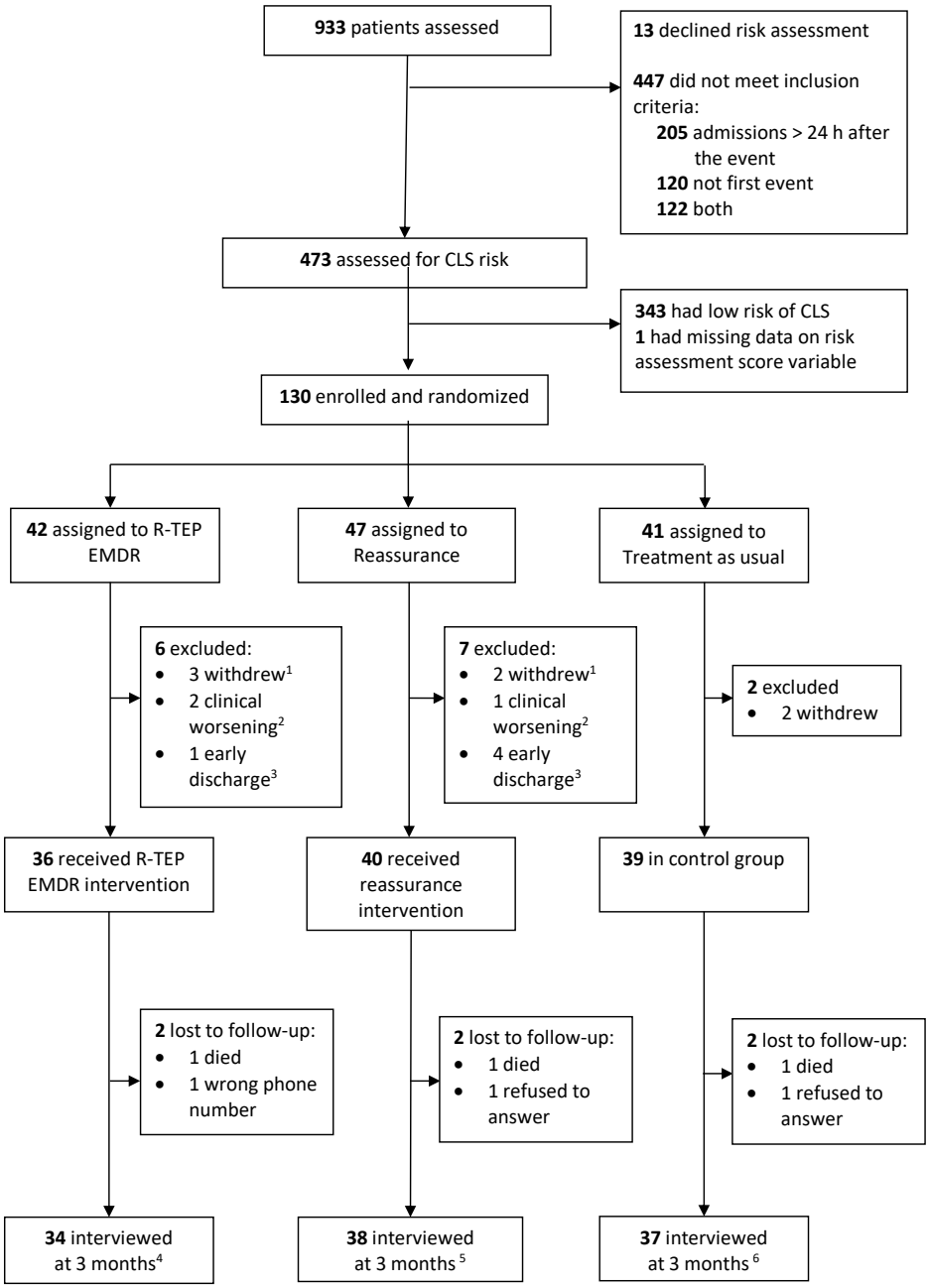

Figure 1: Study flow diagram

Figure 3: Study flow chart

1 Patients who provided consent and eventually declined before discharge

2 Any change in patient clinical condition precluding patient participation

3 Patients who left the emergency room before the discharge questionnaire or the interview with the psychologist, either because refused to wait for the psychologist, or because an ambulance came to pick them up for transfer

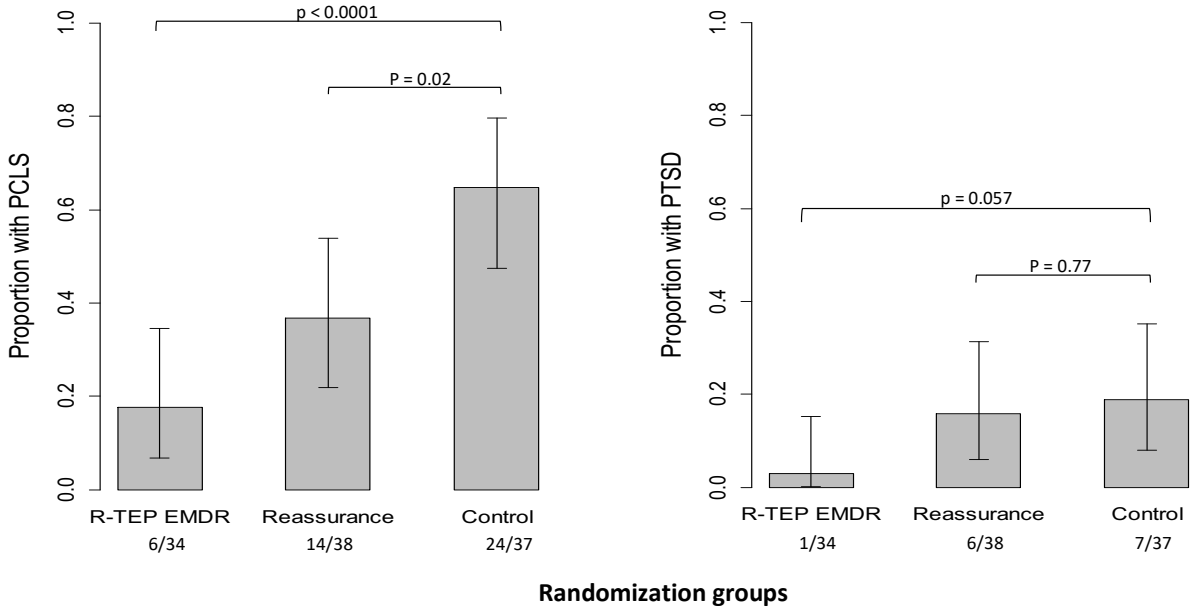

Figure 4. Main outcomes from follow-up interview at 3-months

Proportion of patients with Concussion-Like Symptoms (PCLS) and Post-traumatic stress disorder (PTSD) as defined by the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV). P values are from the double-sided Fisher exact test.

Table 14: Sociodemographic characteristics of patients assessed with low and high risk of Concussion-Like Symptoms.

	Total Sample		Risk Assessment Score				p-value
			<3		>=3		
	n	%	n	%	n	%	
Total	472	100	342	100	130	100	
Age median [IQR[1]]	40	[27 – 57]	38	[26 – 53]	46.5	[30 – 65]	0.10
Female	251	53	143	42	108	83	$< 10^{-5}$
Anxiolytic use	91	19	28	8	63	48	$< 10^{-5}$
Perceived health							$< 10^{-5}$
Poor	31	7	5	1	26	20	
Mean	130	27	43	13	87	67	
Good	198	42	181	53	17	13	
Very good	81	17	81	24	0	0	
Excellent	32	7	32	9	0	0	

1 IQR : Inter Quartile Range

Table 15: Sociodemographic characteristics of the study population and evaluation of principal and secondary outcome.

	R-TEP EMDR (N = 34)	Reassurance (N = 38)	Control (N = 37)
Population characteristics			
Age –median (IQR[1])	49 (34.5 – 67.75)	41.5 (22 - 58.75)	46 (30 - 64)
Gender – N (%)			
Male	5 (14.7)	3 (8.1)	6 (16.2)
Female	29 (85.3)	35 (92.1)	31 (83.8)
Event type – N(%)			
Injury:	16 (47.1)	20 (52.6)	10 (27)
Road traffic crash	5	4	2
Fall	9	10	4
Other accidents[2]	1	4	4
Assault	1	1	0
Suicide attempt	0	1	0
Medical:	18 (52.9)	18 (47.4)	27 (73)
Neurology	10	2	15
Abdominal	2	8	6
Other[3]	6	8	6
Pain intensity, NRS – Median (IQR[1])			
Mean score at admission	5.5 (4-7)	6 (3 - 7)	5 (3 - 7)
Mean score at discharge	3 (0.25 - 5)	5 (0 - 6)	4 (0 - 7)
Intensity of stress, NRS[4] – Median (IQR[1])			
Mean score at admission	4 (2 - 6)	3 (1 - 7)	5 (2 - 7)
Mean score at discharge	2 (1 - 3)	2.5 (1 – 4.75)	4 (1 - 6)
Odds of recovery, NRS[5] – Median (IQR[1])			
Mean score at admission	10 (7.25 - 10)	8.5 6 - 10)	10 (6 - 10)
Mean score at discharge	10 (8 - 10)	9.5 (7.25 - 10)	10 (7 - 10)
Symptoms reported at admission (past 12 months) – N (%)			
Poor concentration	20 (58.8)	20 (52.6)	15 (40.5)
Restlessness	22 (64.7)	28 (73.7)	21 (56.8)
Energy loss	29 (85.3)	32 (84.2)	26 (70.3)
Anxiolytic consumption	17 (50.0)	21 (55.3)	16 (43.2)
Self-rated satisfaction for ER stay, NRS – Median (IQR)	9.5 (8 - 10)	8.5 (7.25 - 10)	8 (6 - 10)

EMDR: Eye Movement Desensitization and Reprocessing. NRS: Numeric Rating Scale (0 to 10).
1 IDR: Inter-Quartile Range.
2 Domestic, sports and work-related injury, excluding road traffic injury.
3 Respiratory, cardiological and general problems.
4 Numeric Rating Scale from 0 to 10: 0 = absence of stress, 10 = unbearable stress
5 Numeric Rating Scale from 0 to 10: 0 = no chance of cure, 10 = complete cure, return to pre-event condition

14.1.4. Interprétation et implications de SOFTER 2

Ce premier essai randomisé nous a permis de savoir que de l'EMDR est faisable aux urgences dans une population à risque de développer des PCLS. Si c'était effectivement l'objectif principal de l'étude, l'impact mesuré de l'EMDR est frappant. Cependant, il faut rester prudent car d'une part l'effectif était modeste et d'autre part l'intervention a été délivrée par deux psychologues très expérimentées.

Les résultats concernant la réassurance sont également frappant et laissent imaginer les bénéfices que l'on pourrait attendre d'une amélioration de la communication avec les patients au cours de leur passage aux urgences. Ce n'est pas l'orientation que nous avons choisie mais d'autres études pourraient être menées en ce sens.

La nature monocentrique de cette étude et la durée des séances d'EMDR posait la question de la faisabilité de telles interventions dans d'autres services d'urgences, d'autant que les patients des urgences sont démographiquement très inégaux d'un site à l'autre, consultent pour des pathologies différentes et bénéficient de prise en charge hétérogènes.

Un élément intéressant est tout de même le taux de patient présentant des PCLS à 3 mois dans le groupe témoin qui correspond exactement au taux prévu par le score. Compte tenu du faible effectif il est impossible de parler ici de validation du score mais il est intéressant de noter qu'il semble être adapté à la sélection des patients à risque.

14.2. Étude SOFTER 3

14.2.1. Justification de l'étude

Les résultats obtenus dans le cadre de l'étude précédente ont conforté notre hypothèse d'un effet bénéfique d'une prise en charge du stress des patients aux urgences.

Cependant, pour conclure sur l'efficacité de l'EMDR aux urgences à un moment aussi aigu, plusieurs éléments doivent être complétés.

D'une part, cette étude était conçue pour évaluer la faisabilité de l'intervention dans le contexte des urgences et en conséquence, les effectifs était très faible, ne permettant pas de conclure formellement sur l'efficacité de l'intervention. Il est donc nécessaire de mener une étude dont l'objectif sera d'évaluer l'efficacité de l'intervention EMDR dans ce contexte.

D'autre part, il s'agissait d'une étude monocentrique conduite dans un CHU qui avait été grandement sensibilisé à cette problématique du stress des patients à travers les études déjà réalisées. La faisabilité de l'EMDR dans les services d'urgences reste donc à préciser.

L'étude SOFTER 3 a ainsi été construite dans le but de tester l'hypothèse de la supériorité de l'EMDR mais également pour confirmer la faisabilité d'une séance d'EMDR aux urgences.

Pour la construction de l'étude nous avons choisi de ne pas inclure un groupe réassurance devant l'efficacité particulièrement importante de l'EMDR dans SOFTER 2 (2 fois moins de PCLS que dans le groupe réassurance), la faisabilité très bonne (>90%) des séances d'EMDR aux urgences et aussi dans un souci de simplifier le design de ce type d'étude, difficile à mener aux urgences.

14.2.2. Protocole d'étude – Publié – Trials (Annexe 3)

Le protocole de l'étude SOFTER 3 a fait l'objet d'une publication dans la revue Trials en 2018 (87). Il a été enregistré sur Clinical Trial sous le numéro NCT03400813. Brièvement, il s'agissait d'un essai bicentrique dont l'objectif était d'évaluer la supériorité de l'EMDR pratiqué aux urgences par rapport aux soins usuels dans la prévention de l'apparition de PCLS.

14.2.3. Résumé

Introduction : Des résultats récents suggèrent qu'après un événement traumatique, 10 à 20 % des patients souffriront pendant plusieurs mois de divers symptômes, appelés « post-

concussion-like symptoms » (PCLS), qui peuvent mener à une baisse de la qualité de vie. Un essai préliminaire randomisé a suggéré que ces PCLS pourrait être prévenus par une seule séance d'EMDR (EMDR) de courte durée réalisée aux urgences.

Objectif : La présente étude a été conçue pour comparer l'impact de l'intervention précoce de l'EMDR par rapport aux soins habituels sur le PCLS à 3 mois chez les patients se présentant aux urgences.

Patients et méthodes : Il s'agissait d'un essai comparatif ouvert bicentrique, randomisé et contrôlé, avec un suivi téléphonique à trois mois. Les participants éligibles étaient des adultes (18 ans) qui se présentaient aux urgences et qui présentaient un risque élevé de PCLS défini au moyen d'un outil dédié.

Interventions : Les groupes de randomisation étaient les suivants : (i) l'intervention EMDR selon le protocole Recent Traumatic Episode Protocol (R-TEP) réalisée aux urgences et (ii) les soins habituels.

Principaux résultats et mesures : Les résultats principaux et secondaires étaient respectivement la fréquence du PCLS et du TSPT trois mois après le passage aux urgences.

Résultats : Cette étude comprenait 313 patients présentant un risque élevé de PCLS qui ont été randomisés deux groupes ; 219 ont été contactés par téléphone à 3 mois. Il n'y avait pas de différence pour le PCLS (EMDR : 53,8 % vs témoin : 49,6 %), mais pour le TSPT, la proportion était plus élevée dans le groupe d'intervention (9,4 % vs 2,7 %, p = 0,04). Dans le groupe EMDR, un niveau élevé de stress autoévalué à l'admission (>6) était fortement associé à l'existence de PCLS (76,9 % vs 40,9 %, p = 0,04) à 3 mois.

Conclusion et pertinence : Les résultats actuels ont montré qu'une seule séance EMDR R-TEP n'a pas réduit la proportion de PCLS à 3 mois chez les patients admis aux urgences. Cependant, le taux de TSPT était plus élevé dans le groupe EMDR. Ces résultats suggèrent qu'il faudrait

recueillir plus de données pour définir les options de traitement qui pourraient être offertes aux patients qui se présentent aux urgences.

Enregistrement de l'essai : Identificateur ClinicalTrials.gov NCT03400813.

14.2.4. Article – Soumis – JAMA Psychiatry

Prevention of post-concussion-like symptoms in emergency room patients: Results from a two-center randomized controlled study comparing an early single-session Eye Movement Desensitization and Reprocessing intervention with usual care

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Abstract

Importance: Recent findings suggest that after a traumatic event, 10–20% of injured patients will suffer for several months from various symptoms, collectively termed post-concussion-like symptoms (PCLS), which can lead to a decline in quality of life. A preliminary randomized controlled trial suggested that this condition may be prevented by a single early short Eye Movement Desensitization and Reprocessing (EMDR) psychotherapeutic session delivered at the ER.

Objective: The present study was designed to compare the impact of the early EMDR intervention versus usual care on 3-month PCLS in patients presenting at the ER. Design, Setting, and Participants: This study was an open-label two-center comparative randomized controlled trial with phone follow-up assessments at 3 months. Eligible participants included adults (≥18 years old) presenting at the ER who have a high risk of PCLS using a 3-item scoring scale.

Interventions: The randomization groups were as follows: (i) EMDR Recent Traumatic Episode Protocol (R-TEP) intervention performed during the ER stay and (ii) usual care. Main Outcomes and Measures: The primary and secondary outcomes were respectively the frequency of PCLS and PTSD at 3 months after the ER visit.

Results: This study included 313 patients with a high risk of PCLS who were randomized into two groups; of these patients, 219 were contacted by phone at 3 months. There was no difference in the primary outcome (EMDR: 53.8% vs. Control: 49.6%), but for the secondary outcome, the occurrence of PTSD was greater in the intervention group (9.4% vs. 2.7%, p = 0.04). In the EMDR group, a high level of self-assessed stress at admission (>6) was strongly associated with persistent PCLS (76.9% vs. 40.9%, p = 0.04).

Conclusion and Relevance: The present results showed that a single EMDR R-TEP session did not reduce the incidence of PCLS at 3 months in patients admitted to the ER. However, the rate of PTSD was higher in the EMDR group. These results suggest that more data should be collected to define which treatment options may be offered to patients attending the ER and the role that psychologist skill plays in this process.

Trial registration: ClinicalTrials.gov identifier NCT03400813.

Keywords: Stress; emergency room; Eye Movement Desensitization and Reprocessing; post-concussion-like symptoms; post-traumatic stress disorder; clinical trial

Background

In 2012, the most recent national survey in France revealed that 10.6 million people came or were taken to the emergency room (ER), sometimes on several occasions, as 18 million visits were recorded that year. Although more than 80% of individuals attending the ER leave within a few hours without hospitalization,(144,145) recent studies(5–8) have consistently documented that 10–20% of injured patients will suffer for several months from very diverse symptoms after the event and that this may lead to a potentially significant decline in their quality of life. This decline could delay or prevent the resumption of school or work activities and also change social and family relationships. Each year in France, approximately 2 million people are confronted by difficulties of varying degrees, but the causes are often unidentified and may be unrelated to the traumatic event. This relationship remains difficult to understand because these symptoms, including headaches, concentration disorders, memory problems, stress intolerance, personality change, and irritability, appear to be non-specific. Such symptoms have been described for more than 50 years in association with head trauma, and

in this context, are referred to as post-concussion syndrome (PCS). However, it is now accepted that these symptoms are not specific to head injuries and can also occur in other patients who visit the ER,(7,9,146) which greatly expands the size of the affected population. In a cross-sectional observational study of 31,958 high school athletes, Iverson et al.(35) found that 19% of uninjured boys and 28% of uninjured girls reported having a symptom burden that resembled a diagnosis of PCS based on the International Classification of Diseases, 10th Revision (ICD-10);(35) subsequently, this diagnosis has frequently been described as post-concussion-like symptoms (PCLS).

The symptoms of PCLS are very similar to, and sometimes exactly the same as, two previously published dimensions of post-traumatic stress disorder (PTSD), i.e., hyperactivation of the nervous system and cognitive and emotional numbing. Thus, most researchers have hypothesized that PCLS and PTSD share, at least in part, the same causal pathway in which stress plays a key role.(9,14) This would be particularly relevant for prevention because only studies that have specifically investigated PTSD are sufficient in number and quality to identify credible modes of intervention.(137) This led our research group to consider using stress management interventions in the ER in the hope of improving outcomes for traumatized patients. To date, the psychotherapeutic intervention that has proven superior to all other methods for the prevention of PTSD is Eye Movement Desensitization and Reprocessing (EMDR).(119,121,123,148,160) In particular, a brief single trauma-focused EMDR protocol, the Recent Traumatic Episode Protocol (R-TEP) method,(127) was developed and can be used in the context of the ER.

Our research group tested this method in a randomized open-label single-center pilot study of 130 patients with a high risk of PCLS that was conducted in the ER of Bordeaux University Hospital. The patients were randomized into three groups: a 15-minute reassurance session,

a 60-minute session of EMDR, and usual care. The proportions of patients with PCLS at 3 months were 18%, 37%, and 65% in the EMDR, reassurance, and control groups, respectively.(86) The present study was designed to replicate this trial with greater statistical power using patients from two sites.

Methods

Study Design

The study population and design of the SymptOms Following Trauma Emergency Response 3 (SOFTER 3) trial have been previously published.(87) Briefly, this was a two-center open-label randomized controlled trial designed to assess the effects of an early EMDR R-TEP session on PCLS at 3 months compared with those of usual care in patients who presented to the ER. The secondary objectives included comparisons between the EMDR R-TEP and control groups regarding PTSD at 3 months, self-reported stress at ER discharge, self-assessed recovery expectations at discharge and 3 months, and self-reported pain levels at discharge and 3 months.

Sites and Patients

All patients who came or were brought to the adult ER at one of the study sites following an event that led to an injury or with a new acute medical condition were included in the present study. The inclusion criteria were as follows: ≥18 years of age, conscious, able to provide informed consent, affiliated with social security, and able to understand the study procedures and to comply with them for the entire length of the study; only French speakers were enrolled in the study. Whatever the cause of injury, the event must have occurred in the past 24 hours. Patients who attended the ER for medical reasons were eligible if their condition was acute and if they were presenting to the ER for this reason for the first time. To assess the risk of PCLS at 3 months in patients who met these conditions, a risk assessment score was

computed as follows: female gender, +1; current use of anxiolytics/antidepressant, +1; and perceived health status prior to admission: excellent or very good (0), good (+1), poor (+2), and bad (+3). To be eligible for enrollment in the study, a patient needed to score above the pre-defined threshold of 1 on the 3-item assessment procedure; this was designed to select patients at risk for PCLS. This score was developed using data from previous studies conducted in the ER setting of the Bordeaux Teaching Hospital.(9,14,86) Patients who were unable to provide written informed consent, unwilling to be contacted at 3 months, and/or under the influence of acute drug or alcohol use or dependence that, in the opinion of the site investigator, could interfere with adherence to study requirements were excluded from the study.

Participants were recruited from among patients who presented to the ERs of the University Hospitals of Bordeaux (Groupe Hospitalier Pellegrin) and Lyon (Groupement Hospitalier Edouard Herriot) and who were determined to have a high risk of PCLS. The identification and recruitment of potential study participants was carried out by emergency personnel under supervision of the project manager. Priority was given to the clinical evaluation and care of each patient, and the recruitment procedure was only initiated when the patient's condition allowed it. First, oral consent for participation was sought during the risk assessment stage. Then, patients who fulfilled the inclusion criteria and were assessed as having a high risk for PCLS were presented with the objectives and procedures of the study and invited to sign an informed consent form.

Intervention

At both sites, patients were allocated to one of the two arms of the study using block randomization. Patients in the EMDR group received a 1-hour psychotherapeutic intervention based on the R-TEP protocol,(161) which incorporates and extends Shapiro's early EMDR

intervention protocols(119) into an integrative and comprehensive intervention that accounts for the fragmented and unconsolidated nature of recent traumatic memories as well as the need for safety and containment; these sessions were carried out by trained psychologists. A standardized questionnaire was completed by the psychologists at the beginning and end of the EMDR session to record the level of disturbance using a Likert scale (0–10) on the Subjective Unit of Disturbance (SUD) scale,(162,163) and free text commentary was provided to record the details of the session. The skill level of each psychologist was evaluated by an EMDR supervisor blind to the intervention as well as the 3-month outcomes. Skill level was defined based on professional background, level of formation in EMDR practice (1 or 2), EMDR certification, and experience in the R-TEP protocol prior to the training delivered for the purpose of the study. Fidelity to the protocol was not assessed.

Patients in the usual care group were medically and psychologically managed by the ER staff without the intervention of a study psychologist. Inclusion in the study was only possible on days when psychologists were deployed in the ER.

Follow-up Assessments

Patients were contacted by phone 3 months after their ER visit using the phone number provided at the time of ER recruitment. Although several attempts were made to contact patients when necessary, the attempts were stopped when the delay exceeded 4 months after ER discharge. Symptoms were assessed using a standardized questionnaire administered by a research assistant blind to the randomization group.

Outcomes

The primary outcome was the proportion of patients with PCLS at 3 months as measured using the Rivermead Post-Concussion Symptoms Questionnaire.(18) The definition of PCS in the Rivermead Questionnaire includes the following symptoms: headache, feelings of dizziness,

nausea/vomiting, sleep disturbances, fatigue, irritability, noise sensitivity, depression, frustration, poor memory, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness. All variables were measured using a Likert scale that ranged from 0 (not experienced at all) to 4 (a severe problem). Consistent with the PCS definition in the context of mild head injury, patients were defined as having PCLS if they reported at least three symptoms of moderate to high severity.

The secondary outcomes included the presence of PTSD (defined using the PTSD Checklist, 5th version),(152) self-assessed recovery expectation at discharge, self-reported chronic pain at 3 months, and self-reported acute pain at discharge. All variables were assessed during the 3-month follow-up phone interview.

Sample Size and Statistical Analysis

Based on previous pilot studies,(86) this protocol shows a PCLS incidence of 47% in patients with a score ≥2. The goal of the present study was to document a decrease of 15% in PCLS prevalence in the EMDR group. Thus, based on a 5% type I error rate and a power level of 80%, the required sample size was 169 patients in each group. Further considerations for 20% of participants lost to follow-up and 5% lost due to missing data for the main variables resulted in an expected number of 223 patients in each group.

The analyses for the primary and secondary outcomes were conducted “per-protocol.” The prespecified stratified analysis was carried out with considerations for study center, stress level, and individual PCLS risk score. An additional post hoc analysis was conducted in the intervention group to assess the potential impact of psychologist skill level. Differences between patients who completed the study and those who were lost to follow-up were assessed for all variables. All statistical analyses were performed blind to arm allocation.

Ethics, Confidentiality of Data, and Data and Safety Monitoring Board guidelines

This research project received a positive endorsement from the French Comité de Protection de Personnes (CPP), Ouest II–Angers-N° RCB = 2017-A01462-51–N° CPP = 2017/36. The study was registered on ClinicalTrial.gov (NCT03400813).

Results

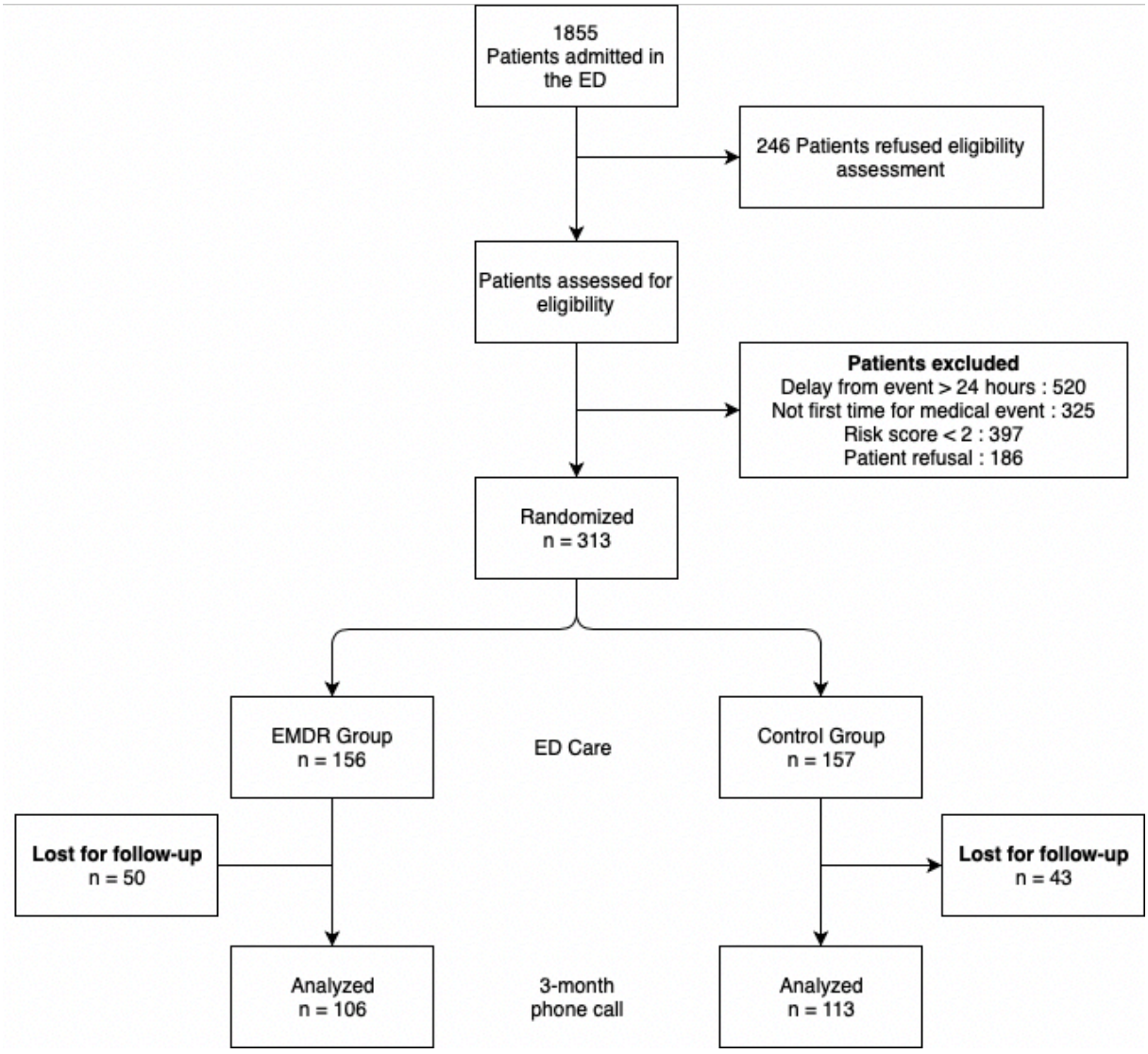

Figure 4*. Study Flow Chart*

Table 16. *Patient characteristics*

			Population Randomized				Completed follow-up					
			Population	EMDR	Control		Population		EMDR		Control	
			N =313	N = 156	N =157		N =219		N = 106		N = 113	
Patients characteristics												
Gender	Female		235 (75.1)	121 (77.5)	114 (72.6)		163	74.4	81	76.4	82	72.6
Age *			46 [29-60]	45 [29-60]	46 [30-62]		46 [31-62]		50.0 [31-65]		46.0 [30-60]	
Inclusion score	= 2		147 (47)	69 (44.2)	78 (49.7)		105	39.7	51	48.1	54	47.7
	≥ 3		166 (53)	87 (55.8)	79 (50.3)		114	38.8	55	51.9	59	52.2
Presence of PCLS at admission			203 (64.9)	105 (67.3)	98 (62.4)		142	64.8	70	66.0	72	63.7
Reason for attending the ED												
Medical disease			112 (35.8)	55 (35.3)	57 (36.3)		87	39.7	43	40.6	44	38.9
Trauma condition			136 (43.5)	67 (42.9)	69 (43.9)		132	38.8	38	35.8	47	41.6
First ED consultation			281 (89.8)	142 (94.0)	139 (90.3)		199	92.1	96	92.3	103	92.0
Tobacco consumption			93 (30.7)	42 (27.8)	51 (33.6)		62	29.0	23	22.1	39	35.5
Alcohol consumption			186 (61.3)	92 (60.9)	95 (61.7)		135	62.5	63	60.6	72	64.4
Cannabis consumption			35 (11.6)	18 (12.1)	17 (11.0)		22	10.3	10	9.8	12	10.7
At ED admission												
Reported pain			233 (74.4)	117 (77.5)	116 (75.3)		158	73 .1	76	73.1	82	73.2
Self-assessed stress *			4.0 [0.0-6.0]	4.0 [1.0-6.0]	3.0 [0.0-5.8]		4.0 [0.0-6.0]		4.5 [1.0-6.3]		3.0 [0.0-6.0]	
Expectation for recovery *			9.0 [6.5-10.0]	9.0 [7.0-10.0]	9.0 [6.0-10.0]		9.0 [6.0-10.0]		9.0 [7.5-10.0]		8.0 [5.5-10.0]	
ED evaluation												
Chronic pain reported			148 (50.0)	79 (53.7)	69 (46.3)		108	51.4	55	54.5	53	48.6
Chronic pain followed			101 (66.0)	54 (66.7)	47 (65.3)		72	64.3	37	66.1	35	62.5
Current daily pain			116 (47.9)	52 (41.6)	64 (54.7)		88	49.4	41	47.1	47	51.6
Thinks having been evaluated by psychologist in the ED			167 (53.4)	154 (98.7)	13 (8.3)		117	53.4	105	99.0	12	10.6
At ED discharge												
Reported pain			144 (62.3)	72 (61.5)	72 (63.1)		101	61.2	51	61.4	50	61.0
Self-assessed stress *			2.0 [0.0-5.0]	2.0 [0.0 -5.0]	1.0 [0.0-5.0]		2.0 [0.0-5.0]		2.0 [0.0 -5.0]		2.0 [0.0-5.0]	
Expectation for recovery *			9.0 [6.0-10.0]	9.0 [7.0-10.0]	9.0 [5.25-10.0]		9.0 [7.0-10.0]		9.0 [7.0-10.0]		9.0 [6.0-10.0]	
Satisfaction for ED cares *			8.0 [7.0-10.0]	9.0 [7.0-10.0]	8.0 [6.0-9.0]		8.0 [7.0-10.0]		9.0 [7.0-10.0]		8.0 [7.0-9.0]	

* median [interquartile range] ;

Risk Score = Risk assessment score : Female gender +1; taking at least one anxiolytic treatment +1; Perceived health status priori to admission Excellent. very good 0 . Good: +1. Poor: +2. Bad +3; PCLS: Post-concussion like symptoms; Reported pain: "Do you have pain?" Yes/No; Self-assessed stress: 10-level licker scale from 0 (no pain) to 10 (worst pain imaginable); Expectation for recovery: 10-level licker scale from 0 (no recovery) to 10 (full recovery)

Between January and July of 2018, 1,855 patients were admitted to the ER at times when psychologists were available; of these patients, 313 (200 at Bordeaux and 113 at Lyon) were eligible for the study and were randomized into one of the two groups (156 in the intervention group and 157 in the control group). Of these 313 patients, 94 were lost to follow-up; thus, 219 patients were ultimately included in the final analysis (Fig. 1). Independent of follow-up, the patient characteristics at inclusion were similar between the intervention and control groups (Table 16). The proportion of patients lost to follow-up in the two groups did not differ.

Delivery of the Intervention

A total of 31 psychologists participated in the study, representing a total of 984 hours of time present in the ER. All of the psychologists had been previously trained in EMDR(164) (Level 1: 9; Level 2: 22), 8 had practiced the R-TEP protocol prior to the training delivered for the present study, and 4 were certified in EMDR practice. The median number of interventions performed by each psychologist was three (inter-quartile range: 1.75–4.5). Of the 106 EMDR sessions performed for patients who completed the follow-up assessment, 66 were completed. The median duration of the EMDR sessions was 50 minutes (interquartile range: 30–90); we did not observe any difference according to whether or not a PCLS was present at 3 months. SUD scores decreased between the beginning and end of the EMDR sessions (difference: -3.9, 95% confidence interval [IC95%]: -4.5 to -3.3).

Effectiveness

There was no difference between the groups in terms of the primary outcome, i.e., the rate of PCLS (EMDR: 53.8% vs. Control: 49.6%). However, among the secondary outcomes, more cases of PTSD were observed in the intervention group than the control group (9.4% vs. 2.7%, p = 0.04). The occurrence of chronic pain was similar between the two groups (41% vs. 39%, p = 0.78), and the levels of acute pain at discharge did not differ (median [inter-quartile range]: 9 [7–10] vs. 9 [6–10], p = 0.89).

Post hoc Analyses

The analysis of PCLS according to psychologist skill level indicated that the qualifications of the practitioner may have influenced the outcome because the incidence of PCLS at 3 months was lower among patients who were seen by the most qualified and skilled psychologists (Table 17). There was no association between an incomplete session and an increased risk of PCLS. However, a high self-assessed stress level at admission (>6) was strongly associated with an

increased risk of PCLS in the EMDR group (76.9% vs. 40.9%; Table 3). The overall incidence of PCLS did not differ between the two study centers (Bordeaux: 50.7%, IC95%: 41.4–57.4; Lyon: 54.2%, IC95%: 32.9–59.2). However, the incidence of PCLS in the EMDR group was 48.8% (IC95%: 37.5–60.1) at Bordeaux and 69.2% (IC95%: 48.1–84.9) at Lyon. The difference in PCLS incidence between the intervention and control groups according was not related to patients' reasons for attending the ER.

Table 17: Primary and secondary outcomes

Variable	Population	EMDR	Control	p-value
	N	N	N	
	% [CI 95%]	% [CI 95%]	% [CI 95%]	
Primary outcome				
Number of patients	219	106	113	
PCLS	53.5% [43.9 to 63.4]	53.8% [43.9% to 63.4%]	49.6% [40.1% to 59.1%]	0.58
Secondary outcomes				
Number of patients	219	106	113	
PTSD	5.9% [3.3% to 10.2%]	9.4 [4.8% to 17.1%]	2.7% [0.7% to 8.1%]	0.04
Number of patients	165	83	82	
Acute pain at discharge	61.2% [53.3% to 68.6%]	61.4% [50.1% to 71.7%]	61.0% [49.5% to 71.4%]	1
Number of patients	218	106	112	
Chronic pain at 3-months	39.4% [33.0% to 46.3%]	40.6% [31.3% to 50.6%]	38.6% [29.5% to 48.1%]	0.78
Number of patient	162	80	82	
Expectation for recovery*	9 [6 – 10]	9 [7 – 10]	9 [6 – 10]	0.89

PCLS: Post-concussion like symptoms
PTSD: Pot traumatic stress disorder
*median [inter-quartile range]

Table 18: Presentation of the impact of psychologist skill level on PCLS occurrence at 3 months

	Population		PCS +		PCS-	
	N	%	n	%	n	%
Level of EMDR training						
N1	34	33.3	17	89.5	17	85.0
N2	68	66.7	2	10.5	3	15.0
Certification						
Yes	7	6.9	3	5.5	4	8.5
No	95	93.1	52	94.5	43	91.5
Experienced in R-TEP EMDR practice before study						
Yes	15	14.7	6	10.9	9	19.1
No	87	85.3	49	89.1	38	80.9
Psychologist skill level						
A	13	12.7	5	9.1	8	17.0
B	32	31.4	16	29.1	16	34.0
C	53	52.0	31	56.4	22	46.8
D	4	3.9	3	5.4	1	2.1

Skill level of the psychologist was evaluated by an EMDR supervisor blinded from both interventions' delivery and 3-month outcomes

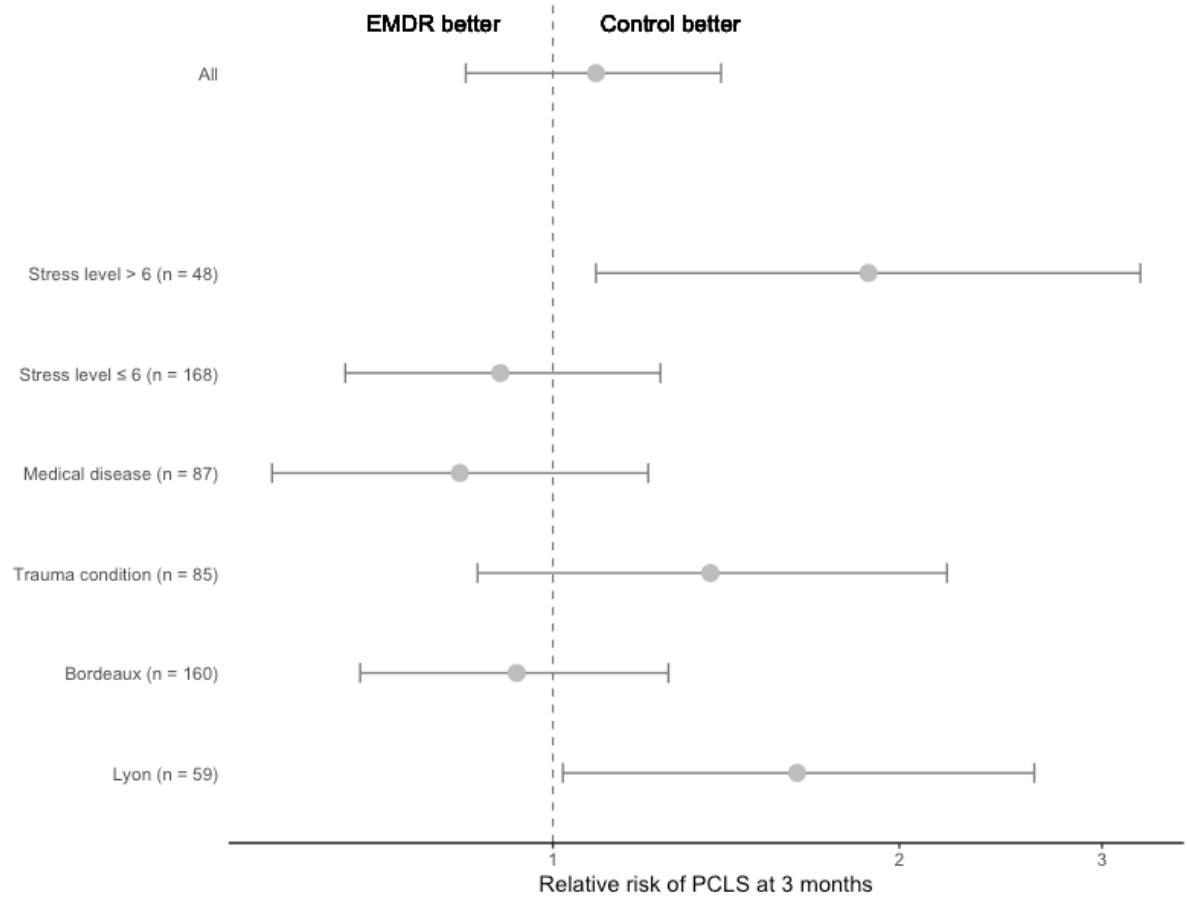

Figure 5: Subgroup analysis: Relative Risk of post-concussion like symptoms occurrence after stratification on different factors

Discussion

The results of the present trial revealed that an early EMDR R-TEP session performed during the ER stay did not reduce the incidence of PCLS at 3 months compared to usual ER care. Moreover, there was a higher incidence of PTSD in the intervention group, and the intervention resulted in an increased incidence of PCLS at 3 months among patients in the highest quartile of self-assessed stress at admission. Finally, there was an association between psychologist qualification level and success of the intervention.

The present study failed to confirm the results obtained during the SOFTER 2 trial.(86) In that study, there was a substantially lower rate of PCLS among patients treated by a psychologist in an EMDR session compared to those treated with usual care in the ER. More specifically, 6 of 34 patients in the EMDR group had PCLS at 3 months compared with 24 of 37 patients in the control group. There are several possible reasons for this discrepancy between the studies. Only two experienced psychologists were involved in the previous pilot study, whereas 31 psychologists with heterogeneous levels of experience were recruited for the present trial. Of these 31 psychologists, only 8 had previous experience with the R-TEP protocol. The present study found clear positive associations between the outcome of the intervention and the various indicators used to assess the psychologists' experience and skill. Although it is possible that this can explain the present results, the assessment of the psychologists' competencies was not planned in the initial protocol and was only conducted after the effectiveness results were known. Therefore, this should remain a hypothesis, but it is also indicative of the need to carefully control the level of training provided to EMDR therapists because the short training period may have been insufficient.(165) Having less experienced and/or trained psychologists might also have reduced patient adherence to the protocol and increased the number of refusals. Thus, future studies should evaluate fidelity to the intervention protocol.

Approximately 30% of patients included in the present trial were lost to follow-up, but the characteristics of the patients who answered the 3-month questionnaire did not differ from those who did not. The proportion of refusals in the SOFTER 3 trial (~40%) was significantly higher than that in the SOFTER 2 trial (~20%). There is no clear explanation for this difference, and it may have influenced the results. In fact, it is possible that the patients who agreed to participate in the study differed from those who did not, which might explain why the expected number of patients was not achieved.

Further analysis of the discrepancies between the present trial and the previous pilot study, which produced more encouraging results, revealed differences in the psychologists' reports about the nature of the points of disturbance in the EMDR sessions. In the pilot study, the psychologists primarily addressed issues that were not directly related to the event that led a patient to the ER, whereas in the present study, a majority of the intervention reports mentioned disturbance points that were directly related to the event. It was also noted that patients with 3-month PCLS exhibited a significant decrease in SUD scores between the beginning and end of the EMDR session.

The present findings also differed from those of some studies in the literature.(86,123,124) A study conducted in Israel reported very promising results following a single session of early modified EMDR provided in a general hospital setting by psychologists who were experienced in EMDR practice.(124) In that study, patients reported the presence of acute stress syndrome and suffered from intrusion distress following accidents and terrorist bombing attacks. However, at the 4-week and 6-month follow-up assessments, the immediate responders in the terror victims group remained symptom free.

The second key finding of the present study concerned the high level of adverse effects associated with the intervention in patients who described themselves as experiencing high

levels of stress. When EMDR is performed by an unqualified practitioner, insufficient attention may be paid to the importance of initially establishing sufficient stabilization and calming, which should be part of the protocol when applied correctly. Importantly, the issue of managing patients with high levels of stress or dissociation remains. In response to this challenge, modified and adapted EMDR-type early intervention protocols have been developed to assist victims.(128,161)

Additionally, in the present study, perceived stress was evaluated using a 10-point Likert scale that had never been validated for stress assessment in the ER. Nonetheless, this scale provided a method with which to measure variations in subjective stress between admission and discharge, and a similar 5-point Likert scale for acute stress (“not at all” to “strongly”) had previously been validated.(72) The use of a 10-point scale likely did not influence the validity of the acute stress measure, especially because this variable was a secondary outcome and was assessed in a post hoc analysis. However, patients in the EMDR group who were experiencing high stress, defined as a numeric score >6, reported many more symptoms than did those in the control group.

Conclusions

Among patients admitted to the ER in the present study, a single EMDR R-TEP session did not reduce the incidence of PCLS at 3 months, particularly among patients who reported high levels of stress at admission. The present results suggest that it will be necessary to collect more data to determine the available treatment options that can be offered to patients attending the ER. Furthermore, the present results must be applied with caution, particularly due to the large degree of heterogeneity in the skill level of the psychologists employed in this study. Regardless of this issue, clinicians should continue attempts to identify the best care options for traumatized patients who present to the ER.

14.2.5. Analyses complémentaires de SOFTER 3

Nous avons mené d'autres analyses post-hoc pour comparer les populations selon l'existence d'un PCLS à 3 mois (tableau 19) ou selon le centre d'inclusion (tableau 20).

Dans le tableau 19, la proportion de patients présentant un PCLS à 3 mois était ainsi associée à l'existence d'un PCLS à l'admission aux urgences, au score d'évaluation du niveau de risque et à l'existence d'une douleur chronique. De la même manière l'espoir de récupération à l'admission et à la sortie était plus bas chez les individus qui déclaraient des PCLS à 3 mois.

Les populations des deux centres étaient relativement différentes (tableau 20). Les patients de Lyon étaient plus jeunes que ceux de Bordeaux (Médiane : 34 vs 51 ; $p < 0,0002$). Les pathologies étaient également très différentes entre les 2 sites, à prédominance traumatologique à Lyon et médicales à Bordeaux. La proportion de patients douloureux était plus faible à Bordeaux à l'admission (65% vs 95%) et à la sortie (51% vs 80%). La proportion de patients déclarant une douleur chronique était plus importante à Bordeaux (65 vs 33%).

Table 19 : Comparaison des caractéristiques des patients selon l'existence de PCLS à 3 mois

		Population		PCLS+		PCLS-		p
		N	%	n	%	n	%	
		219	100	113	51.6	106	48.4	
Caractéristiques des patients								
Sexe	Féminin	163	74.4	88	77.8	75	70.7	NS
Age*		46 [31.0-62.75]		45.0 [29.0- 59.0]		49.0 [34.0 - 66.0]		0.10
Score	= 2	105	47.9	43	38.1	62	58.5	< 0.003
	≥ 3	114	52.1	70	61.9	44	41.5	
Présence de PCLS à l'admission		142	64.8	85	75.2	57	53.7	< 0.002
Motif de venue								
Médical		48	21.9	20	17.7	28	26.4	NS
Traumatique		132	60.3	69	61.6	63	59.4	NS
Première consultation aux urgences		199	90.9	104	93.7	95	90.5	NS
Consommation de tabac		62	29.0	35	31.5	27	26.2	NS
Consommation d'alcool		135	62 .5	69	62.2	66	61.9	NS
Consommation de cannabis		22	10.2	14	12.7	8	7.6	NS
À l'admission aux urgences								
Douleur rapportée		158	72.1	82	73.9	76	72.4	NS
Stress autoévalué		4.0 [0.0-6.0]		4.0 [1.0-7.0]		3.0 [0.0-5.0]		0.08
Espoir de récupération		9.0 [6.0-10.0]		8.0 [5.0-10.0]		10.0 [8.0-10.0]		< 0.0002
Aux urgences								
Douleur chronique rapportée		108	51.4	65	60.7	43	41.7	< 0.01
Douleur chronique suivie		72	64.3	47	72.3	25	53.1	0.09
Douleur quotidienne actuelle		88	49.4	52	56.5	36	41.8	NS
À la sortie des urgences								
Douleur rapportée		101	61.2	57	65.5	44	56.4	NS
Stress autoévalué		2.0 [0.0-5.0]		2.0 [0.0-5.0]		2.0 [0.0 -4.0]		NS
Espoir de récupération		9.0 [7.0-10.0]		8.0 [5.0-10.0]		10.0 [8.0-10.0]		< 0.05
Satifaction des soins *		8.0 [7.0-10.0]		8.0 [7.0-9.0]		9.0 [7.0-10.0]		0.11

* médiane [étendue interquartile] ;

Score = Score d'évaluation du risque : sexe féminin +1; prise d'anxiolytique +1; État de santé perçu avant l'admission Excellent. Très bon 0, Bon : +1, Moyen : +2, Mauvais +3 ; PCLS : Post-concussion like symptoms ; Douleur rapportée : « Avez-vous mal? » Oui/Non ; Auto-évaluation du stress : Échelle de Likert à 10 niveaux de 0 (aucun stress) à 10 (Pire stress imaginable) ; Espoir de récupération : Échelle de Likert à 10 niveaux de 0 (aucune récupération) à 10 (Récupération totale)

Tableau 20 : Caractéristiques des patients suivis selon le centre

			Population		Bordeaux		Lyon		p
			N	%	n	%	n	%	
			219	100	160	73.1	59	26.9	
Caractéristiques des patients									
Sexe	Féminin		163	74.4	123	76.9	40	66.7	NS
Age*			46 [31.0-62.75]		51.0 [23.5- 67.0]		34.0 [23.5 - 53.0]		<0.0002
Score	= 2		105	47.9	76	47.5	29	49.2	NS
	≥ 3		114	52.1	84	52.5	30	50.8	
Présence de PCLS à l'admission			142	64.8	103	64.4	72	66.1	NS
Motif de venue									
Médical			48	21.9	78	48.8	9	15.2	<0.0002
Traumatique			132	60.3	45	28.1	40	67.8	<0.0002
Première consultation aux urgences			199	90.9	143	90.5	56	96.5	NS
Consommation de tabac			62	29.0	23	22.1	39	35.5	< 0.05
Consommation d'alcool			135	62 .5	63	60.6	72	64.4	NS
Consommation de cannabis			22	10.2	10	9.8	12	10.7	NS
À l'admisison aux urgences									
Douleur rapportée			158	72.1	103	65.2	55	94.8	<0.0002
Stress autoévalué			4.0 [0.0-6.0]		4.0 [1.0-6.0]		3.0 [0.0-6.0]		NS
Espoir de récupération			9.0 [6.0-10.0]		9.0 [6.0-10.0]		8.0 [7.0-10.0]		NS
Aux urgences									
Douleur chronique rapportée			108	51.4	89	58.2	19	33.3	<0.002
Douleur quotidienne actuelle			72	64.3	70	51.8	18	41.9	NS
Douleur chronique suivie			88	49.4	61	68.5	11	47.8	NS
À la sortie des urgences									
Douleur rapportée			101	61.2	56	51.3	45	80.4	<0.001
Stress autoévalué			2.0 [0.0-5.0]		2.0 [0.0-5.0]		1.0 [0.0 -5.0]		NS
Espoir de récupération			9.0 [7.0-10.0]		9.0 [7.0-10.0]		9.0 [6.5-10.0]		NS
Satisfaction des soins *			8.0 [7.0-10.0]		8.0 [7.0-10.0]		8.0 [7.0-10.0]		0.09

* médiane [étendue interquartile] ;
Score = Score d'évaluation du risque : sexe féminin +1; prise d'anxiolytique +1; État de santé perçu avant l'admission Excellent. Très bon 0, Bon : +1, Moyen : +2, Mauvais +3 ; PCLS : Post-concussion like symptoms ; Douleur rapportée : « Avez-vous mal? » Oui/Non ; Auto-évaluation du stress : Échelle de Likert à 10 niveaux de 0 (aucun stress) à 10 (Pire stress imaginable) ; Espoir de récupération : Échelle de Likert à 10 niveaux de 0 (aucune récupération) à 10 (Récupération totale)

14.2.6. Interprétation et implication de SOFTER 3

Les résultats de SOFTER 3 avait tout d'abord bouleversé notre point de vue sur la place de l'EMDR comme moyen de prévention et plus généralement sur l'ensemble du projet SOFTER.

En effet, nous avons obtenu dans cette étude un résultat quasiment opposé à celui de notre étude pilote.

Les résultats de notre étude étaient discordants avec ceux de la littérature notamment en ce qui concerne le traitement du TSPT (121,127,130,138). En effet, nous avons trouvé dans l'étude un taux plus élevé de TSPT chez les patients qui avaient bénéficié d'une séance d'EMDR aux urgences que chez les témoins (9,4% vs 2,7%). Cette discordance pouvait trouver une explication à plusieurs niveaux de l'intervention des psychologues. D'une part, à la relecture des fiches psychologues et en les comparant avec celle de SOFTER 2, nous nous sommes rendu compte que l'évènement ciblé dans SOFTER 3 était essentiellement celui qui a conduit les patients aux urgences. Ce n'était pas le cas dans SOFTER 2 au cours duquel les perturbations abordées dans la prise en charge EMDR concernaient souvent un phénomène périphérique à l'événement, comme par exemple la présence d'un proche qui attend en salle d'attente ou une reviviscence d'un autre évènement traumatisant. Au cours de SOFTER 2, nous avions l'impression que les psychologues avaient, au cours de leur prise en charge, traité des évènements qui, s'ils s'étaient ajoutés à la pathologie prise en charge aux urgences, aurait pu développer des PCLS. Une des hypothèses pour expliquer l'échec des prises en charge EMDR dans SOFTER 3 est la suivante. Si l'évènement retraité par l'EMDR était celui en lien avec le passage aux urgences, alors cette intervention précoce et brève se comporte de la même manière et a les mêmes effets néfastes que le « psychological debriefing » : elle perturbe le processus naturel de traitement du stress aigu. L'élément principal qui renforce cette hypothèse est le rôle majeur du stress ressenti à l'admission par les patients. Il est probable que les patients stressés soient « en cours de traumatisme » (« ongoing trauma »). L'intervention EMDR focalisé sur l'évènement aigu les empêcherait probablement de mettre en place les phénomènes physiologiques de gestion du stress.

Ainsi, les urgences se positionneraient plutôt comme une opportunité de prise en charge de patient déjà fragiles et présentant un niveau de stress modéré lors de la prise en charge. La prévention des conséquences psychologiques d'un passage aux urgences passerait donc peut-être par la prise en charge des autres évènements de vie des patients.

Un autre objectif de cette étude bicentrique était d'évaluer la faisabilité de l'EMDR en cours de prise en charge dans un autre service d'urgence. Cette partie n'a pas posé de problème et une séance d'EMDR semble donc envisageable au sein de services d'urgences aux organisations très différentes.

Par ailleurs, il faut noter un autre élément que nous n'avons malheureusement pas le moyen mesurer de manière précise. Il s'agissait de la différence socio-démographique très importante entre les populations des deux sites. Il est possible que cette différence ait nettement influencé l'efficacité de l'EMDR , le faible niveau socio-économique influencerait à la fois l'apparition d'un TSPT mais aussi les choix thérapeutiques (166). Cette différence entre les deux populations est illustrée dans les tableaux 19 et 20. Nous n'avions malheureusement pas d'informations sur le niveau socio-économique des patients mais un certain nombre d'éléments pourrait tout de même avoir affecté le déroulement de l'intervention. La population lyonnaise était beaucoup plus jeune et plutôt victime de traumatismes et à l'inverse la population bordelaise présentait plus de patient douloureux chroniques. Si ces interactions entre les caractéristiques de population et le risque de PCLS restent mal connues, il convient néanmoins de tenir compte de ces inégalités dans l'interprétation des résultats.

Enfin, et même s'il s'agissait d'une analyse post-hoc, l'influence de l'expérience des psychologues était un résultat très intéressant. Cela a déjà été évoqué dans la littérature (165) et il parait important de le prendre en compte dans l'avenir pour les études futures, mais aussi plus généralement dans le cadre de la formation des psychologues à la pratique de l'EMDR.

14.3. Modalité d'évaluation de l'intervention au cours de SOFTER 2 et 3

Au cours des deux essais conduits dans le cadre de ce travail de thèse, nous avons voulu mesurer la faisabilité de l'intervention au cours de la prise en charge des patients aux urgences. Pour juger de cette faisabilité, nous avions choisi de mesurer le taux d'intervention conduite jusqu'à leur terme. Cette approche restait minimaliste et manquait de rigueur scientifique.

Ainsi, dans SOFTER 2 et 3, le taux de séance d'EMDR qui ont pu être réalisées était satisfaisant en tant que tel. Cependant, il ne présume pas des modalités d'accomplissement des séances et de leur impact sur le fonctionnement du service. Cette évaluation n'était malheureusement pas prévue dans le protocole de l'étude. Une mesure plus complète, intégrant un ressenti du personnel soignant (médecin urgentiste, paramédicaux, autres spécialistes…) aurait dû être réalisée de manière formelle. Cependant, le déroulement de cette étude atypique pour un service d'urgence a suscité de nombreuses discussions avec l'ensemble du personnel et personne ne s'est plaint d'un impact sur la prise en charge des patients en lien avec l'étude. Il est évident que le mode de recueil de cette information comporte de nombreux biais, mais elle laisse imaginer que malgré la longueur de l'intervention, elle peut se dérouler sans déranger les soins.

Dans chacune de ces études, il existait une fiche de recueil pour les psychologues qui recueillaient essentiellement les éléments de perturbations traités par les psychologues au cours de la séance. Les deux fiches n'étant pas identiques, il n'était pas possible de comparer le déroulement des séances entre SOFTER 2 et 3. Cependant, une description brève de l'élément retraité par le psychologue au cours de la séance était notée sur chacune des fiches. Il était prévu une analyse du contenu des fiches dans SOFTER 3 par la psychologue référente de l'étude mais celle-ci n'a pour l'instant pas encore été réalisé.

Une relecture attentive a cependant été réalisée par le comité de pilotage et nous avons pu observer des différences concernant la cible de ce retraitement. Ainsi, comme présenté dans le paragraphe précédent, dans SOFTER 3, l'élément de perturbation était plus souvent en lien direct avec l'intervention que dans SOFTER 2.

Les deux autres limites évoquées dans SOFTER 3 sont celles de la formation reçue par les psychologues et de l'« administration » de l'intervention. Si la qualité de la formation peut difficilement être remise en cause étant donné que la formatrice était très expérimentée et reconnu par l'association EMDR Europe, sa durée était brève et elle n'a pas fait l'objet d'une évaluation formative pour s'assurer de la maitrise de chacun des intervenants.

Par ailleurs, nous avons fait l'erreur de croire en la « grande simplicité » de la pratique de l'EMDR. Les discussions avec nos collègues du CASPERTT lors de l'élaboration de SOFTER 2, corroboré par son efficacité, nous ont fait occulter des paramètres comme la variabilité entre les thérapeutes. C'est pourquoi la stratification sur l'expérience du psychologue n'était pas prévue dans le protocole initial.

L'idée de la « simplicité » de l'intervention proposée est également à l'origine de l'augmentation très importante du nombre d'intervenants différent entre SOFTER 2 et 3. C'était très certainement une erreur méthodologique qui compromet la réelle interprétation des résultats.

Concernant la conduite des séances, nous avions envisagé pour cette SOFTER 3 d'enregistrer des séances pour en faire une évaluation a posteriori, mais la lourdeur logistique nous avait amené à abandonner le projet. Il est évident que cette évaluation qualitative fait cruellement défaut à l'interprétation de l'échec de l'intervention.

Ces limites ont été prise en compte pour la suite du projet : l'étude SOFTER 4.

14.4. Étude SOFTER 4

14.4.1. Justification de SOFTER 4

L'échec de l'étude SOFTER 3 aurait pu nous conduire à arrêter ce projet. Cependant, plusieurs éléments nous laissent penser qu'une intervention précoce peut-être bénéfique pour les patients et que le stress des patients joue un rôle important dans l'apparition des PCLS.

D'une part, même si l'expérience des psychologues sur l'efficacité de l'intervention ne peut être tenue pour seule responsable de l'étude, l'effet ne semble pas négligeable. Peu de psychologues étaient effectivement habitués à réaliser le RTEP avant le début de cette étude et celles qui l'utilisaient couramment obtenaient des résultats plus intéressants.

D'autre part, l'analyse stratifiée sur le stress auto déclaré par les patients renforce le rôle clé du stress dans l'apparition des PCLS à distance. Les proportions de PCLS obtenues dans la strate des patients les plus stressés (EMDR : 77% vs Témoin : 41%) nous suggère que le stress initial serait plutôt une réaction physiologique qu'il faut respecter. L'EMDR focalisé sur l'évènement qui a conduit les patients aux urgences comme cela a souvent été le cas dans SOFTER 3, maintiendrait les patients dans ce stress en agissant comme le fait le « psychological debriefing ».

Pour SOFTER 4, les psychologues qui interviendront seront très expérimentés dans la pratique de l'EMDR et ils seront sensibilisés à l'ensemble de ces éléments.

Un autre élément qui justifie pleinement la réalisation de l'étude SOFTER 4 est l'analyse des facteurs de risque de PCLS. Si de nombreuses études ont été conduites en ce sens (9,14,38,167), elles n'incluent pas une typologie de patients aussi large que l'ensemble des patients admis aux urgences.

Cette étude originale pourrait apporter beaucoup d'éléments important dans la compréhension de l'origine des PCLS. Enfin, nous avons bien conscience que notre

positionnement des urgences dans notre étude va à l'encontre des politiques de santé actuelles mais, si les résultats s'avèrent probant, les urgences pourraient constituer un outil puissant et performant de santé communautaire et de lutte contre les inégalités de santé.

14.4.2. Principales évolutions pour SOFTER 4

L'étude SOFTER 4 est une étude d'implémentation. Nous voulons ainsi évaluer si des psychologues positionnés aux urgences permettent de diminuer l'incidence de PCLS trois mois après la prise en charge des patients aux urgences.

Nous avons pris en compte les informations obtenues dans SOFTER 3 et ainsi sélectionné pour l'études des psychologues très expérimenté en EMDR, tous formateurs reconnus dans le domaine.

Si l'EMDR est l'intervention à privilégier, ce ne sera pas la seule. Ils auront la possibilité de choisir l'intervention qui leur paraitra la plus adaptée au patient. Ils seront également sensibilisés à l'important rôle du stress pour le prendre en compte dans leur choix.

Par ailleurs, le score utilisé pour définir l'inclusion des patients dans les études précédentes ne sera ici qu'un outil permettant de reconnaitre les patients les plus fragiles et pour lesquels l'intervention pourrait être la plus bénéfique. L'ensemble des patients admis aux urgences pourrait ainsi être pris en charge si le psychologue juge que cela pourrait être efficace.

14.4.3. Protocole d'étude - Accepté financement PHRC-N 2018

Persistent PostConcussion-Like Symptoms and Post traumatic Stress Disorder for patients presenting at the Emergency Room: A multi-center cluster randomized cross-over implementation study.

SOFTER IV - Sponsor code: CHUBX 2018/XX - ID-RCB number: **XXXXXXXX**.

PROTOCOL FOR INTERVENTIONAL RESEARCH INVOLVING HUMAN PARTICIPANTS (category 2 research project)

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ABSTRACT

Study Title

Persistent Post-Concussion-Like Symptoms and Post-traumatic Stress Disorder for patients presenting at the Emergency Room: A multi-center implementation study.

Objectives

Primary

To assess the impact of effective implementation in ER of an early intervention provided by a trained psychologist PCLS incidence 3 months after attending the ER.

Secondary

To define an improved scoring system for selecting patients eligible for the intervention.

To estimate the cost-benefit of the intervention balancing costs due to the availability of a full-time psychologist in the ER versus cost of medicines and health care consumption due to persistent PCLS and PTSD.

Design and Outcomes

The study is a multi-site cluster randomized cross-over trial with two comparative groups. In each site, the recruitment period span over a period of 10 days (5 days for control and 5 days for intervention). The control period is a period during which no psychologist is available. ER cares will be provided as usual. The intervention period is a period during which trained psychologists are available in the ER and will provide a short early 1-hour R-TEP EMDR intervention for patients selected with high risk of PCLS. Patient's selection will be conducted using a score developed in previous studies. When no high-risk patient is identified, psychologist could assess other patients and treat them if judged necessary. In this context,

they could provide either a R-TEP EMDR or short intervention such as reassurance according to therapist assessment. Otherwise, ER cares will be provided as usual.

In either intervention or control period, all consecutive patients will be proposed to participate in the study that consists in:

(i) completing an inclusion questionnaire to describe reasons for ER attendance, current stress level and preexisting health and symptoms and, in the intervention group, to assess PCLS risk level;

(ii) being contacted 3 months later to assess PTSD (using the PCL-5 checklist) and PCLS (using Rivermead criteria).

The national health insurance ID will be collected in the inclusion questionnaire and sent to the national database (SNIIR-AM). This will allow to compare health care consumption levels in the two groups.

Sample Size and Population

The study population is adult patients presenting at the ER of one of the study sites.

The planned total number of patients to be enrolled will be 4956 in 6 clusters (sites).

Overview study diagrams

Figure 6. Patients flowchart

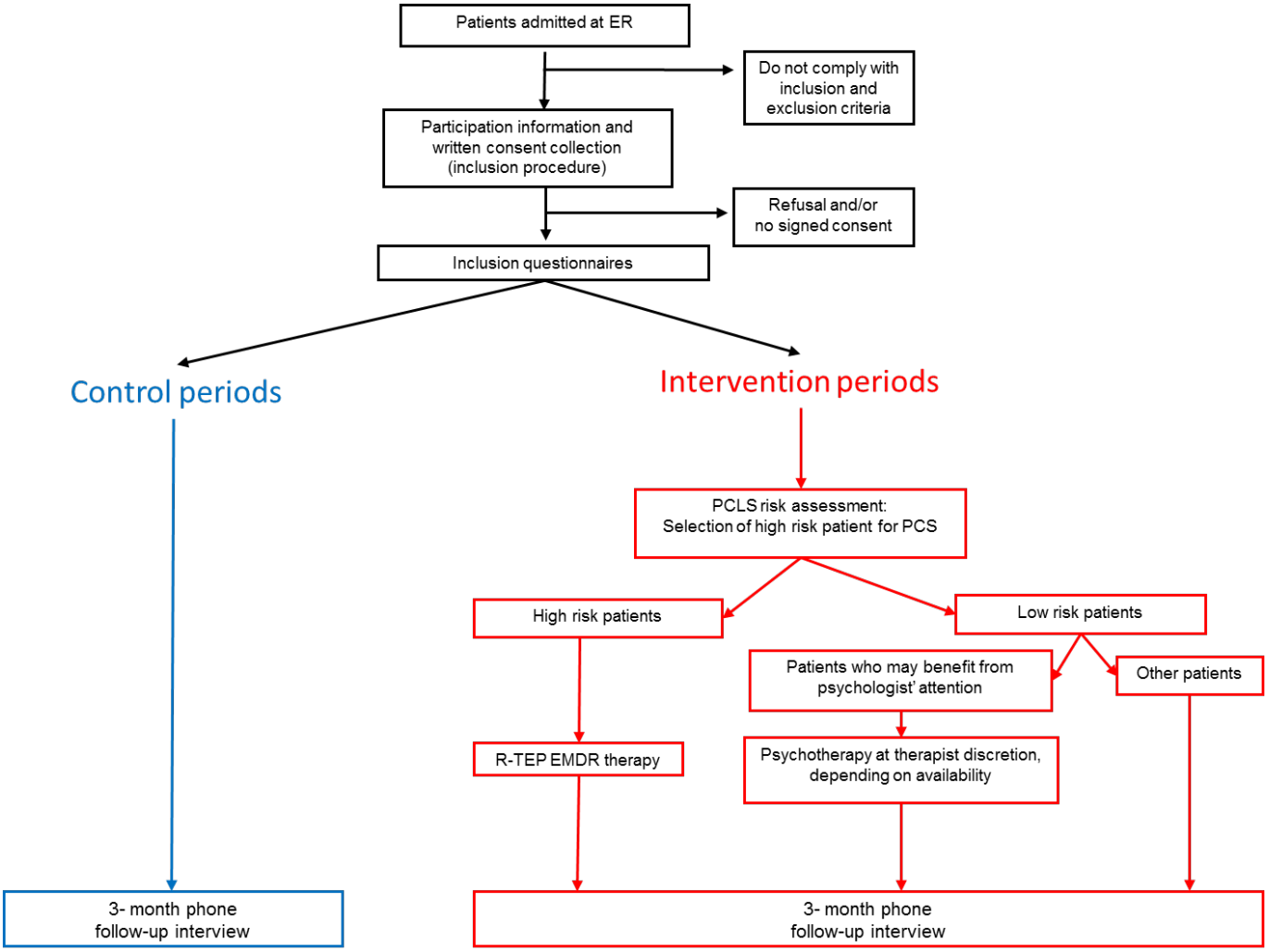
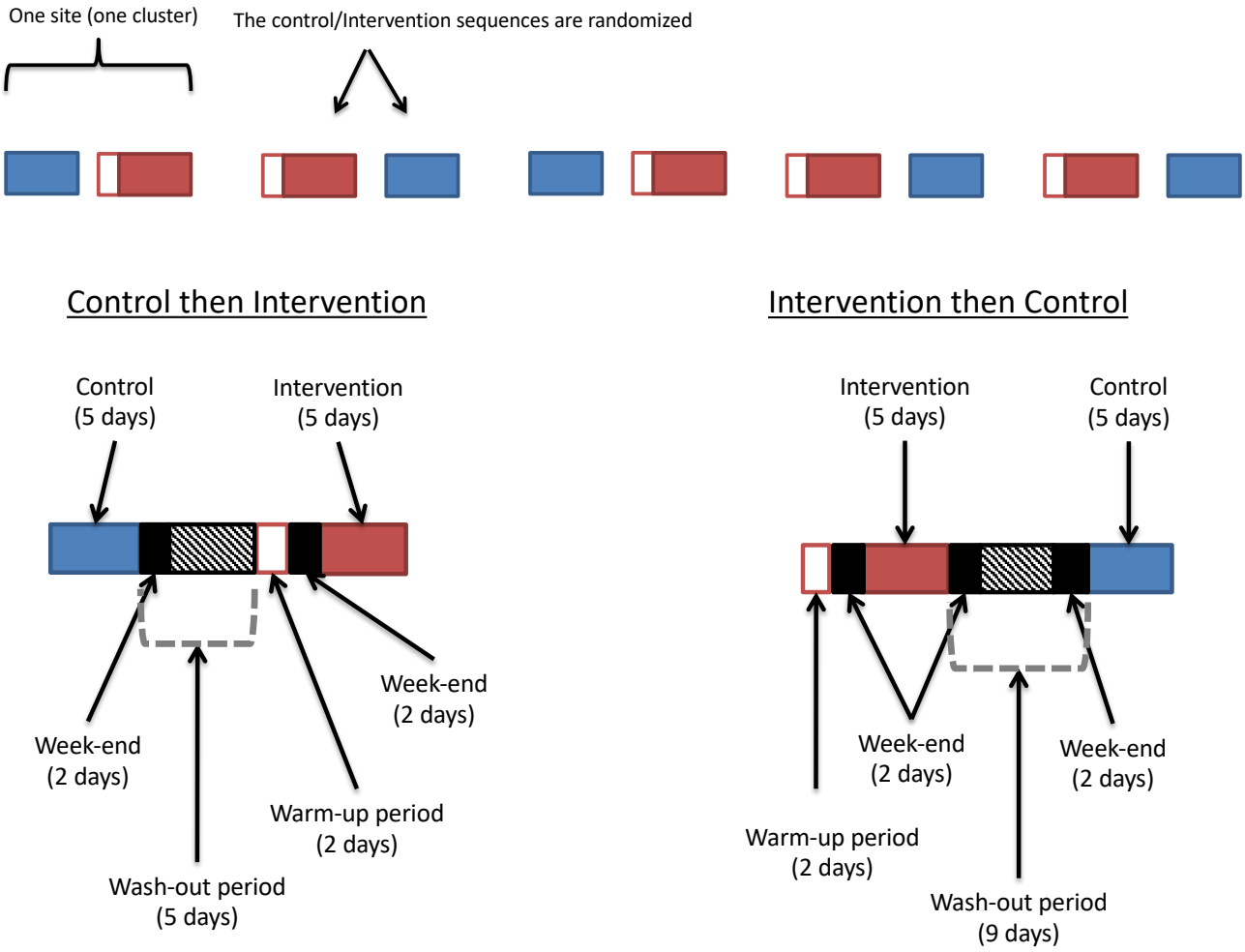


Figure 7. Design of the two-group (intervention/control) cluster crossover trial



MAIN ABBREVIATIONS

PCS	Post Concussion Syndrome
PCLS	Post Concussion-Like Syndrome
PTSD	Post-Traumatic Stress Disorder
EMDR	Eye Movement Desensitization and Reprocessing
ERP	Emergency Response Procedure (a stabilization procedure)
R-TEP	Recent Traumatic Episode Protocol
ER	Emergency Room
ICD-10	International Statistical Classification of Diseases and Related Health Problems
SOFTER	SymptOms Following Trauma: Emergency Response.
DSMB	Data Safety Monitoring Board
SSMS	Shared Study Monitoring System

BACKGROUND AND RATIONALE

Background on Condition

In 2012, the date of the last national survey in France, 10.6 million people came or were taken to the emergency room (ER), sometimes several times since it is 18 million visits that were recorded in the same year. More than 90% of them will leave the service within hours, without hospitalization.

A set of consistent recent study results report on an observation with major public health consequences: the available figures suggest that 10 to 20% of injured patients will suffer for several months after the event from very diverse symptoms, which will lead to a decline in quality of life that can be significant and delay or prevent the resumption of school or work activities, change social and family relationships. It is therefore about two million people each year in France who are confronted to varying degrees of difficulties whose cause is often unidentified and unrelated to the traumatic event. This link is all the more difficult to do as these symptoms appear to be non-specific: headaches, concentration disorders, memory problems, stress intolerance, personality change, irritability... They have been described for now more than 50 years, in the context of head trauma, and in this context were referred to as Post Concussion Syndrome (PCS). Surprisingly, the most recent results show that these symptoms are not specific to brain injuries and can occur for other patients presenting in the ER , greatly expanding the size of the population concerned. In a cross-sectional, observational study of 31 958 high school athlete, Iverson et al. also found that 19% of uninjured boys and 28% of uninjured girls reported having a symptom burden resembling an International Classification of Diseases, 10th Revision (ICD-10) diagnosis of PCS and henceforth frequently described as Post Concussion-Like Symptoms (PCLS).

Recognizing that brain damages are not the main cause of these symptoms, the scientific community has undertaken to compare patients with and without symptoms with two objectives: to predict their occurrence and to understand why they occur.

It is within this framework that a major result emerged: psychological vulnerability on the one hand and stress experienced during and in the aftermath of the event on the other hand, are the two most predictive elements of these lasting symptoms. This finding is repeatedly observed in studies that look for the factors associated with them.

A final discovery sheds light on this major public health phenomenon that affects patients who have suffered an accident, aggression or an acute medical condition and whose general health remains precarious several months or years later. Faced with the psychological pain of soldiers from Western countries returning from outside theaters of operation, the study of Post-Traumatic Stress Disorder (PTSD) has seen a renewed interest. These studies have led to a better characterization of this condition, including the individualization of 4 dimensional components: revivification, avoidance, hyperactivation of the nervous system and cognitive and emotional numbing. Symptoms of PCLS are very similar, and even sometimes exactly the same as the last two dimensions of PTSD: hyper activation of the nervous system and cognitive and emotional numbing. This led most authors to raise the hypothesis that PCLS and PTSD partly share a same causal pathway in which stress plays a key role. This would be particularly relevant for prevention, in particular because only PTSD studies are sufficient in number and quality to identify credible modes of intervention.

Preliminary studies conducted by our research team

Our research team conducted three studies in the past 10 years that enabled us to further our understanding of PCLS and seek for prevention opportunities.

The Pericles Study

In 2007, we conducted a cohort study of 2018 patients with mild traumatic brain injuries and 1447 others injured patients recruited in the adult ER of the Bordeaux University Hospital. Follow-up up to 12 months provided an unprecedented database allowing for in-depth comparisons of patients sub-groups. It was this study that showed that PCS, despite its naming, was not specific to head trauma. It was also this study that highlighted the importance of stress and the overlap between PCS and PTSD. This database allows us today to compare the performances of screening algorithms aimed at selecting patients with an increased PCS risk from variables measured at the ER. This last point is of major importance in the preparation of this research project.

The SOFTER Pilot study 1

Following the Pericles project, we conducted a pilot study to identify the factors explaining the persistence of symptoms three months after an injury event. The key result of this pilot study [publication submitted] is that the stress level reported by patients at the end of their ER stay was a powerful predictor of PCLS and PTSD, irrespective of the stress level reported at the entrance of the ER. This important result prompted us to consider testing the feasibility and then the effectiveness of stress management interventions during ER stay with the hope of improving the outcomes of traumatized patients.

Literature search for intervention

Results from literature and these two studies led us initiate a literature search for the best intervention candidates that would have the potential to lower the stress level during ER stay

Early intervention for PTSD prevention

One of the first ideas proposed for patients that experienced a stressful event was to initiate a stress management procedure before the consolidation of stressful memories. This is partly why Psychological Debriefing, that consists in debriefing sessions conducted 2–10 days after

the critical incident, has been widely disseminated. However, several critical reviews [39] and a Cochrane Review have concluded that this form of intervention lead to an increased rate of PTSD.

More promising, Early Exposure Therapy, which is based on the extinction of fear through engagement with traumatic memories and clues, appears to be an effective treatment of PTSD. The PTSD syndrome can be interpreted as a failure of recovery caused, in part, by failure of the extinction of trauma. This is supported by research conducted on the animal showing that early extinction has the potential to alter the consolidation of memory of original fear. Rothbaum et al. at the Emory University School of Medicine in Atlanta, for the first time in 2012, recruited a sample of 137 patients randomized to three groups showing the effectiveness of an extinction-type intervention (Prolonged exposure) beginning at the ER in the prevention of PTSD. Of note, the intervention also included two other sessions one and two weeks later. The same authors showed 2 years later that such short-term intervention could also lower PSTD risk in patients with genes previously found associated with stress-response.

Trauma-focused cognitive behavioral therapy delivered within weeks of a potentially traumatic event for people showing signs of distress also showed the most evidence in the treatment of acute stress and early PTSD symptoms, and the prevention of PTSD.

However, cognitive behavioral therapies proved so far superior to other methods, and in particular the Eye movement desensitization and reprocessing (EMDR) psychotherapeutic intervention. Invented by Francine Shapiro, EMDR is an empirically validated psychotherapeutic approach that can rapidly process disturbing experiences adaptively together with the aid of eye movements or other forms of bi-lateral stimulation. Several meta-analyzes and Cochrane review have shown that this is one of the most effective treatments

for PTSD. Treatment may be started soon after the trauma, but most often after a complaint from the patient who is already suffering from PTSD symptoms. More recently, a study by Cyril Tarquinio of the University of Lorraine, France shows the effectiveness of an EMDR-based intervention initiated in the first 48 hours. The target population of this study were workers who have suffered professional violence (assaults, robberies, etc.).

A study conducted in Israel showed very promising results with a single-session early modified EMDR session provided in a general hospital inpatient and outpatient setting to 86 patients with acute stress syndrome suffering from intrusion distress following accidents and terrorist bombing attacks. Half of the patients reported immediate fading of intrusive symptoms and general alleviation of distress, 27% described partial alleviation of their symptoms and distress, while 23% reported no improvement. At 4-week and 6-month follow-up, the immediate responders in the terror victims group remained symptom free, while the non-responders endorsed more risk factors for PTSD. These results support other anecdotal reports on the rapid effects of brief EMDR intervention on intrusive symptoms in early uncomplicated posttraumatic cases.

Following the recognition of the failure of Psychological Debriefing, the issue of the difficult access to patients with high levels of stress or dissociation was raised. This latter point was all the more critical as it was known that dissociation at the time at which exposure therapy starts was found to be associated with poorer response. In response to this challenge and to the increasing number of patients in need of care after manmade catastrophes such as bomb attacks, modified EMDR procedures and protocols adapted for early intervention have been developed to help victims that can be applied soon following a trauma: the Emergency Response Procedure (ERP) and the Recent Traumatic Episode Protocol (R-TEP).

The ERP is a short procedure described in 2014 in a book edited by Martin Luber. The ERP is implemented according to procedures designed and tested in emergency contexts, including ER.

. The individuals who arrive in ER shows a wide range of disturbance. The best benefit of the ERP intervention is expected for patients in a highly agitated" state (scoring 7–10/10 on the Subjective Units of Disturbance (SUD) scale, where 0 = no disturbance and 10 = the highest disturbance possible) to those who have moved into a "silent terror" (SUD 10+/10).

The R-TEP protocol is an early EMDR current trauma focused intervention that incorporates and extends the main ideas of Francine Shapiro's original Recent Event Protocol guidelines. It was first described by Shapiro and Laub in 2008.

Pharmacological treatment and prevention of PTSD

As regard to pharmacological intervention, several substances have been tested as an early intervention with the hope of preventing further PTSD. These include propranolol, morphine, ketamine and hydrocortisone. Only the latter so far demonstrated a significant impact.

PCS and its prevention.

The International Statistical Classification of Diseases and Related Health Problems ICD-10 established a set of diagnostic criteria for PCS. In order to meet these criteria, a patient has had a head injury "usually sufficiently severe to result in loss of consciousness" and then develop within four weeks at least three of the eight symptoms of the following list : headache, dizziness, fatigue, irritability, sleep problems, concentration problems, memory problems and problems tolerating stress. There is relatively little systematic research on the prevention and treatment of PCS. A systematic review published in 2010 suggested that CBT

may be effective in the treatment of PCS. However, the authors found no quality studies and call for more rigorous trials of Cognitive Behavioral Therapy for post-concussion symptoms. Other strategies include information, education and reassurance. A growing literature is indeed emerging suggesting the independent impact of expectations and coping on chronic conditions following trauma in particular for patients with whiplash and low back pain. Reassurance as provided in the context of cancer, low back pain, and mild head trauma was found to help patients in their recovery process. It is therefore possible that at least a subgroup of patients who experienced a traumatic injury may benefit from such intervention.

Selected candidate interventions

Available data, both from our studies and literature, led us to select the EMDR R-TEP procedure.

This choice was based on the following considerations:

- The absence of sufficient literature related to preventative intervention for PCLS
- The part overlap between PCLS and PTSD
- The results of our preliminary studies strongly suggesting the major role of stress in PCLS
- The consensus for the use of EMDR in early prevention of PTSD
- The growing evidence of a significant psychological component to persistent complaints.
- The failure of early Psychological Debriefing to prevent PTSD

Feasibility of candidate interventions: the SOFTER Pilot study 2

We then conducted a new pilot study intended this time to study the feasibility of stress management sessions during the ER stay with candidate interventions as selected by our literature search. To this end, we recruited 130 patients (see Figure 8 for study flowchart)

presenting at the adult ER of the University Hospital of Bordeaux with either a trauma or an inaugural acute medical condition, randomized to three arms: one arm with a psychotherapeutic Eye Movement Desensitization and Reprocessing session (EMDR, described below), an arm with a reassurance session and a control arm (usual care).

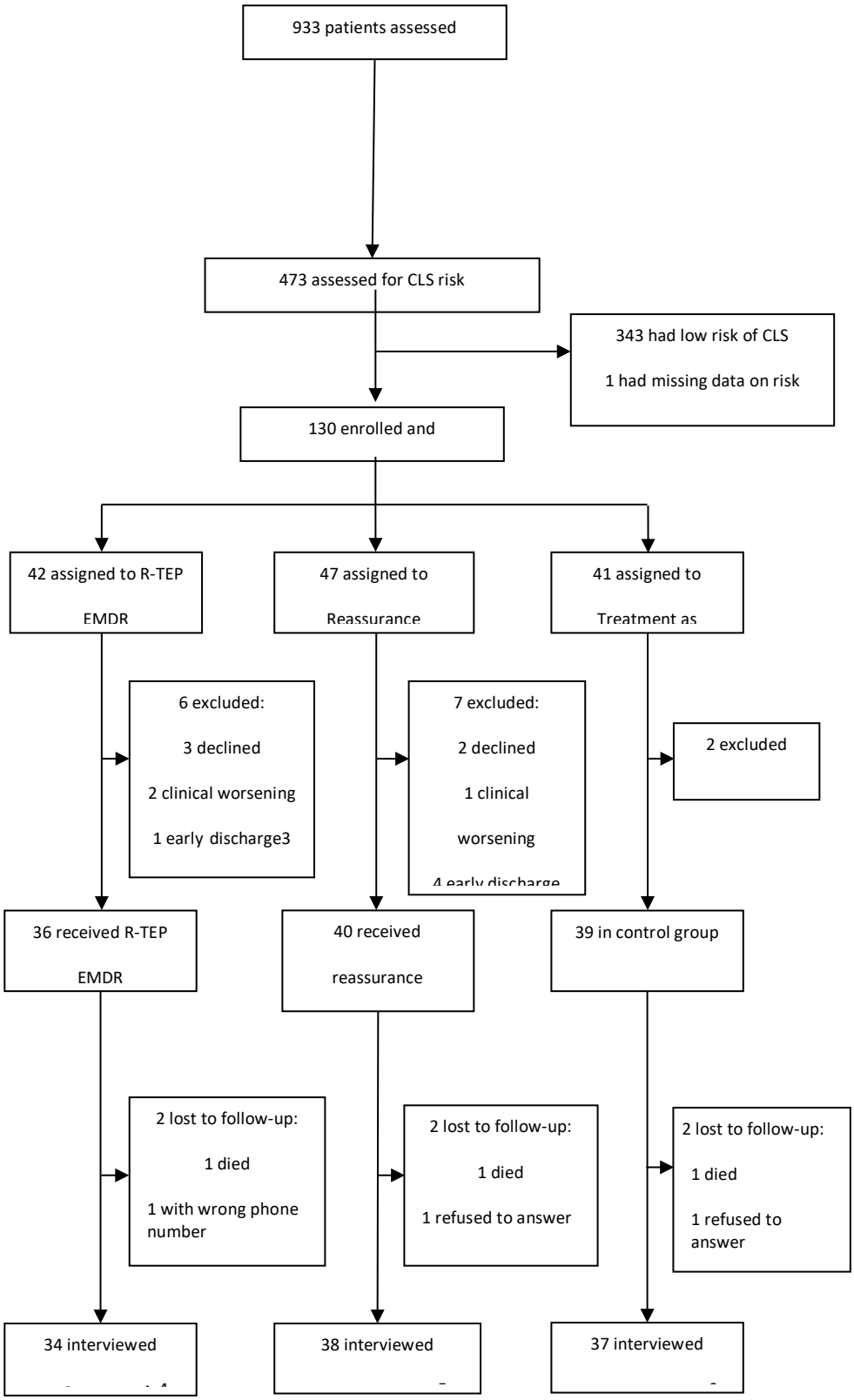


Figure 8. SOFTER Pilot Study 2 Flowchart

Among the inclusion criteria, a scoring algorithm was used to select the patients most at risk for PCLS and PTSD. This algorithm was developed thanks to the Pericles database. The recruitment and intervention phase were completed in December 2016 and the follow-up in March 2017. Results show that the implementation of EMDR in the context of an emergency service for patients selected on vulnerability criteria is feasible. Only one patient could not receive the EMDR intervention for logistical and organizational reasons (The EMDR session requires the use of an isolated room for about one hour).

Participants in each randomization group are described in Table 21.

Table 21: Sociodemographic characteristics of the study population and evaluation of principal and secondary outcome.

	R-TEP EMDR (N = 34)	Reassurance (N = 38)	Control (N = 37)
Population characteristics			
Age, year –Median (IQR[1])	49 (34.5 – 67.75)	41.5 (22 - 58.75)	46 (30 - 64)
Gender – N (%)			
Male	5 (14.7)	3 (8.1)	6 (16.2)
Female	29 (85.3)	35 (92.1)	31 (83.8)
Event type – N(%)			
Injury:	16 (47.1)	20 (52.6)	10 (27)
Road traffic crash	5	4	2
Fall	9	10	4
Other accidents[2]	1	4	4
Assault	1	1	0
Suicide attempt	0	1	0
Medical:	18 (52.9)	18 (47.4)	27 (73)
Neurology	10	2	15
Abdominal	2	8	6
Other[3]	6	8	6
Pain intensity, NRS – Median (IQR[1])			
Mean score at admission	5.5 (4-7)	6 (3 - 7)	5 (3 - 7)
Mean score at discharge	3 (0.25 - 5)	5 (0 - 6)	4 (0 - 7)
Intensity of stress, NRS[4] – Median (IQR[1])			
Mean score at admission	4 (2 - 6)	3 (1 - 7)	5 (2 - 7)
Mean score at discharge	2 (1 - 3)	2.5 (1 – 4.75)	4 (1 - 6)
Odds of recovery, NRS[5] – Median (IQR[1])			
Mean score at admission	10 (7.25 - 10)	8.5 6 - 10)	10 (6 - 10)
Mean score at discharge	10 (8 - 10)	9.5 (7.25 - 10)	10 (7 - 10)
Symptoms reported at admission (past 12 months) – N (%)	20 (58.8)	20 (52.6)	15 (40.5)
Poor concentration	22 (64.7)	28 (73.7)	21 (56.8)
Restlessness	29 (85.3)	32 (84.2)	26 (70.3)
Energy loss	17 (50.0)	21 (55.3)	16 (43.2)
Anxiolytics consumption			
Self-rated satisfaction for ER stay, NRS – Median (IQR)	9.5 (8 - 10)	8.5 (7.25 - 10)	8 (6 - 10)

The 3-month follow-up interview by interviewers blind to the intervention group enabled us to compute the proportion of patients with self-reported PCLS and PTSD symptoms (See figure 3 and 4). The comparison strongly suggests a superiority of EMDR intervention to usual care and to reassurance, both for PCLS and PTSD. Group comparison between reassurance and usual care group suggested an impact of reassurance for PCLS and not for PTSD.

Comparison of self-assessed stress levels between admission and discharge are consistent with the observational results found in SOFTER pilot study 1 that showed an association between a decreased stress level during ER stay and 3-month PCLS (see Figure 9).

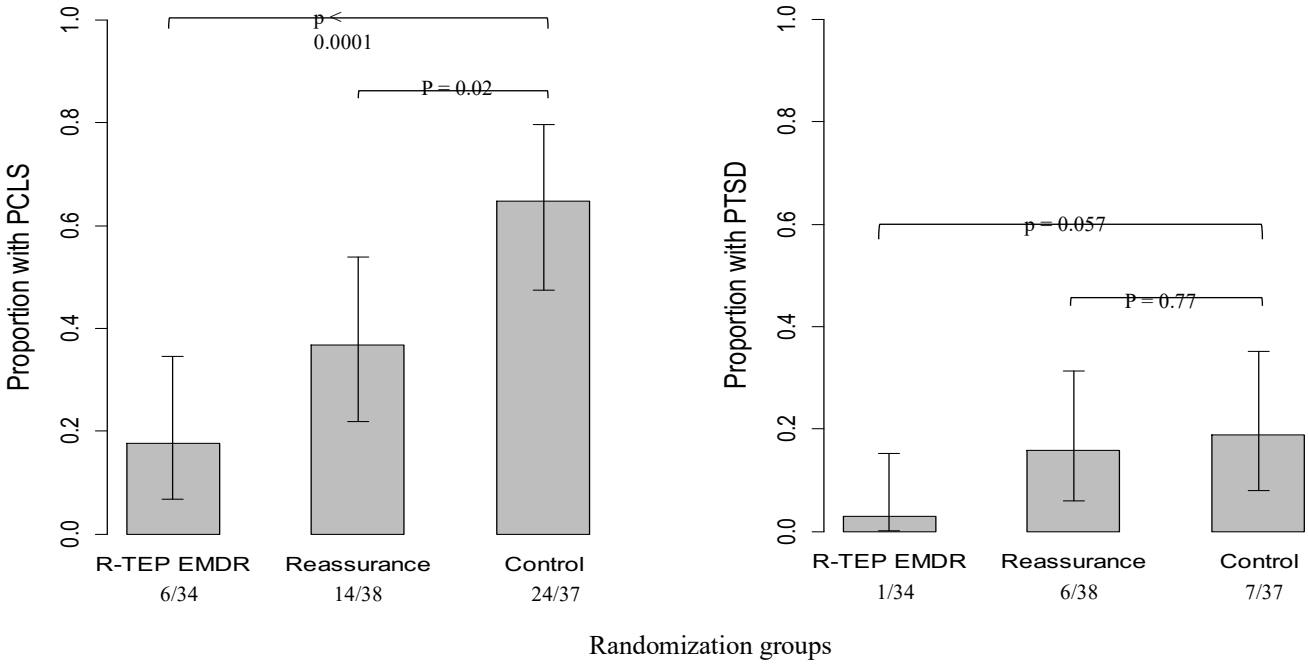


Figure 9: Outcomes from follow-up interview at 3 months (bars represents proportions: number of patients with condition / number of patients in randomization group)

The SOFTER 3 randomized trial

Because of the promising results of the SOFTER 2 trial, the team decided to launch The SOFTER 3 randomized trial, a bi-centric (Bordeaux and Lyon, France) randomized controlled trial to compare the impact on PCLS and PTSD of early EMDR R-TEP Intervention and usual care for patients presenting at the ER. The main exclusion and inclusion criteria are the same as those defined for the SOFTER 2 trial. The score threshold used to screen patients at risk of PCLS was

however set to 2 instead of 3. According to data collected during the Pericles study, this corresponds to a risk of 47% of PCLS at 3 months, instead of 65% for a score of 3.

The study aims to recruit 223 patients in each group. The recruitment started on January the 15th, 2018 and the follow-up is expected to be completed by November 2018.

SOFTER 4 Study rational

Assessing the impact of an effective implementation of early psychological care provided by therapist in the ER

Promising results of early EMDR intervention on PCLS at three months have been shown, suggesting that the availability of psychological care at the ER will be useful. The actual impact of such offer of health care service remains to be measured. Several factors may modulate the impact of such a measure that leaves uncertain the extent of its public health benefit.

Improving the selection of at-risk patients

One of the main unknown parameters of the SOFTER 2 and 3 trials is the fact that the score used for the selection of patients with a high risk of PCLS was developed from data collected during the Pericles study which included only injury patients. The SOFTER 2 trial was conclusive using this score despite the fact that non-injury patients were also included. As a matter of fact, the impact of EMDR on PCLS prevention appeared to be higher for those non-injury patients. Subgroup sample sizes were however too small to conclude. A proper definition of a selection score remains to be done to make sure that the ER patients' selection for preventive intervention is optimal.

The most appropriate study design for such an objective is to follow a cohort of ER patients and assess the main risk factors for PCLS 3 months later. For this purpose, all consecutive patients need to be asked to participate a study and fill a risk factor questionnaire, irrespective of their risk level of PCLS.

Measuring the cost-benefit ratio of the intervention

In order to help health authorities to appreciate the relevant of implementing an offer of psychological care in ER, a cost benefit analysis needs to be conducted.

An additional implementation trial is therefore necessary in order to test the actual impact and cost of an offer of psychological EMDR-based care at the ER.

Study objectives

Primary Objective

To assess the impact of the effective implementation in ER of an early intervention provided by a trained psychologist on PCLS incidence 3 months after attending the ER

Secondary Objectives

To assess the impact of the effective implementation in ER of an early intervention provided by a trained psychologist on PTSD incidence 3 months after attending the ER

To define an improved scoring system for selecting patients eligible for the intervention.

To estimate the cost-benefit of the intervention balancing costs due to the availability of a full-time psychologist in the ER versus cost of medicines and health care consumption due to persistent PCLS and PTSD.

STUDY DESIGN

General study design

The study is a multi-site cluster randomized cross-over trial with two comparative groups. In each site, the control period and intervention period span over a period of 10 days (5 days for control and 5 days for intervention). The sequence of the control and intervention period will be set at random.

- The **control period** is a 5-day period during which no psychologist is available. ER cares will be provided as usual.

- The **intervention period** is a 5-day period during which trained psychologists are available in the ER and will provide a R-TEP EMDR intervention for patients selected with high risk of PCLS and who may provide psychotherapeutic care or reassurance to other patients should they be identified in need of help.

- The **warm-up period** will be of 2 days. Experience from previous studies showed that therapists need a few days to get used to the ER environment. The consecutive 5 days allocated for the intervention will then be preceded by a 2 days period during which the therapist will be present in the ER and will be asked to follow the same protocol as the one of the intervention days. Data from this warm-up period will not be included in the main analysis.

- A **wash-out period**, for a duration of 5- or 9-days regarding cluster control/intervention sequence (see figure 2 for details) will separate each control or intervention period.

In either intervention or control period, all consecutive patients will be proposed to participate in the study that consists in:

(i) completing an inclusion questionnaire to describe reasons for ER attendance, current stress level and preexisting health and symptoms and, in the intervention group, to assess PCLS risk level;

(ii) being contacted 3 months later to assess PTSD (using the PCL-5 checklist) and PCLS (using Rivermead criteria).

The national health insurance ID will be collected in the inclusion questionnaire and sent to the national database (SNIIR-AM). This will allow to compare health care consumption levels in the two groups.

Primary outcome

- Proportion of patients at 3-month with PCLS as measured with the Rivermead Post concussion Symptoms Questionnaire.

Secondary outcome

- Proportion of patients at 3-month with PTSD as measured with the PTSD Checklist-5

- List of predictive factors of 3-month PCLS in an attempt to improve the current PCLS risk scoring system

- Health care consumption (medicinal drugs, medical consultation and hospitalization) in the 3 months following inclusion, as recorded in the national insurance system database (SNIIR-AM).

Randomization and blinding

In cluster randomized cross-over trials, clusters receive interventions in a randomized sequence over time. In the present study, each cluster (site) will be randomly assigned to one of the two sequences: intervention then control or control then intervention.

Centers will be randomly assigned to: i) control period then intervention period; ii) intervention period then control period.

The only possible blinding procedure will be implemented for data analysis.

Participating sites selection

Statistical power analysis (see below) indicates that we need to include a minimum of 6 clusters with a patient enrollment rate of at least 70 per days in each site. We built the study sample based on the participation of French sites only as sites outside France cannot guaranty

their participation (they are requesting funds separately). The foreign sites will however be listed here as we hope that all or part of them will be able to join the study.

Recruiting centers in France

- Teaching Hospital of Bordeaux (cedric.gil-jardine@chu-bordeaux.fr and eric.tellier@chu-bordeaux.fr)

- Teaching Hospital of Lyon (karim.tazarourte@chu-lyon.fr)

- Teaching Hospital of Toulouse (charpentier.s@chu-toulouse.fr)

- Teaching Hospital Louis Mourier, AP-HP (nicolas.javaud@aphp.fr)

- Teaching Hospital of Beaujon (philippe.decq@aphp.fr)

- Hospital of Libourne (juliane.bosc@hotmail.fr)

SELECTION AND ENROLLMENT OF PARTICIPANTS

Inclusion Criteria

All patients coming or brought to the adult ER of one of the study sites. The inclusion criteria are as follows:

Age 18 and more

Conscious, able to provide informed consent, able to understand study procedures and to comply with them for the entire length of the study. Speaking French.

Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation.

Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

Inability or unwillingness of individual or legal guardian/representative to give written informed consent.

Inability or unwillingness to be contacted for 3-month follow-up interview

Study Enrollment Procedures and screening procedures

PCLS risk assessment pre-enrolment procedures:

The identification and recruitment of potential study participants is carried out by emergency personnel under the supervision of the project manager as soon as the patient's condition permits and in all cases after the initial clinical evaluation conducted in the framework of the usual care. First oral consent is then being sought to participate in the assessment stage that consists in selecting patients with a high risk of PCLS.

A set of three items will be recorded for each injured patient including: gender (+1 for female), perceived health status prior to admission (Excellent, very good: 0; Good: +1 Poor: +2; Bad: +3), anxiolytics/antidepressants current use (+1 if yes).

To be enrolled in the study patient will need to score above a pre-defined threshold of 3 and more on the scoring procedure based on the three items and designed to select patients at risk for PCLS.

The score has been developed using data from the Pericles study and validated on data of the SOFTER Pilot 1 and 2 study.

Inclusion enrollment procedure:

Selected patients will be presented with the objective and procedures and invited to sign an informed consent form.

A screening log will be filled in to describe reasons for ineligibility and for non-participation of eligible candidates.

STUDY INTERVENTIONS

Interventions administration, and Duration

Intervention period: Early EMDR: EMDR Recent Traumatic Episode Protocol (R-TEP)

During the intervention period, trained psychologists are available in the ER and will provide a short early 1-hour R-TEP EMDR intervention for patients selected with high risk of PCLS. Patient's selection will be conducted using a score developed in previous studies [10,59]. When no high-risk patient is identified, the therapist could assess other patients and treat them if judged necessary. In this context, they could provide either a R-TEP EMDR or short intervention such as reassurance according to therapist assessment. Three trained psychologists will be settled in the ER from 7.00 to 0.00; i) 7.00 to 14.00; ii) 14.00 to 21.00; iii) 21.00 to 0.00. Otherwise, ER cares will be provided as usual. - A warm-up period of 2 days will precede the intervention period in order for the therapist to get used to the ER environment. Due to the situation and conditions in the Emergency Department, a brief EMDR intervention, utilizing the Recent Traumatic Episode Protocol (R-TEP), was selected. The SOFTER Pilot 2 and 3 studies showed R-TEP EMDR sessions are feasible in the context of the ER and last one hour. This protocol is specially designed for victims of recent traumatic events. It incorporates and extends Francine Shapiro's early EMDR intervention protocols into an integrative and comprehensive intervention taking into account the fragmented, unconsolidated nature of recent traumatic memories and the need for safety and containment. Following the eight phases of the standard EMDR protocol it introduces four new procedural concepts (Traumatic Episode, Episode Narrative, "Google Search/ Scan" for identifying disturbing fragments and Current Trauma Focused processing strategies).

These sessions are carried out by a trained psychologist who are part of a team specialized in the management of patients with psychological trauma. Training and intervention coordination and standardization will be carried by the Centre d'Accueil SPEcialisé dans le

Repérage et le Traitement des Traumatismes psychiques (CASPERTT) of the Cadillac hospital center (Gironde, France).

Control period: Treatment as usual

Patients in the treatment as usual group will be medically and psychologically attended to by ER staff with no intervention of the study therapists.

Adherence Assessment

Adherence to the study regimen will be defined as the extent to which participants comply with study intervention requirements. A log of intervention sessions will be recorded for each participant with duration, completeness and patients' satisfaction. This log will be regularly reviewed by the Steering Committee and be part of the decision to continue or discontinue the study.

STUDY PROCEDURES

Study Calendar

Duration of enrollment: 6 months

Follow-up : at 3 months by telephone interview

Total study duration: 12 months

Schedule of Patient Evaluations

Assessment	Baseline, Enrollment, (Day 0)	Follow-up: 3-month Visit ((M3)	During the analysis period
Eligibility assessment	x		
Informed consent for Screening			
Informed consent for enrollment	X		
Demographics	X	X	
Stress and disturbance evaluation	X		
Recruitment log	X		
General Physical Examination	X		
Current Medications	X	X	
PCLS (Rivermead)		X	
PTSD (PCL)		X	
Adverse Events	X	X	
Health care consumption from SNIIR-AM			x

Description of Evaluations

Screening evaluation

Consenting procedures

A written informed consent will be sought from eligible patients to participate in the study. The investigating physician informs the patient, explain further study procedures and answers all questions the patient may have regarding the objective, the nature and constraints, the anticipated risks, and the expected benefits of the study. The physician also explains to the patient their rights in the context of a clinical study. If the patient agrees to participate: a copy of the patient information letter and the consent form are then given to the participant by the investigating physician.

PCLS risk assessment

If the informed consent is obtained, then a risk assessment form is immediately filled-in on the Shared Study Monitoring System (SSMS) by the medical ER staff in charge of the clinical evaluation. The outcome of the risk assessment procedure is then explained to the patient.

Baseline form at admission

For participants who are successfully assessed for eligibility and are enrolled into the study, a baseline form is filled in. Baseline evaluation includes:

- Demographics (age, sex, education, occupation, marital status)
- Alcohol, drugs and tobacco addictions/consumptions
- Admission causes
- Self-assessed health
- Symptoms before admission according to the Rivermead Post-concussion Symptoms Questionnaire (RPQ) (list of 8 symptoms)

- History of PTSD diagnosis
- History of serious injuries
- History of chronic pain
- Current medication and psychotropic medicines used in the past 12 months
- Telephone contact for 3-month interview
- Self-assessed acute pain level
- Self-assessed stress level
- National social security number (NIR)
- Baseline form at discharge
- An evaluation is performed at discharge from the ER including:
- Admission causes
- Self-assessed stress level
- Self-rated satisfaction for ER stay
- Self-assessed acute pain level
- Follow-up interview at 3 months
- 3 months after enrolment, patients will be contacted for a 15 minutes standardized interview to measure primary and secondary outcomes. Questionnaires items are listed below:
- PCLS (Rivermead Post concussion Symptoms Questionnaire)
- PTDS (PTSD Checklist for DSM-5 using a validated French translation)
- Self-assessed recovery
- Current medication
- Self-assessed health

- Self-assessed chronic pain level
- Self-assessed stress level
- Addiction assessment

Premature withdrawal and withdrawal of consent from the study

The participant has the right to withdraw from the research at any time. If the participant decides to withdraw from all components of the study, he/she is no longer followed up in the protocol.

Premature withdrawal from the research strategy must be notified promptly to the Steering committee. The reasons and the date of the withdrawal must be documented.

The withdrawal of consent is a decision of a participant to reconsider his/her decision to participate in the research and to assert his/her right to withdraw consent at any time during follow-up and without any resulting prejudice thereby and without having to justify it. When a participant withdraws consent for participation in the research, data already collected for this patient will be kept for analysis.

Protocol deviations

Deviations can affect all aspects of a research protocol: inclusion, monitoring, measurement of endpoints, treatment process. All must be documented by the investigator and discussed by the Steering Committee and Data management Centre.

Even in the event of deviation from the protocol, participants must be monitored until the date planned in the protocol.

Personnel involved

Recruitment of patients

The task of patients' recruitment will be assigned to nurses of the ER who will be hired on overtime hours. The pool of nurses already involved with the ER is sufficient to recruit a number of them for two periods of 5 and 7 days. The benefit if such a solution will be to work with a staff who knows and is already used to work in the context of the emergency ward. A nurse of the study will be available 24/24 during the intervention and the control period, serving to one of the following shifts: 7 am- 2 pm, 2 pm—9 pm or 9 pm-7 am. This nurse will be in charge of patients' recruitment and questionnaire.

Psychologists

During the intervention periods, a psychologist with full training in EMDR/R-TEP EMDR will be available in the ER from 7 am to 12 pm. This will correspond to 3 shifts: 7 am to 2 pm, 12 am to 7 pm and 5 pm to 12 pm. The psychologist will be in charge of recruited patients' assessment (for the risk of PCSL), of the assessment of the needs of other patients, and of providing R-TEP EMDR intervention to patients selected as high risk. In case of time constraints, the latter task will prevail on the assessment of patients with low PCLS risk.

3-months interviews

The 3-months interviews will be subcontracted to a CRO with call center expertise in the field of health and clinical research. Previous experience from SOFTER 2 and 3 shows that a follow-up rate of 70-80% can be achieved. This requires planning several calls per participants with the possibility to reschedule interviews according to participants availability and convenience.

Monitoring tools

Computer assisted tools will be developed by an IT engineer from INSERM U1219.

Data analysis

Data analysis will be performed by a trained statistician under the supervision of Emmanuel Lagarde.

Study recruitment monitoring

A project coordinator will be recruited for 12 months to monitor the recruitment periods. The coordinator will have to move in each study center and be on site on each intervention and control days. He/she will also be in charge of data quality monitoring.

Psychologists monitoring

Juliane Tortes-James will be in charge of psychologists training and coordination. She is an EMDR European coordinator, part of the CASPERTT service, Centre Hospitalier de Cadillac

STATISTICAL CONSIDERATIONS AND PLAN FOR ANALYSIS

General Design Issues

The general design of the trial was set to answer the following questions:

Should psychotherapists with training in early short EMDR be available in the ER in order to prevent long term PCSL and PSTD?

The main statistical hypothesis is:

The proportion of patients with PCSL at 3-month is lower among those recruited during the intervention periods as compared to those recruited during the control period.

Sample Size and Randomization

We considered that PCLS risk in the high-risk population (score > 2, about 20% of the ED admission) will be around 65%, during control period, 45% during intervention period and around 20% among other patients during both weeks. Thus, the global prevalence of PCLS at 3 months for “control period” and “intervention period” patients would be 33 and 29%. At the national scale, such a decrease of 4% in the prevalence of PCLS 3-months after an ED cares could represent more than 750.000 patients who will not suffer from these disabling symptoms.

Regarding data from previous studies we conducted, we assumed an intraclass correlation coefficient of 0.001, an intra- period correlation of 0.002 and a mean cluster size for one period of 350 patients, the cluster design effect would be of $D = 0.649$. To assess superiority of the "Psychologist implementation group," with 1- sided alpha = 5 %, beta = 20 %, a decrease of 20% in the high-risk population, 4130 subjects and 6 clusters are needed. Considering 20 % patients lost for follow-up, a total of 4956 patients is needed to the superiority of the intervention.

Interim analyses and Stopping Rules

No interim analysis is planned. The study can be stopped by the DSMB for safety issues or because of poor study performance (losses-to-follow-up>25%), poor quality control, slow accrual (recruitment rate<75% than expected), SAE advocated as caused by the intervention, increased frequency of AE. Such findings are presented to the DSMB to review the events to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the DSMB. The findings are used to determine what steps will be taken.

Outcomes

Primary outcome

-Proportion of patients at 3-month with PCLS as measured with the Rivermead Post-concussion Symptoms Questionnaire.

Secondary outcomes

- Proportion of patients at 3-month with PTSD as measured with the PTSD Checklist-5

- List of predictive factors of 3 months PCLS in an attempt to improve the current PCLS risk scoring system

- Health care consumption (medicinal drugs, medical consultation and hospitalization) in the 3 months following inclusion, as recorded in the national insurance system database (SNIIR-AM).

Data Analyses plan

Main hypothesis

The proportion of patients with PCLS at 3-month will be compared between intervention and control periods.

An unweighted cluster-level summary regression will be used to test the main study hypothesis as it was recently shown by Morgan and colleagues to perform best overall to maintain an error rate close to 5% in scenarios where extra within-period correlation is present.

Secondary analyses

Proportion of patients at 3-month with PTSD

This outcome will be analyzed in the same manner as the primary outcome.

Risk factors for 3-month PTSD and PCLS and new screening tool development

This outcome will be assessed for univariate analysis using Fisher test for categorical variables and Wilcoxon test for continuous variables. A multivariable logistic regression will provide association between variables and either PTSD or PCLS to define risk factors.

The cohort of the control period will be randomly divided between creation and validation cohort (respectively 2/3 and 1/3 of the participants). Beta coefficients derived from final model of multivariate logistic regression in the creation cohort will be used to compute a score for each variable in the screening tool. ROC curves will assess the accuracy of the proposed screening tool. Diagnostic performance will be assessed with negative predictive value and positive predictive value.

Cost-benefit analysis: health care consumption versus costs for therapists

We assume that the intervention is cost saving from a social perspective in France.

Three types of cost are considered: (i) health care expenses, (ii) implementation costs of the intervention (psychologist working hours) and (iii) opportunity cost of sick leaves.

Data extraction and matching

- Health care consumptions (all kinds of care with reimbursement are included: inpatient, outpatient, medicines …) will be collected through claims data of the national health insurance (SNIIR-AM). The national health insurance ID collected at the inclusion will be used as the matching variable.
- Implementation costs of the intervention will be evaluated thanks to a micro-costing approach in each French center (direct observation of the time devoted by psychologists to the intervention).
- Sick leaves will be collected by questionnaire (at three months) and valued by the patients' incomes.

Analysis

Total costs with and without intervention will be compared during the follow-up period. Statistical tests (H0: the intervention is cost saving) will be implemented considering sampling uncertainty (estimated through bootstrap sampling) and uncertainty of the micro-costing approach (using gamma distribution for the implementation costs).

SAFETY ASSESSMENTS

The adverse events / incidents will be reported to the different circuits of health vigilance depending on the product or the procedure concerned (pharmacovigilance, material vigilance, haemovigilance ...).

INTERVENTION DISCONTINUATION

Criteria for discontinuing the study will be discussed during the DSMB meetings. Temporary discontinuation is a possible option if one need to wait for a short period of time to assess patients' conditions (typically a few days for example for Acute Stress Disorder).

Subjects may withdraw voluntarily from participation in the study at any time and for any reason. Participants continue to be followed, with their permission, even if the study intervention is discontinued.

Safety data on any subject discontinued due to an AE or SAE will be collected and recorded. Every effort will be made to undertake protocol-specified safety follow-up procedures. If voluntary withdrawal occurs, the subject is asked to continue scheduled evaluations, and to complete an end-of-study evaluation.

Quality control and quality assurance

Instructions for data collection

All information required by the protocol must be recorded on case report forms (CRF) and questionnaires (in the appendix section).

An explanation must be provided for any missing data. The data must be collected as it is obtained and transcribed in these files clearly and legibly.

Appropriate methods for maintaining confidentiality of participant records will be implemented in the SSMS.

Quality control

A clinical research associate mandated by the sponsor will be present in each study center at the period of operation (intervention, control, warm-up and wash-out period). During these visits, and in accordance with the monitoring plan, the following elements shall be reviewed:

Informed consent,

respect of the research protocol and procedures defined in it,

quality of the data collected in the report file: completeness, accuracy, missing data, consistency of data with source documents (medical records, appointment books, original laboratory results, etc.).

Any visit shall be subject to a written monitoring report.

Protocol deviations will be captured, documented, and reviewed by the Steering Committee.

Data management

The Steering Committee will ensure of quality and standardization of all data collection procedures.

Right of access to personal data and source documents

Access to data

The sponsor is responsible for obtaining the agreement of all parties involved in the study so as to guarantee direct access to study site, source data, source documents, and reports so that the sponsor may control data quality and perform an audit.

Investigators will make available the documents and individual data strictly required for monitoring, quality control and audit of the biomedical study to persons having access to these, in accordance with the statutory and regulatory provisions in place (the French Public Health Code).

Source data

Any original document or object that allows the existence or accuracy of a data point or information recorded during the study to be proved is defined as a source document.

Confidentiality of data

In accordance with the statutory provisions in place (the French Public Health Code), persons having direct access to source data will take every precaution required to ensure the confidentiality of information relating to investigational medicinal products, studies,

participants, notably concerning the identity of these, as well as the results obtained. These persons, like the investigators themselves, are subject to professional confidentiality.

During the clinical study or at its conclusion, data collected regarding participants that is sent to the sponsor by the investigators (or all other specialists involved) will be anonymized. At no point should the names of participants or their address appear unencrypted.

Only the first letters of the first name and full name of included patients will be recorded, followed by a specific research number indicating the rank of inclusion and the origin of the investigator site.

The sponsor will ensure that each study participant has given his/her consent for access to his/her personal data that is strictly required for study quality control.

ETHICAL CONSIDERATIONS

The sponsor and the investigator(s) undertake to ensure that the research is conducted in compliance with Law no. 2012-300 on research involving human participants of 5 March 2012, in accordance with Good Clinical Practices (I.C.H version 4 of 9 November 2016 and Decision of 24 November 2006), and the Declaration of Helsinki (which can be found in its entirety on the website http://www.wma.net).

The research shall be conducted in accordance with the present protocol. Except in emergency situations requiring specific medical procedures, the investigator(s) undertake(s) to comply with the protocol in all respects, particularly with regard to the collection of consent, and the reporting and monitoring of serious adverse events.

This research project will start when receiving a positive endorsement of the CPP (Comité de protection de Personnes).

The CHU of Bordeaux, sponsor of this research, has taken out a civil liability insurance contract with Gerling-Biomedicinsure in accordance with the provisions of the public health code.

The data recorded in the course of this research shall be subject to computer processing on behalf of INSERM U1219 Bordeaux Population Health Research Center in compliance with Law No. 78-17 of 6 January 1978 relating to data processing, files and freedoms, as amended by Law 2004-801 of 6 August 2004.

This research project falls within the framework of the "Reference Methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the amended law of 6 January 1978 relating to information, files and freedoms. This change was approved by the decision of 5 January 2006, updated on 21 July 2016. The INSERM U1219 Bordeaux Population Health Research Center has signed a commitment to comply with this "Reference Methodology".

The research project will be registered on the website http://clinicaltrials.gov/

Amendments to the protocol

Any substantial amendment, i.e. any amendment that may have a significant impact on the protection of persons, on the validity conditions and on the results of the research, on the quality and safety of tested products, on the interpretation of scientific documents that support the conduct of the research or on its conduct methods, shall be subject to a written amendment submitted to the sponsor; the latter must obtain, prior to implementing the amendment, a positive endorsement of the CPP.

Non-substantial amendments, i.e. those that do not have a significant impact on any aspect of the research project, shall be reported to the CPP for information purposes only.

All amendments shall be validated by the sponsor and all of the participants affected by the amendment, prior to submission to the CPP.

All amendments to the protocol must be reported to the investigators carrying out the research. The investigators shall commit to respecting their content.

Any change that modifies the care of the participants, or the benefits, risks and constraints of the research shall be subject to a new information note and a new consent form, obtained through the same procedure as the one above.

COMMITTEES

Steering committee

The Steering Committee is formed by representatives of study partners. The Steering Committee's role is to provide advice, ensure delivery of the project outputs and the achievement of project outcomes

Data and Safety Monitoring Board (DSMB)

The DSMB is an independent group of experts that advises the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to (i) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and (ii) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking and voting procedures prior to initiating any data review.

The study DSMB consists in three independent experts:

One expert in the clinical aspects of the stressed/injured patient population

One biostatistician

One investigator with expertise in current clinical trials conduct and methodology.

The DSMB is appointed prior to study initiation.

ARCHIVING STUDY DOCUMENTS AND STUDY DATA

The following documents related shall be archived in accordance with the Good Clinical Practices:

- for a period of 15 years following the end of the research

The protocol and any changes to the protocol

The report files (copies)

Source files of participants who gave consent

All other documents and correspondence related to the research

- for a period of 30 years following the end of the research (all other types of research)

The original informed consent forms of participants

No displacement or destruction may be carried out without the agreement of the sponsor. At the end of the prescribed archiving period, the sponsor shall be consulted for their destruction. All data, documents and reports may be subject to audit or inspection.

PUBLICATION Policy of RESEARCH FINDINGS

Scientific communications

Analysis of data provided by the investigating center is performed by the methodology and data management center. This analysis results in a written report that is submitted to the sponsor, who transmits it to the ethics committee and the competent authority.

Any presentation, abstract, or manuscript of study results must receive prior approval from the Steering committee.

The publication of the principal results cites the name of the sponsor, all investigators having included or followed participants in the study, methodologists, biostatisticians, and data managers having participated in the study, the members of the study committee(s), and the

source of funding. The international requirements for writing and publication will be considered (The Uniform Requirements for Manuscripts, ICMJE, April 2010).

Communication of results to participants

In accordance with act No. 2002-303 of 4 March 2002, the patients will be informed, at their request, of the overall results of the study.

Transfer of data

The collection and management of data is carried out by the methodology and data management center. The conditions for data transfer of any or part of the study database are decided by the study sponsor and are the subject of a written contract.

14.4.4. État d'avancement

L'étude SOFTER-IV a été acceptée pour financement par la DGOS dans le cadre du Programme Hospitalier de Recherche Clinique National 2018. Actuellement, le protocole de l'étude est en cours de soumission au comité de protection des personnes pour avis éthique.

L'étude intégrera également une analyse secondaire concernant les facteurs associés à l'existence d'une douleur chronique à trois mois en collaboration avec l'Institut Français des Sciences et Technologie des Transports, de l'Aménagement et des Réseaux (IFSTTAR) de l'université de Lyon.

15. Conclusion

Chaque année, de nombreux patients sont pris en charge dans les services d'urgence, en France et dans le monde. L'évènement aigu qui les conduit aux urgences ainsi que les conditions de prise en charge sont autant d'éléments qui provoquent un stress important. Ceci est à l'origine des nombreux symptômes regroupés dans la littérature sous l'intitulé PCLS. Nous avons retrouvé dans SOFTER 1 que les PCLS à 4 mois sont associés au stress à la sortie des urgences. On a ensuite cherché à identifier les interventions que nous pouvions proposer au cours d'un passage aux urgences pour prendre en charge le stress des patients. Notre choix s'est ainsi porté sur l'EMDR.

Grâce à l'élaboration d'un outil d'évaluation du niveau de risque, les études que nous avons menées récemment montre qu'il est possible de conduire des séances d'EMDR au cours du séjour dans les services pour prendre en charge les patients les plus fragiles.

Par ailleurs, il apparait que de nombreux facteurs comme le niveau socio-économique des patients, leur niveau de stress et l'expérience des psychologues influent énormément sur l'efficacité de l'intervention que nous avons choisie, l'EMDR. Ces éléments seront pris en compte pour la mise en place de l'implémentation proposée dans SOFTER 4.

Enfin, les résultats actuellement disponibles suggèrent que les structures d'urgences pourraient être un lieu privilégié pour prendre en charge des patients fragiles, à risque de développer ces symptômes invalidants qui constituent le PCLS. L'opportunité offerte par le passage aux urgences pourrait avoir un impact important en termes de santé publique pour une population peu sélectionnée. A ce titre, les urgences pourraient constituer un outil puissant et performant de santé communautaire et de lutte contre les inégalités de santé.

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Annexe 1

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Stress and lasting symptoms following injury: Results from a 4-month cohort of trauma patients recruited at the emergency department

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ABSTRACT

Background: Recent research suggests that up to 20% of minor trauma patients admitted to the emergency department (ED) will suffer from non-specific chronic conditions over the subsequent several months. Thus, the present study assessed the correlates of symptoms that persisted at 4 months after an ED visit and, in particular, evaluated the associations between these symptoms and self-reported stress levels at ED admission and discharge.
Method: This study was a prospective observational investigation conducted in the ED of Bordeaux University Hospital that included patients admitted for minor trauma. All participants were contacted by phone 4 months after presentation at the ED to assess the occurrence of post-concussion-like symptoms (PCLS).
Results: A total of 193 patients completed the follow-up assessment at 4 months; 5.2% of the participants suffered from post-traumatic stress disorder (PTSD) and 24.5% suffered from PCLS. A multivariate analysis revealed an association between PCLS and stress level at discharge from the ED (odds ratios [OR]: 2.85, 95% confidence interval [CI]: 1.10 7.40).
Conclusions: The risk of PCLS at 4 months after an ED visit for a minor injury increased in association with the level of stress at discharge from the ED. These results may improve the quality of life for the millions of patients who experience a stressful injury event every year.

1. Introduction

Tens of millions of people worldwide suffer from minor injuries and many of these individuals are admitted to an emergency department (ED) [1]. Each year, this represents approximately 5 million ED admissions in France and nearly 40 million across Europe [2]. More than 90% of patients who present at an ER for a minor injury will be discharged within a few hours and do not require hospitalization [2]. However, recent research suggests that up to 20% of such patients will suffer from non-specific chronic conditions for the subsequent several months [3 7]. These conditions can include symptoms such as headache, concentration difficulties, memory loss, intolerance of stress, change in personality, and irritability [8], which, in combination, often lead to significant impairments in quality of life, fewer social and family activities, and delayed return to work or to school. If the available results are representative of an entire population, then up to 1 million people in France alone have been affected by this significant and unrecognized public health burden.

In particular, these symptoms co-occur in the context of mild traumatic brain injury (MTBI), which has been identified as post-concussion syndrome (PCS) [9]. However, several studies have suggested that the symptoms encompassed by this syndrome are not specific to MTBI and may manifest as a consequence of any type of traumatic event [10]. Another striking characteristic of these symptoms is that they appear to be more frequent when the traumatic event was stressful. For example, several of these symptoms (e.g., sleeping disorders, irritability, and trouble concentrating) are also listed as components of the hyperarousal and numbing dimensions of post-traumatic stress disorder (PTSD) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V)[DSM-V; 10].

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Moreover, in addition to the stress associated with the MTBI event itself, patients may experience stressful events during their ED stay. For example, a recent study of 474 patients found that the evaluation of a potentially life-threatening cardiac event in the ED is associated with subsequent post-traumatic stress symptoms [11]. However, data supporting the effects of non-specific stress-related consequences remain scarce.

Thus, the present longitudinal observational study of patients who were admitted to the ED of Bordeaux University Hospital for a minor injury was conducted to determine the correlates of symptoms that persisted at 4 months after the ED visit and, in particular, to evaluate the associations of these symptoms with self-reported stress levels at ED admission and discharge.

2. Methods

2.1. Study design and settings

This prospective observational study evaluated patients who presented at the ED of Bordeaux University Hospital, which serves both rural and urban areas that include a total of 1.4 million inhabitants, for a minor injury over 3 weeks from February 24th to March 15th, 2015. Clinicians interviewed patients who had recently been admitted for a minor trauma prior to their medical examination and recorded the general health conditions and current stress levels of each patient. At the end of the ED stay, the same physician interviewed the patient again. Approximately 4 months after the ED stay, a physician contacted each participant by phone to assess the occurrence of symptoms that are listed as components of PCS according to the definitions of the International Classification of Diseases, 10th Revision (ICD-10) [12], Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) [9], and Rivermead Post-concussion Symptoms Questionnaire [13] as well as symptoms listed as part of PTSD according to the DSM-IV-TR.

2.2. Participants

The present study included all patients 18 years of age who were able to answer the interviewer (Glasgow Coma Score = 15 when interviewed) and had been admitted in the first 24 h after an injury. Patients who required medical attention in the operating room or the critical care unit were excluded.

2.3. Data collected

Using a numerical scale ranging from 0 to 10, all participants were asked to describe their stress levels, expectation for recovery, and whether they felt overwhelmed by the events at the ED both at admission and at discharge. In the admission questionnaire, the participants were also asked to rate their overall health condition just prior to the event and in the previous 1 year using a 5-point Likert scale. The participants were also asked whether they had experienced any concentration problems, sleeping disorders, loss of energy, or need for anxiolytics in the past 12 months. These four items were selected because they are predictive of symptoms listed as components of post-concussion-like symptoms (PCLS) [8]. Upon discharge, the participants were also asked to rate their level of satisfaction with the ED care they were provided.

The third quartile of the self-reported stress scale distribution was used to define the stressed population at each stage of the study (admission and discharge). Subsequently, these two variables were used to classify further the participants into three categories: those who were never stressed, those who were stressed at admission only, and those who were stressed at discharge irrespective of their stress status at admission. Several attempts were made to contact all participants by phone 4 months after ED admission using the phone number provided by the patient to assess the following nine symptoms based on the DSM-IV-TR definition for PCLS [9]: headache, dizziness, personality change, sleeping disorders, tiredness, irritability, depression, anxiety, and lack of spontaneity. PCLS was defined as the presence of at least three of these symptoms and the same definition was applied to all participants, including those with non-head injuries. Thus, the term PCLS will be applied hereafter to patients even when the injury was not a head injury.

The following 14 symptoms included in the DSM-IV-TR definition for PTSD were also selected for assessment [9]: intrusion symptoms (reliving the event through upsetting thoughts, nightmares, or flashbacks and/or having very strong mental and physical reactions when reminded of the event), avoidance (avoiding activities, thoughts, feelings, or conversations that remind the person of the event; feeling numb to one's surroundings; and/or being unable to remember details of the event), negative alterations in cognition and mood (loss of interest in important activities, feeling alone, being unable to have normal emotions, or feeling that there is nothing to look forward to in the future), alterations in arousal and reactivity (feeling that one can never relax and must be on guard all the time to protect oneself, trouble sleeping, feeling irritable, overreacting when startled, angry outbursts, or trouble concentrating), and functional significance and exclusion. A diagnosis of PTSD required that one or more symptoms from each of these categories be present for at least 1 month and that the symptom or symptoms seriously interfered with leading a normal life.

2.4. Statistical analysis

Univariate analyses were performed to evaluate the associations between PCLS and the risk factors using Student s t-tests for continuous variables and Chi-square tests for categorical variables. Variables with a p-value < 0.20 were selected for the multivariate logistic analysis. Subsequently, all significant variables ($p < 0.05$) and confounders (variation of $> 20\%$) were selected using a manual step-by-step backwards selection process and then the odds ratios (OR) and 95% confidence intervals (95% CI) were estimated. Then, interactions between independent variables that were kept in the final model were tested. Additionally, sensitivity analyses were performed by changing the cut-off for the stress definition and stratifying the analysis according to location of the injured body part. All data were analyzed using SAS Software (v9.4, SAS Institute Inc©; North Carolina, USA)

3. Results

Of the 296 ED patients who provided self-assessments of stress at both admission and discharge, 103 could not be contacted at 4 months and, therefore, the present study included a total of 193 patients. Patients who were lost to follow-up did not differ from the patients who were contacted in terms of sex, age, injury location, stress levels, or health condition. The only significant difference between these two groups was in terms of satisfaction such that patients lost to follow-up were more likely to be unsatisfied ($p = 0.03$).

The third quartile of the stress scale distribution provided a threshold of 4 as a definition for the status of stressed for the present study. Accordingly, 28.0% and 17.6% of ED patients were stressed at admission and discharge, respectively. Additionally, 25.9% and 19.2% of patients reported being overwhelmed by events at admission and discharge, respectively. These two variables were highly associated with self-reported stress levels beyond the first quartile threshold ($p < 0.001$ at admission and at discharge).

Overall, 24.5% of the participants had PCLS at 4 months. The proportions of PCLS and PTSD are presented according to patient characteristics (Tables 1 and 2), ED stay experience, and stress levels (Table 3 for questions asked during ED stay and Table 4 for questions asked at 4 months). A multivariate analysis (Table 5) revealed an association between PCLS and stress at discharge from the ED (OR: 2.85, 95% CI: 1.10 7.40). Additionally, patients who expected a good chance of recovery and reported no loss of energy in the past 12 months were significantly more likely to report PCLS 4 months later. The impact of stress level at discharge on the risk of PTSD was the only correlate, albeit a very strong correlate, of PTSD (OR: 32.58, 95% CI: 3.65 290.90). A sensitivity analysis (Table 6) did not reveal any significant variations in these estimates when potential confounders, including sex, age, self-estimated chance of recovery, body part of the injury, injury type, and stress at admission, were introduced to the models.

4. Discussion

4.1. Main findings

The present longitudinal observational study evaluated patients who presented to the ED for a minor injury and were then contacted 4 months later for a self-assessment of their health status. The present results showed that the risks of PCLS and PTSD at 4 months post-injury increased with the level of stress at discharge but not at admission.

Table 1
Patient characteristics and PTSD and PCLS at 4 months.

	N	PTSD (%)	p value	PCLS (%)	P value
All	193	5.2		24.5	
Sex			<0.05		<0.05
Male	131	3.0		19.1	
Female	62	9.7		35.5	
Age			NS		NS
15 29	109	3.7		19.3	
30+	84	7.1		30.9	
Cause of admission					
Road traffic crash	30	16.7	<10 ^{2}	30.0	NS
Sport	47	2.1		12.8	<0.05
Violence	11	0.0		18.2	NS
Fall	53	5.7		34.0	0.056
Work injury	49	10.2		30.6	NS
Domestic injury	16	12.5	NS	37.5	NS
School injury	3	33.3		33.3	NS
Leisure injury	13	7.7		7.7	NS
Other	14	21.4		35.7	NS
Injury type			NS		NS
Head	26	0.0		15.4	
Bruise	83	6.0		25.3	
Wound	11	0.0		27.3	
Sprain	54	3.7		24.1	
Dislocation	2	0.0		0.0	
Fracture	5	20.0		20.0	
Body part			NS		<10 ^{2}
Head	29	0.0		17.2	
Upper limb	33	0.0		24.2	
Spine/Thorax	19	10.5		57.9	
Lower limb	92	6.5		18.5	
Multiple	8	0.0		12.5	

Table 2
Patient health prior to the injury event and PTSD and PCLS at 4 months.

	N	PTSD (%)	P value	PCLS (%)	P value
Difficulty with concentration in the past 12 months			<0.05		<10 ^{2}
No	147	2.7		19.1	
Yes	34	14.7		44.1	
Restlessness in the past 12 months			NS		<10 ^{4}
No	126	3.2		15.1	
Yes	59	8.5		42.4	
Loss of energy in the past 12 months			NS		<10 $^{-4}$
No	127	3.9		14.2	
Yes	60	8.3		45.0	
Medicine consumption for anxiety in the past 12 months			NS		< 10 $^{-4}$
No	163	4.3		19.6	
Yes	19	10.5		57.9	
Health condition before the event			NS		NS
Excellent	62	3.2		6.5	
Very good	64	5.7		25.0	
Good	37	2.7		35.1	
Fair	22	9.1		40.9	
Bad	6	33.3		83.3	
Health condition as compared to 1 year ago			NS		NS
Much better	28	7.1		21.4	
Better	30	13.3		43.3	
Identical	121	2.5		19.0	
Worse	9	0.0		33.3	
Much worse	3	0.0		33.3	
Have relatives at home that can help			NS		NS
No	15	0.0		33.3	
Yes, occasionally	36	0.0		30.6	
Yes, if necessary	137	6.6		21.9	

4.2. Strengths and weaknesses

To the best of our knowledge, this study is the first to investigate the impact of self-reported stress throughout one s stay at the ED on symptoms related to PCLS and PTSD at 4 months post-injury. Based on the typical attendance statistics of the ED at Bordeaux University Hospital, approximately 75% of eligible patients were included in this study. However, this should be considered a rough estimate because it was not possible to collect data from all potentially eligible patients due to the complex patient-flow times and spatial environment. Of the recruited patients, 35% were lost to follow-up but exhibited the same characteristics as the patients who were contacted 4 months later, except for satisfaction regarding their stay at the ED. However, it is unlikely that this difference biased the present results as there was no association between self-reported stress levels and satisfaction.

Although several tools have been designed and validated for the assessment of chronic cumulative stress, no such instruments for measuring acute stress at a given timepoint are currently available. The Stanford Acute Reaction Stress Questionnaire (SARSQ) [14] is one of the few instruments that is focused on acute stress but this measure must be administered 3 5 days after the event and, therefore, could not be used in the present study. A previous study has validated the use of a 5-point Likert scale for this purpose [15] but it

Table 3
Patient ED experiences and PTSD and PCLS at 4 months.

	N	PTSD (%)	p value	PCLS (%)	P value
Self-estimated chances of recovery at admission			< 0.05		< 10 [2]
9	142	2.8		19.0	
< 9	49	10.2		38.8	
Self-estimated chances of recovery at discharge			NS		NS
9	149	4.0		22.2	
< 9	42	9.5		30.9	
Overwhelmed by events as reported at admission			< 10 [2]		< 10 [2]
< 4	142	1.4		19.0	
4	48	14.5		39.6	
Overwhelmed by events as reported at discharge			< 10 [4]		< 10 [3]
< 4	155	0.7		18.7	
4	37	21.6		47.4	
Stress at admission			< 10 [2]		< 10 [2]
< 4	138	1.5		18.1	
4	54	13.0		37.0	
Stress at discharge			< 10 [4]		< 10 [4]
< 4	159	1.3		18.9	
4	34	23.5		50.0	
Time since admission			NS		NS
< 100 min	57	7.0		28.1	
100 to 149 min	49	6.1		20.4	
150 to 199 min	34	0.0		17.6	
200 min	53	5.7		28.3	
Satisfied by ED stay			NS*		NS*
No	23	8.7		21.7	
Yes	170	4.7		24.7	

Table 4
Questions asked at 4 months and PTSD and PCLS at 4 months.

	N	PTSD (%)	p value	PCLS (%)	P value
4-month variables					
Is there anything that you can t do anymore because of the symptoms following your accident?			< 10 [4]		< 10 [4]
No	123	1.6		16.3	
Yes	37	21.6		70.3	
No symptoms	33	0.0		0.0	
Work stoppage			NS		NS
No	95	4.2		22.1	
Yes	78	6.4		29.5	
No occupation	20	5.0		15.0	
Health condition as compared to before the event			< 10 [2]		NS
Much better	21	0.0		14.3	
Better	30	6.7		26.7	
Almost identical	98	2.0		19.4	
Worse	36	8.3		33.3	
Much worse	8	37.5		50.0	
Satisfied by ED stay			NS		NS
No	34	11.8		29.4	
Yes	159	3.7		23.3	

Table 5
Multivariate logistic models of the predictors of PTSD and PCLS at 4 months.

	PTSD*		PCLS*	
	OR	95% CI	OR	95% CI
Self-estimated chances of recovery at admission				
No	Ref.		Ref.	
Yes	0.55	(0.12 2.46)	0.28	(0.12 0.68)
Loss of energy in the past 12 months				
No			Ref.	
Yes			4.46	(1.98 10.03)
Medicine consumption for anxiety in the past 12 months				
No			Ref.	
Yes			8.22	(2.60 25.96)
Stress at discharge				
No	Ref.		Ref.	
Yes	41.43	(4.83 355.39)	3.19	(1.25 8.10)

Table 6
Multivariate analysis of the factors associated with PTSD and PCLS: Results from a logistic regression adjusted for potential confounders and the sensitivity analysis.

	PTSD		PCLS	
	OR	95% CI	OR	95% CI
Model 1				
Stress at discharge	32.58	(3.64 290.90)	2.85	(1.10 7.40)
Model 2				
Stress at discharge	40.18	(4.64 347.75)	3.08	(1.20 7.90)
Model 3				
Stress at discharge	30.84	(3.38 288.45)	3.10	(1.06 9.05)
Model 4				
Stress at discharge	32.09	(3.57 355.39)	2.50	(0.91 6.83)
Model 5				
Stress at discharge	56.43	(3.78 842.74)	3.53	(1.05 7.04)

Model 1: adjusted for sex and self-estimated chances of recovery at admission.
Model 2: adjusted for age and self-estimated chances of recovery at admission.
Model 3: adjusted for body part and self-estimated chances of recovery at admission.
Model 4: adjusted for injury type and self-estimated chances of recovery at admission.
Model 5: adjusted for stress at admission and self-estimated chances of recovery at admission.

was assumed for the present study that this number of levels would be insufficient to identify variations in stress over such a short period of time. Consequently, the patients were asked to describe their current level of stress using a 10-point numerical scale at both admission and discharge. The difference in the number of levels on the scale is likely not to have influenced the validity of this tool. In fact, there was a strong and consistent association between this measure and responses regarding whether the patients felt overwhelmed by the current events.

Recent studies, including one that assessed 1361 injury patients, have suggested that PCLS may not be specific to MTBI (10). However, even though the present authors believe that this syndrome should be renamed with no reference to the location of the injured body part, the DSM-IV-TR definition of PCLS was used in the present study so as to be consistent with previous studies. The self-reported stress levels of the ED patients were likely to have depended on several factors, including injury severity, the mental health and anxiety levels of each patient, ED affluence (stress contamination between patients), context of care delivery, duration of stay, and quality of at-

tention provided by caregivers. Although several of these factors were accounted for in the present analyses (e.g., mental vulnerability and injury severity), it was not possible to isolate all, if any, of the components of the stress triggers that may have influenced the potential long-term consequences of the participants.

4.3. Interpretation

The present study identified strong associations between self-reported stress at discharge and PCLS and PTSD at 4 months post-injury, which is interesting because these findings indicate that the early management of stress may prevent, at least in part, a very significant component of the public health burden. A multivariate analysis also revealed that loss of energy and treatment for anxiety in the year prior to ED admittance were associated with PCLS. This finding suggests that people with anxiety and mood disorders may have an increased risk of long-lasting post-traumatic symptoms, which has been previously observed in cases of military-related MTBI [16] and in trauma patients admitted to the ED [17]. The prevalence of PCLS in the present study was similar to that reported in previous MTBI studies [8,10,17 21]This indicates that these symptoms, which are described in the DSM-IV-TR as PCLS [9], are likely to be related to all injury events, as previously suggested by several authors [10,23,24], as well as other stressful non-injury medical events.

The screening of individuals who are most at-risk for PCLS using tools such as the Whittaker prediction model [25] or lists of simple symptoms [26,27] has been proposed for brain injury patients. The present results suggest that this proposal could be extended to non-head injury patients and that self-assessed stress levels should be included in the scoring systems of screening tools. However, the actual predictive performance of these tools and symptoms remains to be tested. The present results also suggest that stress during an ED stay may play a causal role in the risks of PCLS and PTSD. However, further studies will be necessary to determine whether addressing stress levels in the early stages after an event could impact long-term health. Interventions proposed for the prevention of PTSD [28 30], such as eye movement desensitization and reprocessing (EMDR) and cortisol treatments, should be tested as ED-based early prevention tools. Based on the present findings, our research group conducted a pilot study that successfully assessed the impact of an early EMDR session on PCLS after an ED visit [31] and designed a larger bicentric randomized controlled trial that has recently ended [32]. Screening tools that can aid in the selection of candidates for these interventions can be designed based on the available results of prospective cohorts of injured patients, such as the cohort built for the present study.

5. Conclusions

Minor injuries constitute the basis of a significant number of ED visits. The present study found that the risks of PCLS and PTSD at 4 months post-injury increased with the level of self-reported stress at discharge but not at admission. These results suggest that early interventions in the ED have the potential to improve the quality of life of patients who may be at a high risk of PCLS and PTSD several months later. The next step will be to identify the best interventions for lowering stress and arousal levels in the ED and then conduct a randomized controlled trial to evaluate the feasibility and efficacy of these interventions on symptoms at 4 months after the injury.

6. Prior presentation

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[22].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributor's statement

(1) substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data for the work (all authors); and (2) drafting of the work (CGJ, SH and EL) or revising it critically for important intellectual content (all authors); and (3) final approval of the version to be published (all authors); and (4) agreement to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (all authors).

Ethical approval

The protocol was approved by the French data protection authority and the regional ethics committee. All participants gave informed consent.

Transparency declaration

The lead authors (CGJ and EL) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/NUrD3a.

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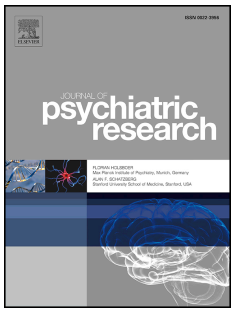
Annexe 2

Accepted Manuscript



Emergency room intervention to prevent post concussion-like symptoms and post-traumatic stress disorder. A pilot randomized controlled study of a brief eye movement desensitization and reprocessing intervention versus reassurance or usual care

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Emergency room intervention to prevent post concussion-like symptoms and post-traumatic stress disorder. A pilot randomized controlled study of a brief eye movement desensitization and reprocessing intervention versus reassurance or usual care.

Running title: Early Eyes Movement Desensitization and Reprocessing in the Emergency Department.

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Contributor's Statement

(1) substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data for the work (all authors); and (2) drafting of the work (CGJ and EL) or revising it critically for important intellectual content (all authors); and (3) final approval of the version to be published (all authors); and (4) agreement to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (all authors).

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no financial relationships with any organization that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

The protocol was approved by the French data protection authority and the regional ethics committee. All participants gave informed consent.

Transparency declaration

The lead authors (CGJ and EL) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

Abstract

Up to 20% of patients presenting at an emergency room (ER) after a stressful event will for several months suffer from very diverse long-lasting symptoms and a potentially significant decline in quality of life, often described as post concussion-like symptoms (PCLS). The objectives of our randomized open-label single-center study were to assess the feasibility of psychologist-led interventions in the context of the ER and to compare the effect of eye movement desensitization and reprocessing (EMDR) with reassurance and usual care. Conducted in the ER of Bordeaux University Hospital, the study included patients with a high risk of PCLS randomized in three groups: a 15-minute reassurance session, a 60-minute session of EMDR, and usual care. Main outcomes were the proportion of interventions that could be carried out and the prevalence of PCSL and post-traumatic stress disorder (PTSD) three months after the ER visit.

One hundred and thirty patients with a high risk of PCLS were randomized. No logistic problem or patient refusal was observed. In the EMDR, reassurance and control groups, proportions of patients with PCLS at three months were 18%, 37% and 65% and those with PTSD were 3%, 16% and 19% respectively. The risk ratio for PCLS adjusted for the type of event (injury, non-injury) for the comparison between EMDR and control was 0.36 [95% CI 0.20-0.66].

This is the first randomized controlled trial that shows that a short EMDR intervention is feasible and potentially effective in the context of the ER.

The study was registered at ClinicalTrials.gov (NCT03194386).

Introduction

According to a 2012 national survey in France, 10.6 million people came or were taken to the emergency room (ER), several times in some cases, accounting for 18 million visits recorded that year (Vuagnat, 2013). About half of these visits are the consequence of injury and more than 90% of patients will leave the service within hours, without hospitalization (Carrasco and Baubeau, 2003). Consistent recent studies (de Leon et al., 2009; Friedland and Dawson, 2001; McLean et al., 2009; Stovner et al., 2009) reveal that 10 to 20% of these injured patients for several months after the event will suffer from very diverse symptoms often associated with a potentially significant decline in quality of life, delay in return to school or work activities and change in social and family relationships. Extrapolating these figures to the annual number of ER visits in France led us think that at least one million people each year could be concerned by varying degrees of difficulty in the months following an ER visit. The potential link with the initial event, often unidentified, is all the more difficult to make as these symptoms are non-specific: headaches, concentration disorders, memory problems, stress intolerance, personality change, irritability. They have been described for more than 50 years, in the context of head injury, and thus referred to as the post-concussion syndrome (PCS). Recent studies suggest that these symptoms are not specific to brain injuries and can occur for all types of trauma (Laborey et al., 2014; Lagarde et al., 2014; McLean et al., 2009; Smith-Seemiller et al., 2003), greatly expanding the size of the population concerned. They are henceforth now frequently described as post concussion-like symptoms (PCLS) (Edmed and Sullivan, 2012).

Further, the results of a study we conducted among injured patients admitted to the ER (Lagarde et al., 2014) reinforced the hypothesis that concussion-like symptoms included ones that were very similar to those of the hyperactivation and numbing dimensions of post-traumatic stress disorder (PTSD) (*Diagnostic and Statistical Manual of Mental Disorders, Fifth edition*, 2013). This led us, with

other authors (Edmed and Sullivan, 2012), to raise the hypothesis that PCS and PTSD partly share a causal pathway in which stress plays a key role. Another interesting result of our previous study (Lagarde et al., 2014) was that a small set of measurable factors were associated with the risk of PCS and PTSD, paving the way to the development of simple assessment tools to identify a subset of high-risk patients. Consistently, several studies conducted in the past five years noted that patients' psychological vulnerability and stress experienced during and in the aftermath of the event that led to ER admission were the two most predictive elements of these long-lasting symptoms (Bernard et al., 2016; Lee et al., 2015; Losoi et al., 2016; Manners et al., 2016; Stein et al., 2016). These result prompted us to consider testing the feasibility and the effectiveness of stress management interventions during ER stay, with the hope of improving outcomes of injured patients, but also of all patients presenting at the ER and who experience stress either related to an event (accident or medical condition) or to the ER stay. While no result is available in the literature concerning the prevention of PCLS, studies evaluating interventions for PTSD prevention are sufficient in number and quality to identify credible modes of intervention. We identified eye movement desensitization and reprocessing (EMDR) (Bisson et al., 2013) as an intervention both promising and potentially suitable for use in the ER:, for which . Because of (i) the strong overlap between PTSD and PCLS, (ii) the importance of stress as reported in the ER in the sustained PCLS three months later, and (iii) the availability of a shortened adapted protocol (Jarero et al., 2011; Quinn, 2013; Shapiro, E., & Laub, B., 2013), we decided to define a first comparison group of the trial with patients recieving the EMDR intervention by trained psychologists. We selected reassurance as a second comparison group as a small number of study reports suggest a preventive potential of reassuring patients about recovery and persistent symptoms (Absolom et al., 2007; Odeen et al., 2013; Pincus et al., 2013; Schmulson et al., 2006). This second intervention group will allow us to compare the impact of EMDR with a shorter interaction by the same trained psychologists.

We conducted a pilot randomized controlled study to assess the feasibility of psychologist-led interventions in the context of the ER and to compare the 3-month rate of PTSD and PCLS among patients presenting at the ER, assessed as being at high risk for these two syndromes and randomized in three groups: a 15-minute reassurance session, a single 60-minute session of EMDR, compared with usual care

Patients and Method

Study design

Between October 1st and December 31st 2016, we conducted a randomized open-label single-center study in the ER of Bordeaux University Hospital, one of the main ERs in the region of Nouvelle-Aquitaine, accounting for more than 52 000 admissions per year. Patients were then contacted at 3 months by phone, to assess the prevalence of PCLS and PTSD symptoms.

Participants

All patients aged 18 years or more, admitted to the ER were assessed for study inclusion using a scoring tool designed to select patients with a high risk of PCLS. The score items were selected using data from a previous study we conducted among more than 1 963 injured patients presenting to the ER (Lagarde et al., 2014) and split into a training sample (2/3) and a testing sample (1/3). Items included gender (+1 point for Female), self-assessment of health conditions before admission (0 for Excellent to +3 for Poor), and history of anxiolytic use (+1). The assessment tool developed in the training sample was validated in the testing sample, and yielded an sample an area under the curve of 0.67, a positive predictive value of 51%, and a negative predictive value of 74% for a score threshold of 2. Patients with a score strictly higher than 2 therefore had a PCLS prevalence at 3 months of 51%, as compared with 29%. Exclusion criteria were altered consciousness (defined as

Glasgow coma scale score less than 14), cognitive impairment, confusion according to the attending ER physician, not speaking French, unable to be contacted by phone, requiring admission to the operating room or critical care unit. Patients admitted to the ER for an injury were excluded if the event had occurred more than 24 hours before. People admitted to the ER for a medical disorder were excluded if the problem had already been assessed or discovered during a previous ER visit. All participants provided written informed consent to participate.

Recruitment and randomization

The identification and recruitment of potential study participants were carried out between 8 am and 6 pm by the ER staff, under the supervision of the project manager, as soon as the patient's condition permitted, always after the initial clinical evaluation conducted as part of usual care. Included patients were randomized into one of three groups: (i) care as usual; (ii) 15-minute reassurance session; (iii) 60-minute EMDR session (using the EMDR recent traumatic episode protocol as described below).

The randomization plan was established before the study began. The study protocol was open-label, but the randomization group allocation was masked to the personnel in charge of calling the participants at 3 months and to the statistician in charge of the analysis.

Interventions

Care as usual

Patients in this control group were medically and psychologically attended to by ER staff with no intervention of the study psychologist.

Reassurance

During the 15-minute reassurance intervention, participants were educated regarding the response to stressful medical events. The therapist also identified, discussed, and challenged any

cognitive distortions such as unrealistic beliefs about being responsible for their injury or medical event.

The EMDR recent traumatic episode protocol (R-TEP)

Due to the situation and conditions in the ER, a brief EMDR intervention, utilizing the *R-TEP protocol,* was chosen (Shapiro, E., & Laub, B., 2013). This protocol is specially designed for victims of recent traumatic events based on Francine Shapiro's early EMDR intervention protocols (Shapiro, 1989). It takes into account the fragmented, unconsolidated nature of recent traumatic memories and the need for safety and containment. After identification, disturbing fragments are processed using a current trauma focus. Sessions were carried out by two trained psychologists from a team specialized in the management of patients with psychological trauma (Centre d'Accueil SPEcialisé dans le Repérage et le Traitement des Traumatismes psychiques (CASPERTT) of the Cadillac hospital center (Gironde, France)).

One of the two psychologists was present every day of the study and performed either an EMDR or reassurance session. No specific room was allocated to the study. The intervention sessions could be performed in any available closed treatment room, at the bedside. The psychologist had to make sure that no specific care was needed in the following hour (15 minutes for reassurance) before starting the intervention.

Data collection during ER stay

Participants were asked at ER admission and discharge to describe, using 0-to-10 numerical rating scales, their stress level, acute pain intensity, and their expectation for recovery. In the admission questionnaire, patients were asked to rate on a 5-item scale their overall health condition just before the event, and one year earlier. Finally, they were asked in the discharge questionnaire to rate their satisfaction with the ER stay using a 0-to-10 numeric rating scale.

Measure of primary outcome: EMDR completion rates

Feasibility was assessed by the completion rate of the intervention in the EMDR group defined by the proportion of patients randomized in the EMDR group who received the intervention before leaving the ER. The reasons for noncompletion were also recorded (patient refusal, logistic problems).

Measurement of secondary outcomes: PCLS and PTSD at 3 months.

Patients were contacted by phone 3 months after the ER visit using the phone number provided by the patient during ER recruitment. Whenever needed, several attempts were made; attempts to contact a patient were interrupted when the time since admission exceeded 3 months plus one week. Symptoms were assessed with a standardized questionnaire administered by one of the investigators, none of whom were aware of the randomization group of the interviewee. PCSL was defined using the ICD-10 definition of PCS ("WHO | International Classification of Diseases," n.d.). PCLS was defined as reporting at least 3 symptoms among the following: headache, dizziness, sleeping disorders, fatigue, irritability, decreased stress tolerance, memory trouble and concentration disorders. Further, questions related to symptoms listed in the DSM-IV-TR definition of PCS and Rivermead Post-concussion Symptoms questionnaire (King et al., 1995) were added to the 3-month questionnaire in order to test the sensitivity of our results to the definition of PCS.

As regard to PTSD, because the risk assessment score was developed from a previous study we conducted using the fourth version of the diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR) (American Psychiatric Association, 2000), it was assessed using the PTSD checklist – civilian version based on DSM-IV-TR. (Blanchard, E. B., Jones-Alexander, J., Buckley, T. C., & Forneris, C. A. (1996). Psychometric properties of the PTSD checklist (PCL). Behavioral Research &

Therapy, 34, 669-673). PTSD was defined as follows: Criterion A: all patients were supposed to have been exposed to a traumatic event; Criterion B: at least one of the re-experiencing symptoms (reliving the event through upsetting thoughts, nightmares or flashbacks, or having very strong mental or physical reactions if something reminds the person of the event); Criterion C: at least three of the avoidance and numbing symptoms (avoiding activities, thoughts, feelings, conversations, people, or places that remind the person of the event; having markedly diminished interest or participation in significant activities; feeling of detachment or estrangement from others; having restricted range of affect; having sense of foreshortened future; or being unable to recall important aspects of the event); Criterion D: at least two alterations in arousal and reactivity (feeling that one can never relax and must be on guard all the time to protect oneself; trouble sleeping; feeling irritable or angry outbursts; overreacting when startled; or trouble concentrating), functional significance and exclusion; Criterion E: the duration of disturbance was more than 1 month; Criterion F: reported symptoms interfere seriously with leading a normal life.

Sample size

The sample size was planned to be able to evidence a 40% decrease in PCLS in the EMDR group as compared with the "care as usual" control group. With a 20% prevalence of PCLS in the general population as estimated from our previous study (Lagarde et al., 2014), of 70% in the high-risk population, an alpha risk of 5% and a power of 80%, we needed 32 patients in each group. Anticipating a 10% rate of loss to follow-up, the protocol aimed to include 36 patients per group.

Statistical analysis

Primary outcome analysis simply consisted in observing the proportion of patients randomized to the EMDR group who successfully received the intervention. Secondary outcome analyses were performed using the chi-square test to compare the of 3-months prevalence of PCLS and PTSD

among the three treatment groups. Because the phone number was only collected at the end of the ER stay (discharge questionnaire), it was not possible to contact participants who were randomized but did not go on to receive the intervention they were allocated to. Consequently, only a per-protocol analysis could be performed.

A Mantel-Haenszel estimates of the risk ratio for the association between PCLS and treatment group stratified on the cause of ER admission (injury or non-injury) was performed. Complementary analyses were performed using DSM-IV-TR and Rivermead PCS definitions instead of ICD-10. A worst-case scenario was also analyzed in which all participants who were randomized in an intervention group but who did not complete the protocol and could therefore not be contacted 3 months later were recorded as having PCLS.

Role of the funding source, administrative and ethical clearance

The study was approved by the local institutional ethics committee (Comité de protection des personnes Sud-Ouest Outre-Mer III).

The study was registered at ClinicalTrials.gov (NCT03194386).

Results

Recruitment, follow-up and EMDR R-TEP feasibility

Of 933 patients assessed for inclusion, 13 declined and 447 were excluded either because the event occurred more than 24 hours before ER admission or because the cause of ER admission was a non-injury condition that was already known (Figure 1). Finally, we included 343 patients with a low risk of PCLS and 130 with a high risk of PCLS. Patients of the latter group were randomized. There were no differences in the characteristics of the three treatment groups except for a lower proportion of injury events in the control group (Table 2). The numbers of patients who declined participation did not differ between groups (3, 2 and 2 patients in the control, reassurance, and EMDR groups, respectively). No exclusion due to clinical state worsening or early discharge was recorded in the

control group, while respectively 3 and 5 patients were excluded for these reasons in the EMRD and reassurance groups. At 3 months, the number of patients lost to follow-up was low, with 1 patient who could not be contacted and 1 patient who died in each group (overall follow-up proportion was 95%). The patient in the control group was a 78-year-old man admitted to the ER following a hemorrhagic stroke. He was diagnosed with metastatic lung cancer and transferred to the intensive care unit where he died from massive hemoptysis 7 days later. The patient in the reassurance group was a 62-year-old man admitted to the ER because of anemia. He received a blood transfusion and returned home after 24 hours. The patient died before the three-month follow-up call. The patient in the EMDR group was a 67-year-old man who attempted to commit suicide by poisoning 5 days after the intervention. He was admitted to the intensive care unit and then transferred to the psychiatric hospital where he committed suicide by hanging the following day. The patient had been diagnosed 2 months before participating in the study with relapsed glioblastoma. The case was reviewed by an independent psychiatrist who looked for any potential link between the intervention and the suicide attempt. The review concluded that the study participation was unrelated to the suicide attempt.

All but 2 patients were contacted within 86 to 93 days after recruitment; the two remaining patients were interviewed at day 84 and day 95. As regards the feasibility of the EMDR R-TEP procedure (primary outcome of the study), no logistic problem or patient refusal related to the intervention was observed.

Intervention outcomes

Figure 2 shows the proportion of patients with PCLS (according to the ICD-10 definition of PCS) and PTSD (according to the DSM-IV-TR definition of PTSD) in the three randomization groups. In the control, reassurance and EMDR groups, the proportions of patients with PCLS were 65%, 37% and 18% and the proportions of patients with PTSD were 19%, 16% and 3% respectively. According to

the DSM-IV-TR definition of PCS, the proportions of PCLS at 3 months were 65%, 50% and 15% respectively. According to the Rivermead definition of PCS, the proportions of PCLS at 3 months were 62%, 42%, and 18%, respectively.

Because of the imbalance observed between groups as regards the type of event (63 patients with a medical event and 46 patients with injury), a complementary analysis was performed adjusting for the type of event. The risk ratio for the comparison between EMDR and control was 0.41 [95% CI 0.25-0.68] and was 0.36 [95% CI 0.20-0.66] when adjusted for the type of event (injury, non-injury). Regarding the rest of comparisons, reassurance vs control groups risk ratio were 0.56 [95% CI 0.38-0.82] and 0.52 [95% CI 0.33-0.82] when adjusted for the type of event and respectively 0.73 [95% CI 0.41-1.32] and 0.75 [95% CI 0.43-1.34] for EMDR vs reassurance groups.

In the worst-case scenario, in which patients who abandoned the protocol after randomization for reasons related to clinical worsening or early discharge were designated as having PCLS at 3 months, the proportions of PCLS (according to DSM-IV-TR definition of PCS) in the control, reassurance, and EMDR groups were 65%, 44%, and 24%, respectively. The prevalence of PCLS in the EMDR group remained significantly lower than in the control group (Fisher test p = 0.001).

Discussion

This pilot study suggests that a single session of EMDR R-TEP psychotherapy performed at the ER in the first hours following a traumatic event is feasible and has the potential to significantly reduce the rate of both PCLS and PTSD symptoms 3 months after ER admission.

These results provide several new insights and prospects for care. While EMDR psychotherapy has been shown to help in PTSD prevention and treatment (Bisson et al., 2013; Sack et al., 2016; Shapiro, 1989), similar work has not been performed for PCLS. As discussed above, while the two

conditions partly overlap, PCLS is much more frequent than PTSD (10-20% versus 5% for a population attending an ER). The use of EMDR in a high-risk population therefore carries a great potential of benefit in terms of public health and savings to society as both PTSD and PCLS are associated with costs due to treatment and to dysfunctions impacting work, education, and health care (Solomon and Davidson, 1997). To our knowledge, only one early single-session EMDR intervention (EMDR-recent Event) has been evaluated so far in a controlled comparative study and showed promising results for victims of workplace violence: none of the 19 patients who received the EMDR intervention reported PTSD symptoms after 3 months (Tarquinio et al., 2016). In this study, however, the treatment was provided 48 hours after the traumatic event and lasted between 1.5 and 2 hours, a protocol incompatible with the ER context. No such attempt has yet been made for PCLS. Price et al. (Price et al., 2014) compared PTSD symptoms 4- and 12-months after trauma among 68 patients using a Prolonged Exposure Therapy protocol, with the first session initiated at the ER, and 69 controls. Dissociation at the time of the traumatic event was associated with poorer response to treatment. It will therefore be important to verify in a larger studywhether EMDR R-TEP is suitable for this small subset of patients. Assessment of the impact of an EMDR intervention over a longer time-period (12 months) will also be needed.

No difference in prevalence of PCLS between EMDR group and reassurance group can be explained by a lack of power of the study. Indeed, the gap between the two rates suggests that the benefit of the EMDR intervention might not stem solely from the interaction with a psychologist, even if the shorter duration (15 minutes) of the reassurance session should be stressed here. The reason for the short duration of the reassurance treatment was to assure that interaction does not include elements of psychological debriefing, which has been identified as potentially harmful for the patient (Rose et al., 2002).

No exclusion due to clinical state worsening or early discharge was recorded in the control group while 3 (EMDR) and 5 (Reassurance) patients were in this situation in the two intervention groups. This may be partly related to the fact that, on average, the latter patients had to stay longer in the ER to receive the intervention than patients of the control group. To make sure this potential source of bias did not compromise our results, we performed a worse-case scenario analysis assuming that patients excluded at this stage all had PCLS. Even in this extreme situation, the 3-month prevalence of CSL remained significantly lower in the EMDR group than in controls.

The number of patients included in the study was low and replications with a larger sample size, in several other ERs, are needed before reaching a definitive conclusion. In particular, the imbalance between medical and injury patients prevented us from reaching any definitive conclusion as regardsthe impact in the latter group. In spite of the fact that we used no block randomization, there was no major between-group imbalance in sample size.

Individual factors used for the assessment of the risk of PCLS were selected from the literature and from the results of a prospective study we conducted among 534 patients with head injury and 927 patients with other nonhead injuries presenting at the ER (Lagarde et al., 2014), with no patients with non-injury reason for ER admission. It was therefore significant that 74% of the 24 non-injury patients in the control group had PCLS. Among the 10 injury patients in the control group, 4 had PCLS at 3 months.

As mentioned in the method section, we assessed PTSD prevalence at three months using the PTSD checklist – civilian version. Because criterion A in the DSM IV version refers to “threat to physical integrity of self or others”, we assumed this was the case for all patients attending the ER. However, the required extra criterion related to person’s response involving “intense fear” was clearly not met for all study participants. Consequently, the prevalence of PTSD at 3 months should probably be considered as exaggerated.

EMDR is a psychotherapy first developed by Francine Shapiro in 1987 (Shapiro, 1989), has subsequently been adapted for use for recent trauma: recent event protocol (REP) (Shapiro, E., & Laub, B., 2013), recent traumatic episode protocol (R-TEP) (Jarero et al., 2011) and EMDR-protocol for recent critical incidents (PRECI) (Schmulson et al., 2006). REP and PRECI were designed to be used between two days and six months after trauma and their suitability for intervention in the first few hours after trauma, directly in the ER, was not documented. By contrast, EMDR R-TEP was designed to be used even hours after a trauma.

As regards the procedure itself, the mechanism by which EMDR impacts memory processing is poorly understood. While not unusual for psychotherapy, knowledge in this matter will be helpful in improving its efficacy and adapting it to different contexts. For example, there is an ongoing debate on whether eye movements are a necessary part of the EMDR protocol (Jeffries and Davis, 2013). Sack et al. suggested that eye movements have no advantage compared with visually fixating on a nonmoving hand (Sack et al., 2016), and Lyaduraye and colleagues suggested that an early trauma memory reminder cue plus playing Tetris for 20 minutes in the 6 hours following a road traffic crash was associated with fewer intrusive memories in the following weeks (Iyadurai et al., 2017). These observations support the “working memory” hypothesis that stipulates that benefits occur when patients divides their attention between traumatic memory and another competing task (Theeuwes et al., 2009; van den Hout and Engelhard, 2012). It has been suggested that eye movements may be more effective because they include visual and spatial components (Jeffries and Davis, 2013). Another neurobiological model stipulates that EMDR enhances episodic retrieval through increased interhemispheric connectivity caused by eye movements (Samara et al., 2011) but this hypothesis has yet to be supported by conclusive studies. Here again, we reviewed results obtained in PTSD and no such work is available for PCLS, a condition that has yet to be properly characterized before being acknowledge as a frequent and debilitating condition.

Observed self-assessed levels of stress as recorded at admission and at discharge support our hypothesis that early stress and hyperarousal management have a large potential for proper recovery after a traumatic event. One strength of our results is the feasibility of the intervention in a place where a significant number of patients with a risk of PCLS and PTSD are concentrated, despite a limited time for assessment and treatment. The dissemination of this intervention depends, however, on the availability of trained psychologists in the ER, with additional costs that need further medical economics studies to quantify the overall cost/saving balance of such an amendment to the ER care system. In this respect, testing shortened treatment options in non-inferiority studies would certainly contribute to the future generalization of an intervention that may have the potential to ease the life of several hundred thousands people in France each year.

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Conflict of interest

The authors declare no conflicts of interest with respect to this article**.**

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Legends

Table 1: Sociodemographic characteristics of patients assessed with low and high risk of Concussion-Like Symptoms.
1 IQR : Inter Quartile Range.

Table 2: Sociodemographic characteristics of the study population and evaluation of principal and secondary outcome.
EMDR: Eye Movement Desensitization and Reprocessing. NRS: Numeric Rating Scale (0 to 10).
1 IDR: Inter-Quartile Range.
2 Domestic, sports and work-related injury, excluding road traffic injury.
3 Respiratory, cardiologic and general problems.
4 Numeric Rating Scale from 0 to 10: 0 = absence of stress, 10 = unbearable stress
5 Numeric Rating Scale from 0 to 10: 0 = No chance of cure, 10 = complete cure, return to pre-event condition

Figure 1: Study flow chart
1 Patients who provided consent and eventually declined before discharge

2 Any change in patient clinical condition precluding patient participation

3 Patients who left the emergency room before the discharge questionnaire or the interview with the psychologist, either because refused to wait for the psychologist, or because an ambulance came to pick them up for transfer

Figure 2. Main outcomes from follow-up interview at 3-months
Proportion of patients with Concussion-Like Symptoms (PCLS) and Post-traumatic stress disorder (PTSD) as defined by the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV). P values are from the double-sided Fisher exact test.

Tables

Table 1: Sociodemographic characteristics of patients assessed with low and high risk of Concussion-Like Symptoms.

	Total Sample		Risk Assessment Score				p-value
			<3		>=3		
	n	%	n	%	n	%	
Total	472	100	342	100	130	100	
Age median [IQR[1]]	40	[27 – 57]	38	[26 – 53]	46.5	[30 – 65]	0.10
Female	251	53	143	42	108	83	$< 10^{-5}$
Anxiolytic use	91	19	28	8	63	48	$< 10^{-5}$
Perceived health							$< 10^{-5}$
Poor	31	7	5	1	26	20	
Mean	130	27	43	13	87	67	
Good	198	42	181	53	17	13	
Very good	81	17	81	24	0	0	
Excellent	32	7	32	9	0	0	

1 IQR : Inter Quartile Range

Table 2: Sociodemographic characteristics of the study population and evaluation of principal and secondary outcome.

	R-TEP EMDR (N = 34)	Reassurance (N = 38)	Control (N = 37)
Population characteristics			
Age, year –median (IQR[1])	49 (34.5 – 67.75)	41.5 (22 - 58.75)	46 (30 - 64)
Gender – N (%)			
Male	5 (14.7)	3 (8.1)	6 (16.2)
Female	29 (85.3)	35 (92.1)	31 (83.8)
Event type – N(%)			
Injury:	16 (47.1)	20 (52.6)	10 (27)
Road traffic crash	5	4	2
Fall	9	10	4
Other accidents[2]	1	4	4
Assault	1	1	0
Suicide attempt	0	1	0
Medical:	18 (52.9)	18 (47.4)	27 (73)
Neurology	10	2	15
Abdominal	2	8	6
Other[3]	6	8	6
Pain intensity, NRS – Median (IQR[1])			
Mean score at admission	5.5 (4-7)	6 (3 - 7)	5 (3 - 7)
Mean score at discharge	3 (0.25 - 5)	5 (0 - 6)	4 (0 - 7)
Intensity of stress, NRS[4] – Median (IQR[1])			
Mean score at admission	4 (2 - 6)	3 (1 - 7)	5 (2 - 7)
Mean score at discharge	2 (1 - 3)	2.5 (1 – 4.75)	4 (1 - 6)
Odds of recovery, NRS[5] – Median (IQR[1])			
Mean score at admission	10 (7.25 - 10)	8.5 6 - 10)	10 (6 - 10)
Mean score at discharge	10 (8 - 10)	9.5 (7.25 - 10)	10 (7 - 10)
Symptoms reported at admission (past 12 months) – N (%)			
Poor concentration	20 (58.8)	20 (52.6)	15 (40.5)
Restlessness	22 (64.7)	28 (73.7)	21 (56.8)
Energy loss	29 (85.3)	32 (84.2)	26 (70.3)
Anxiolytic consumption	17 (50.0)	21 (55.3)	16 (43.2)
Self-rated satisfaction for ER stay, NRS – Median (IQR)	9.5 (8 - 10)	8.5 (7.25 - 10)	8 (6 - 10)

EMDR: Eye Movement Desensitization and Reprocessing. NRS: Numeric Rating Scale (0 to 10).
1 IDR: Inter-Quartile Range.
2 Domestic, sports and work-related injury, excluding road traffic injury.
3 Respiratory, cardiological and general problems.
4 Numeric Rating Scale from 0 to 10: 0 = absence of stress, 10 = unbearable stress
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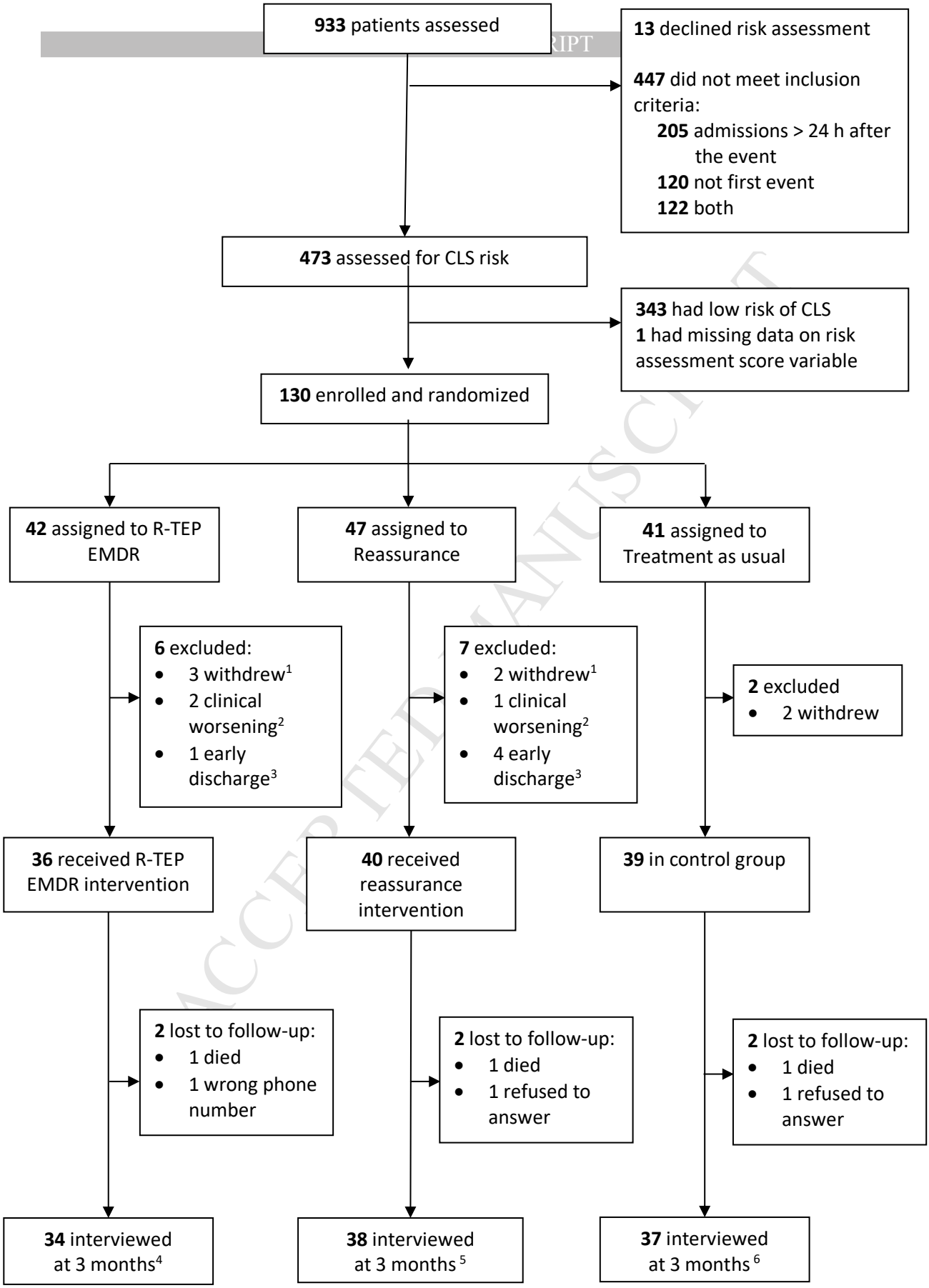
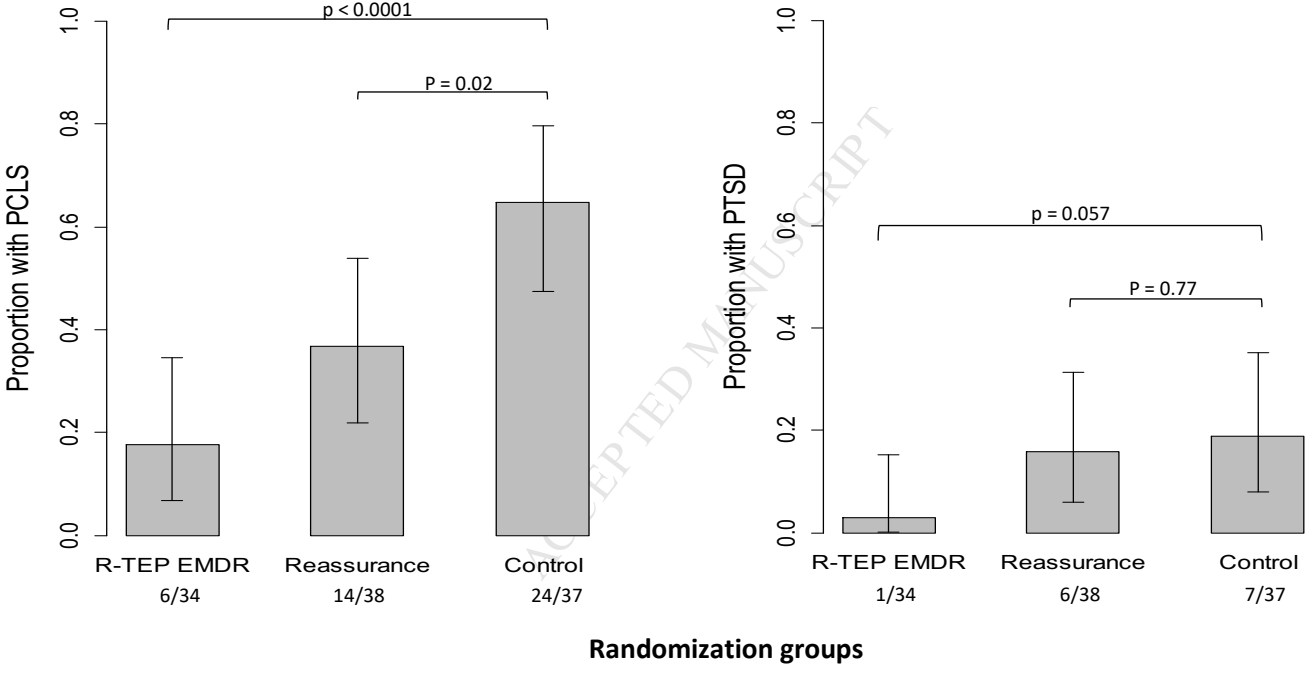


Figure 1: Study flow diagram



Emergency room intervention to prevent concussion-like persistent symptoms and Post-Traumatic Stress Disorder. A pilot randomized controlled study of a brief Eye Movement Desensitization and Reprocessing intervention versus reassurance or usual care.

Running title: Early Eyes Movement Desensitization and Reprocessing in the Emergency Department.

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Conflict of interest

The authors declare no conflicts of interest with respect to this article**.**

Annexe 3

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Trials

STUDY PROTOCOL Open Access

Prevention of post-concussion-like symptoms in patients presenting at the emergency room, early single eye movement desensitization, and reprocessing intervention versus usual care: study protocol for a two-center randomized controlled trial

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Abstract

Background: Recent data suggest that 10–20% of injury patients will suffer for several months after the event from diverse symptoms, generally referred to as post-concussion-like symptoms (PCLS), which will lead to a decline in quality of life. A preliminary randomized control trial suggested that this condition may be induced by the stress experienced during the event or emergency room (ER) stay and can be prevented in up to 75% of patients with a single, early, short eye movement desensitization and reprocessing (EMDR) psychotherapeutic session delivered in the ER.
The protocol of the SOFTER 3 study was designed to compare the impact on 3-month PCLS of early EMDR intervention and usual care in patients presenting at the ER. Secondary outcomes included 3-month post-traumatic stress disorder, 12-month PCLS, self-reported stress at the ER, self-assessed recovery expectation at discharge and 3 months, and self-reported chronic pain at discharge and 3 months.

(Continued on next page)

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(Continued from previous page)

Methods: This is a two-group, open-label, multicenter, comparative, randomized controlled trial with 3- and 12-month phone follow-up for reports of persisting symptoms (PCLS and post-traumatic stress disorder). Those eligible for inclusion were adults (≥18 years old) presenting at the ER departments of the University Hospital of Bordeaux and University Hospital of Lyon, assessed as being at high risk of PCLS using a three-item scoring rule. The intervention groups were a (1) EMDR Recent Traumatic Episode Protocol intervention performed by a trained psychologist during ER stay or (2) usual care. The number of patients to be enrolled in each group was 223 to evidence a 15% decrease in PCLS prevalence in the EMDR group.

Discussion: In 2012, the year of the last national survey in France, 10.6 million people attended the ER, some of whom did so several times since 18 million visits were recorded in the same year. The SOFTER 3 study therefore addresses a major public health challenge.

Trial registration: Clinical Trials. NCT03400813. Registered 17 January 2018 – retrospectively registered.

Keywords: Stress, Emergency department, Eye movement desensitization and reprocessing, Post-concussion-like symptoms, Post-traumatic stress disorder, Clinical trial

Background

In 2012, when the latest national survey was conducted in France, 10.6 million people reported having attended the emergency room (ER), some of whom did so several times since 18 million ER visits were recorded in the same year [1]. In general, over 90% of those attending the ER will be discharged within hours, without hospitalization [2].

Recent consistent observations [3–6] that 10–20% of injury patients will suffer for several months after the event from diverse symptoms, with a subsequent decline in quality of life that can be significant and delay or prevent the resumption of school or work activities, as well as changing social and family relationships, are of major public health consequences. Approximately 2 million people each year in France are confronted by difficulties of varying degrees whose cause is often unidentified and unrelated to the traumatic event. This link is all the more difficult to make as these symptoms appear to be non-specific, and include headaches, concentration disorders, memory problems, stress intolerance, personality change, and irritability. These symptoms have been described for more than 50 years in the context of head trauma, and were therefore referred to as post-concussion syndrome (PCS). Surprisingly, the most recent results show that these symptoms are not specific to brain injuries and can occur in other patients presenting to the ER [5, 7, 8], greatly expanding the size of the population concerned. In a cross-sectional, observational study of 31,958 high school athletes, Iverson et al. [9] also found that 19% of uninjured boys and 28% of uninjured girls reported having a symptom burden resembling an ICD-10 diagnosis of PCS; thereafter, these symptoms were frequently described as post-concussion-like symptoms (PCLS).

Recognizing that brain damage is not the main cause of these symptoms, researchers have compared patients with and without PCLS with two objectives, namely to predict their occurrence and to understand why they occur. This framework led to the major conclusion that psychological vulnerability, on the one hand, and stress experienced during and in the aftermath of the event, on the other, are the two best predictors of these lasting symptoms. This finding has been repeatedly observed in studies that assess the factors associated with PCLS [9–15].

The study of post-traumatic stress disorder (PTSD) has received renewed interest in view of the psychological pain of soldiers from Western countries returning from overseas following medical trauma, shedding light on this major public health phenomenon also affecting patients who have suffered an accident, physical assault, or an acute medical condition and whose general health remains precarious several months or years later. These studies have led to a better characterization of PTSD, including the individualization of four dimensional components, namely re-experiencing, avoidance, hyperactivation of the nervous system, and cognitive and emotional numbing [16]. Symptoms of PCLS are very similar and even sometimes exactly the same as the last two dimensions of PTSD (hyperactivation of the nervous system and cognitive and emotional numbing). This led various authors to hypothesize that PCLS and PTSD partly share the same causal pathway, in which stress plays a key role. This would be particularly relevant for prevention of PCLS, in particular because, in contrast to PTSD studies, PCLS studies include insufficient numbers and are of low quality to identify credible modes of intervention [17].

Our research team has conducted two studies in the past 10 years that enabled us to further our understanding of PCLS and to look for prevention opportunities. In 2007, we conducted a cohort study of 2018 patients with mild traumatic brain injuries and 1447 other injury

patients recruited in the adult ER of Bordeaux University Hospital (Pericles project) [8, 10]. Follow-up to 12 months provided an unprecedented database allowing for in-depth comparisons of patient subgroups. It was this study that showed that PCS, despite its name, was not specific to head trauma [8], and highlighted the importance of stress and the overlap between PCS and PTSD [8, 10]. The data obtained allows us today to compare the performance of risk assessment tools designed to select patients at increased risk of PCS from variables measured in the ER. This last point is of major importance in the preparation of this protocol.

Following the Pericles project, we conducted a pilot study to identify the factors explaining the persistence of symptoms 3 months after an injury event. The key result of this pilot study (manuscript submitted) was that the stress level reported by patients at the end of their ER stay was a powerful predictor of PCLS and PTSD, irrespective of the stress level reported on entering the ER. This important result prompted us to consider testing the feasibility and then the effectiveness of stress management interventions during an ER stay, in the hope of improving the outcomes of traumatized patients.

Results from the literature and these two studies led us to initiate a literature search for the best intervention candidates that would have the potential to lower stress levels during an ER stay.

One of the first ideas proposed for patients who experience a stressful event was to initiate a stress management procedure before the consolidation of stressful memories. This is partly why the practice of psychological debriefing, which consists of debriefing sessions conducted 2–10 days after the critical incident, has been widely disseminated. However, several critical reviews [18] and a Cochrane review [19] have concluded that this form of intervention leads to an increased rate of PTSD.

More promisingly, early exposure therapy, which is based on the extinction of fear through engagement with traumatic memories and clues, appears to be an effective treatment of PTSD [20, 21]. PTSD syndrome can be interpreted as a failure of recovery caused, in part, by failure of the extinction of trauma [22]. This is supported by research conducted on animals showing that early extinction has the potential to alter the consolidation of memory of original fear [23–25]. Rothbaum et al. [18] were the first to show the effectiveness of an extinction-type intervention (prolonged exposure) beginning in the ER in the prevention of PTSD in a sample of 137 patients randomized to three groups. The intervention also included two other sessions 1 and 2 weeks later. The same authors showed that such short-term intervention could also lower PTSD risk in patients with genes previously found to be associated with stress response [26]. Trauma-focused cognitive behavioral therapy delivered within weeks of a potentially traumatic event for people showing signs of distress was also effective in the treatment of acute stress and early PTSD symptoms, and in the prevention of PTSD [27–31].

However, the psychotherapeutic intervention that has thus far proven superior to all other methods is eye movement desensitization and reprocessing (EMDR). Conceived by Francine Shapiro [32], EMDR is an empirically validated psychotherapeutic approach that can rapidly process disturbing experiences adaptively together with the aid of eye movements or other forms of bi-lateral stimulation. Several meta-analyses and Cochrane reviews have shown that this is one of the most effective treatments for PTSD [32–35]. Treatment may be started soon after the trauma, but most often after a complaint from the patient who is already suffering from PTSD symptoms. More recently, a study by Tarquinio et al. [36] showed the effectiveness of an EMDR-based intervention initiated in the first 48 h. The target population of this study was workers who have suffered professional violence (assaults, robberies, etc.).

A study conducted in Israel showed very promising results with a single-session, early modified EMDR session provided in a general hospital inpatient and outpatient setting to 86 patients with acute stress syndrome suffering from intrusion distress following accidents and terrorist bombing attacks [37]. Half of the patients reported immediate fading of intrusive symptoms and general alleviation of distress, 27% described partial alleviation of their symptoms and distress, while 23% reported no improvement. At the 4- and 6-month follow-up, the immediate responders in the terror victims group remained symptom free, while the non-responders endorsed more risk factors for PTSD. These results support other anecdotal reports on the rapid effects of brief EMDR intervention on intrusive symptoms in early uncomplicated post-traumatic cases.

Following the recognition of the failure of psychological debriefing, the issue of difficult access to patients with high levels of stress or dissociation was raised. This was all the more critical as it was known that dissociation at the time at which exposure therapy starts was associated with a poorer response [18]. In response to this challenge and to the increasing number of patients in need of care after manmade catastrophes such as bomb attacks, modified EMDR procedures and protocols adapted for early intervention have been developed to help victims and can be applied soon after trauma, including the emergency response procedure (ERP) [38] and the recent traumatic episode protocol (R-TEP) [39, 40].

The ERP is a short procedure implemented according to procedures designed and tested in emergency contexts, including the ER [40, 41]. The individuals who arrive at the ER show a wide range of disturbance. The greatest benefit of the ERP intervention is

expected for patients in a 'highly agitated' state (scoring 7–10/10 on the Subjective Units of Disturbance scale, where 0 = no disturbance and 10 = the highest disturbance possible) to those who have moved into a 'silent terror' (scoring 10+/10 on the Subjective Units of Disturbance scale).

The R-TEP is an early EMDR current trauma-focused intervention that incorporates and extends the main ideas of the original Recent Event Protocol guidelines first described by Shapiro and Laub in 2008 [42].

The ICD-10 established a set of diagnostic criteria for PCS. In order to meet these criteria, a patient must have had a head injury *"usually sufficiently severe to result in loss of consciousness"* followed by the development, within 4 weeks, of at least three of the eight following symptoms: headache, dizziness, fatigue, irritability, sleep problems, concentration problems, memory problems, and problems tolerating stress. There is relatively little systematic research on the prevention and treatment of PCS [43–46]. A systematic review published in 2010 [45] suggested that cognitive behavioral therapy may be effective in the treatment of PCS. However, the authors found no quality studies and call for more rigorous trials of cognitive behavioral therapy for post-concussion symptoms. Other strategies include information, education and reassurance [47–49]. An emerging literature points to the independent impact of expectations and coping on chronic conditions following trauma, in particular for patients with whiplash and low back pain [50–55]. Reassurance, as provided in the context of cancer [50], low back pain [51, 52], and mild head trauma [47, 49], was found to help patients in their recovery process. It is therefore possible that at least a subgroup of patients who experienced a traumatic injury may benefit from such intervention.

Available research data, both from our studies and that available in the literature, led us to select the EMDR R-TEP procedure. This choice was based on the following considerations:

1) The absence of sufficient literature related to preventive interventions for PCLS
2) The partial overlap between PCLS and PTSD
3) The results of our preliminary studies strongly suggesting that stress plays a major role in PCLS
4) The consensus for the use of EMDR in early prevention of PTSD
5) The growing evidence of a significant psychological component to persistent complaints
6) The failure of early psychological debriefing to prevent PTSD

We then conducted a new pilot study [53], intended to examine the feasibility of stress management sessions during the ER stay with candidate interventions as selected by our literature search. To this end, we conducted a randomized open-label, single-center study to assess the feasibility of psychologist-led interventions in the context of the ER and to compare the effect of EMDR with reassurance and usual care. Conducted in the ER of Bordeaux University Hospital, the study included patients with a high risk of PCLS randomized into three groups, as follows: (1) a 15-min reassurance session, (2) a 60-min session of EMDR, and (3) usual care. Main outcomes were the proportion of interventions that could be carried out and the prevalence of PCLS and PTSD 3 months after the ER visit.

A total of 130 patients with a high risk of PCLS were randomized. No logistic problem or patient refusal was observed. In the EMDR, reassurance and control groups, the proportions of patients with PCLS at 3 months were 18%, 37%, and 65% and those with PTSD were 3%, 16%, and 19%, respectively. The relative risk for PCLS adjusted for the type of event (injury, non-injury) for the comparison between EMDR and control was 0.24 (95% CI 0.095–0.61). This first randomized controlled trial therefore shows that a short EMDR intervention is feasible and potentially effective in the context of the ER. The study was registered at ClinicalTrials.gov (NCT03194386).

The present protocol aims to replicate the latter trial in order to confirm or reject our hypothesis of a beneficial impact of early R-TEP EMDR on PCLS and PTSD in two different ERs. SPIRIT Checklist for this trial is provided as an Additional file 1.

Potential benefit

The trial is designed to test the impact of early EMDR intervention on PCLS and PTSD in patients presenting to the ER. In 2012, the year of the last national survey in France, 10.6 million people attended the ER, some of whom several times, since 18 million visits were recorded that year. The SOFTER 3 study therefore addresses a major public health challenge.

Methods/design

The main objective in our two-site, open-label, randomized controlled trial is to compare the impact on 3-month PCLS of early EMDR R-TEP intervention and usual care in patients presenting to the ER. Secondary objectives include the comparison between EMDR R-TEP and control of 3-month PTSD, 12-month PCLS, self-reported stress at ER discharge, self-assessed recovery expectation at discharge and 3 months, and self-reported pain at discharge and 3 months.

The outcomes are therefore defined as follows:

Primary outcome

- 3-month PCLS as measured with the Rivermead Post-Concussion Symptoms Questionnaire [54]
Secondary outcomes
- 12-month PCLS as measured with the Rivermead Post-Concussion Symptoms Questionnaire
- 3-month PTSD as measured with PTSD Checklist-5 [55]
- Self-assessed recovery expectation at discharge and 3 months
- Self-reported chronic pain at 3 months
- Self-reported acute pain at discharge
- Psychotropic medicine use at 3 months as measured by drug delivery data extracted from the Caisse national d'assurance maladie des travailleurs salariés (CNAM-TS) database, the French social insurance system

Randomization and blinding

Patients will be allocated to one of the two arms with block randomization by clinical center sites. Statistical analysis will be performed blinded to arm content, revealed only by the Data Safety Monitoring Board (DSMB) report. It is not possible to blind the participants to their allocation due to the nature of the intervention.

Inclusion criteria

All patients attending the adult ER of one of the study sites following an event that led to an injury, or with a new acute medical condition, will be assessed for inclusion. The inclusion criteria are as follows:

- Age 18 and above
- Conscious, able to provide informed consent, able to understand study procedures and to comply with them for the entire length of the study; French speaker
- Injured, whatever the cause of injury (the event causing the injury must have occurred in the past 12 h) or experiencing a medical event associated with an acute medical condition and presenting for the first time to the ER for this reason
- Score resulting from the screening tool > 1: female: + 1, taking at least one anxiolytic treatment: + 1, perceived health status prior to admission: excellent, very good 0; good: + 1; poor: + 2; bad + 3
- Affiliated to the French insurance system

Exclusion criteria

Any candidates to whom any of the exclusion criteria apply at baseline will be excluded from study participation. The exclusion criteria are as follows:

- Acute drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
- Inability or unwillingness of individual or legal guardian/representative to give written informed consent
- Inability or unwillingness to be contacted for 3- and 12-month follow-up interviews

Study enrollment procedures and randomization

Study protocol and time of collection of outcomes are presented in Figs. 1 and 2. Participants will be recruited among patients presenting to the ERs of the University Hospital of Bordeaux (Groupe Hospitalier Pellegrin) and Lyon (Groupement Hospitalier Edouard Herriot) and assessed with a high risk of PCLS. The identification and recruitment of potential study participants will be carried out by emergency personnel under the supervision of the project manager as soon as the patient's condition permits and in all cases after the initial clinical evaluation conducted in the framework of the usual care. First oral consent will then be sought for participation in the assessment stage, which consists in selecting patients with a high risk of PCLS.

A set of three items will be recorded for each injured patient, including sex (+ 1 for female), perceived health status prior to admission (excellent, very good: 0; good: + 1 poor: + 2; bad: + 3), current use of anxiolytics/antidepressants (+ 1 if yes).

To be enrolled in the study, the patient will need to score above a pre-defined threshold of 2 on the scoring procedure based on the three items and designed to select patients at risk for PCLS. The score has been developed using data from the Pericles study and validated on data of the SOFTER Pilot 1 and 2 studies.

Patients fulfilling inclusion criteria and assessed as at risk for PCLS will be presented with the objective and procedures and invited to sign an informed consent form. A screening log will be filled in to describe reasons for ineligibility and for non-participation of eligible candidates.

The randomization procedure for assigning a participant to an intervention group will then be performed and the results will be recorded in the Shared Study Monitoring System. Electronic block randomization will be stratified according to study center. Block sizes will be randomly modified and kept secret.

Intervention

Patients in the EMDR group will receive a 1-hour psychotherapeutic intervention, utilizing the R-TEP [40]. This protocol is specially designed for victims of recent traumatic events, and incorporates and extends the early

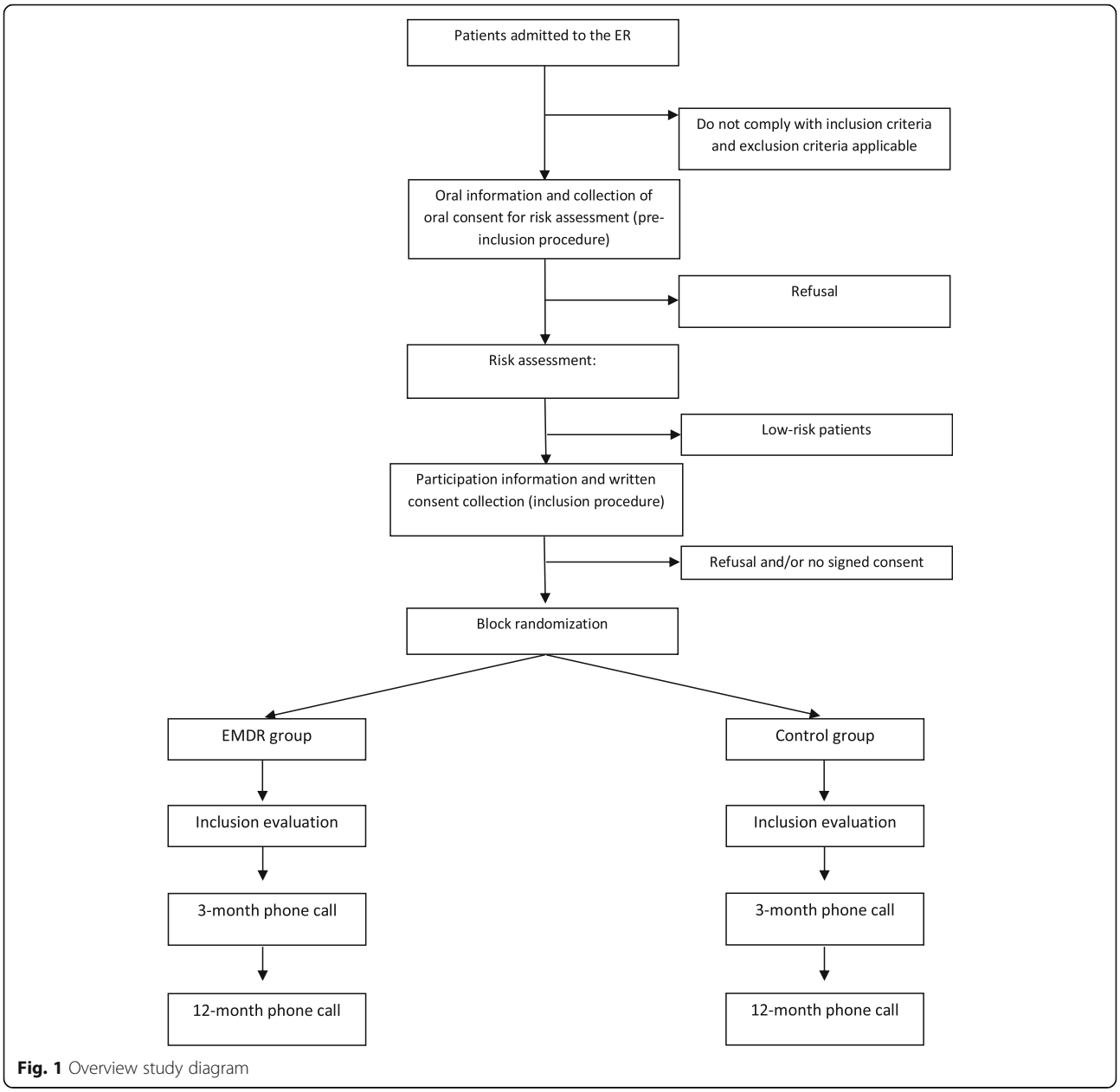

Fig. 1 Overview study diagram

EMDR intervention protocols [32] into an integrative and comprehensive intervention considering the fragmented, unconsolidated nature of recent traumatic memories and the need for safety and containment. Following the eight phases of the standard EMDR protocol, it introduces four new procedural concepts (Traumatic Episode, Episode Narrative, "Google Search/ Scan" for identifying disturbing fragments and Current Trauma Focused processing strategies). These sessions will be carried out by trained psychologists.

Patients in the treatment-as-usual group will be medically and psychologically attended to by ER staff with no intervention of the study psychologist.

Sample size

The study sample size is calculated using PCLS rates expected at 3 months after an ER admission in a patient population assessed to be at high risk of PCLS.

Our pilot study showed that, using the criteria described above, the incidence of PCLS among patients selected and enrolled in the study will be of approximately 47%. Our aim is to design the present study to be able to evidence a 15% decrease in PCLS prevalence in the EMDR group. Assuming an alpha risk of 5% and a power of 80%, the required sample size will be 169 patients in each group. We further assumed 20% loss to follow-up and 5% missing data for the main variables.

	STUDY PERIOD			
	Enrolment	Allocation	Post-allocation	
TIMEPOINT	*Month 1-5*	0	*Month 3*	*Month 12*
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Risk level assessment	X			
Allocation		X		
INTERVENTIONS:				
R-TEP EMDR		X		
Care as usual		X		
ASSESSMENTS:				
Demographics		X		
Stress and disturbance evaluation		X		
General physical examination		X		
Current medications		X		
PCSL		X	X	X
PTSD			X	X
Adverse events		X	X	X

Fig. 2 Schedule of enrolment, interventions, and assessments

Thus, we plan to include 223 patients in each group (112 per center in each group).

A study therapist will be available from 10 am to 6 pm, 5 days a week. Considering EMDR session duration and emergency care, patients will be assessed for eligibility from 8 am to 6 pm. Data from our ER registry and experience from our pilot study show that, during this period, approximately 50 patients will be assessed for eligibility. The screening tool used in this study will select approximately 10% of patients admitted to the ER. We also estimate that 10% of eligible patients will be missed in the ER and assume a 5% refusal rate. Consequently, we can expect approximately four inclusions per day, corresponding to an inclusion period of 3 months.

Adherence assessment

Adherence to the study regimen will be defined as the extent to which participants comply with study intervention requirements. The SOFTER Pilot study 2 showed that over 95% adherence can be expected in the EMDR group. A log of intervention sessions will be kept for each participant and will include duration, completeness, and patient satisfaction. This log will be regularly reviewed by the Steering Committee and used as part of the decision to continue or discontinue the study.

Interim analyses and stopping rules

No interim analysis of efficacy is planned. The study can be stopped by the DSMB for safety reasons or because of poor study performance (losses to follow-up > 25%), poor quality control, slow accrual (recruitment rate < 75% than expected), serious adverse events considered to be caused by the intervention, or increased frequency of adverse events. Such findings are presented to the DSMB for review of the events to determine whether there are statistical as well as clinical concerns. The statistician reports their findings to a closed session of the DSMB and these are used to determine what steps will be taken.

Data analyses

Descriptive and inferential statistical methods will be used to analyze the outcomes and other study data. Confounding variables will include cause of admission (injury versus medical), age group, and sex. The analyses will be conducted as intent-to-treat for primary endpoint and per-protocol for secondary analyses. Randomization codes will only be revealed at the end of the analysis.

Primary analyses will be conducted using a Fisher exact test. A stratified analysis will be carried out considering study center and PCLS risk score. For other variables, Wilcoxon test will assess differences for continuous variables and Fisher exact test for categorical variables.

Differences between patients who completed the study and those who were lost to follow-up will be assessed for all variables.

Dissemination

The results of the trial will be published regardless of the direction of effect. Communications will be presented at specialized conferences and reports will be submitted to peer-reviewed medical journals.

Quality control

A clinical research associate mandated by the sponsor will regularly visit each study center, when the research is set up, once or several times during the course of research, according to the rhythm of the inclusions and at the end of the research. During these visits, and in accordance with the monitoring plan, the following will be reviewed:

Informed consent

- Respect of the research protocol and procedures defined in it

– Quality of the data collected in the report file: completeness, accuracy, missing data, consistency of data with source documents (medical records, appointment books, original laboratory results, etc.)

All visits will be subject to a written monitoring report.

Confidentiality of data

In accordance with the statutory provisions in place (the French Public Health Code), persons having direct access to source data will take every precaution required to ensure the confidentiality of information relating to investigational medicinal products, studies, and participants, notably concerning their identity, as well as the results obtained. These persons, like the investigators themselves, are subject to professional confidentiality.

During the clinical study or at its conclusion, data regarding participants that is collected and sent to the sponsor by the investigators (or all other specialists involved) will be anonymized. At no point will the names of participants or their addresses appear unencrypted.

Only the first letters of the first name and full name of included patients will be recorded, followed by a specific research number indicating the rank of inclusion and the origin of the investigator site.

The sponsor will ensure that each study participant has given their consent for access to their personal data, which is strictly required for study quality control.

Data and Safety Monitoring Board (DSMB)

The DSMB is an independent group of experts that advises the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and (2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking, and voting procedures prior to initiating any data review.

The study DSMB consists of three independent experts, inclduing one expert in the clinical aspects of the stressed/injured patient population; one biostatistician with expertise in current clinical trial conduct and methodology; and one expert in psychotherapeutic EMDR interventions.

The DSMB has been appointed prior to study initiation.

Premature withdrawal from the study and withdrawal of consent

The participant has the right to withdraw from the research at any time. If participants decide to withdraw from all components of the study, they are no longer followed up in the protocol. Premature withdrawal from the research strategy must be notified promptly to the Steering Committee. The reasons for and the date of withdrawal must be documented. The withdrawal of consent is a decision by a participant to reconsider their decision to participate in the research and to assert their right to withdraw consent at any time during follow-up, without resulting in any prejudice thereby and without having to justify it. When a participant withdraws consent for participation in the research, data already collected for this patient will be kept for analysis.

Protocol deviations

Deviations can affect all aspects of a research protocol such as inclusion, monitoring, measurement of endpoints, and treatment process. All deviations must be documented by the investigator and discussed by the Steering Committee and Data Management Center.

Even in the event of deviation from the protocol, participants must be monitored until the date planned in the protocol.

Archiving study documents and study data

The protocol and any changes to the protocol, report files (copies), source files of participants who gave consent, and all other documents and correspondence related to the research will be archived in accordance with good clinical practices for a period of 15 years following the end of the research. The original informed consent forms of participants will be archived for a period of 30 years following the end of the research.

Ethical approval

The sponsor and the investigator(s) undertake the responsibility to ensure that the research is conducted in compliance with Law no. 2012–300 on research involving human participants of 5 March 2012, in accordance with Good Clinical Practices (I.C.H. version 4 of 9 November 2016 and Decision of 24 November 2006), and the Declaration of Helsinki.

The research will be conducted in accordance with the present protocol. Except in emergency situations requiring specific medical procedures, the investigator undertakes the responsibility to comply with the protocol in all respects, particularly with regard to the collection of consent, and the reporting and monitoring of serious adverse events.

This research project has received positive endorsement from the French CPP (Comité de protection de Personnes

Ouest II - Angers). N° RCB = 2017-A01462–51 – N°CPP = 2017/36.

The University Hospital of Bordeaux, the sponsor of this research, has taken out a civil liability insurance contract with Gerling-Biomedicinsure in accordance with the provisions of the public health code.

The data recorded in the course of this research shall be subject to computer processing on behalf of INSERM U1219 Bordeaux Population Health Research Center in compliance with Law No. 78–17 of 6 January 1978 relating to data processing, files and freedoms, as amended by Law 2004–801 of 6 August 2004.

This research project falls within the framework of the "Reference Methodology" (MR-001) in application of the provisions of article 54, paragraph 5 of the amended law of 6 January 1978 relating to information, files and freedoms. This change was approved by the decision of 5 January 2006, updated on 21 July 2016. The INSERM U1219 Bordeaux Population Health Research Center has signed a commitment to comply with this "Reference Methodology".

A specific request for clearance will be submitted to the Commission Nationale Informatique et Liberté (CNIL) in order to obtain the authorization to use the national social security ID to retrieve medication data at 3 and 12 months.

Discussion

The trial is designed to test the impact of early EMDR intervention on PCLS and PTSD in patients presenting to the ER. In 2012, the year when the last national survey in France was undertaken, 10.6 million people attended the ER, some of whom several times, since 18 million visits were recorded that year. The SOFTER 3 study therefore addresses a major public health challenge.

We already described the feasibility of short EMDR sessions in the ED during the SOFTER 2 study [53], which also found a superiority of EMDR versus reassurance versus control. We need to confirm these results in a larger and more diverse population.

Trial status

The present publication refers to the 4.0 version of the SOFTER 3 protocol dates on 01/02/2018. Recruitment began on January 15, 2018, and is expected to be completed by the June 15, 2018.

Additional file

Additional file 1: SPIRIT Checklist (DOC 121 kb)

Abbreviations

DSMB: Data Safety Monitoring Board; EMDR: eye movement desensitization and reprocessing; ER: emergency room; ERP: emergency response procedure; PCLS: post-concussion-like symptoms; PCS: post-concussion syndrome; PTSD: post-traumatic stress disorder; R-TEP: recent traumatic episode protocol; SOFTER: SymptOms Following Trauma, Early Response

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Availability of data and materials

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to CGJ, GV, KT and EL.

Authors' contributions

EL and CGJ drafted this paper. SAJ and JTSJ trained study psychologist. GD and CGJ followed study inclusions in both centers. CGJ, EL, KT, LRS, MG, GV, RRG, PR, EP, SAJ, and JTSJ contributed in study protocol. All authors contributed to revisions of the manuscript, and read and approved the final manuscript.

Ethics approval and consent to participate

The protocol was approved by the French data protection authority and the regional ethics committee. All participants gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors of this paper have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

Publisher's Note

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Facteurs de risque, dépistage et prévention des syndromes post-traumatiques à la suite d'un passage aux urgences

Résumé : Dans le monde entier, des dizaines de millions de personnes sont victimes de blessures mineures et beaucoup d'entre elles sont admises aux urgences. Cela représente chaque année environ 5 millions d'admissions aux urgences en France et près de 40 millions en Europe. Depuis plusieurs années, des études suggèrent que jusqu'à 20 % de ces patients souffriront pendant des mois de symptômes chroniques décrits initialement dans le traumatisme crânien léger (TCL) et appelés ainsi « Syndrome post-commotionnel » (SPC). Aujourd'hui, ces symptômes ont été identifié comme non spécifique du TCL et la plupart des auteurs utilise le terme de « Post-Concussion-Like Symptoms » (PCLS). Une telle combinaison de symptômes peut entraîner une détérioration importante de la qualité de vie sociale et familiale ou retarder le retour au travail ou à l'école. Rien qu'en France, si les résultats décrits dans la littérature sont représentatifs de l'ensemble de la population, jusqu'à un million de personnes pourraient être concernées par cette problématique, actuellement mal identifiée, de santé publique.
Les différents objectifs de ce travail de thèse étaient ainsi :

- Identifier les facteurs associés à l'apparition de « Post-Concussion like symptoms » à distance d'un passage aux urgences,
- Élaborer un outil d'évaluation du niveau de risque de développer ces symptômes pour les patients pris en charge aux urgences
- Identifier les interventions qui pourraient être proposer aux urgences comme moyen de prévention.
- Évaluer l'intérêt de la mise en place d'interventions au cours du passage aux urgences pour prévenir la survenue de ces symptômes.

Nous avons retrouvé dans SOFTER 1 que les PCLS à 4 mois sont associés au stress à la sortie des urgences. Puis grâce à l'élaboration d'un outil d'évaluation du niveau de risque, nous avons montré qu'il est possible de conduire des séances d'EMDR au cours du séjour dans les urgences. L'efficacité de cette intervention semblerait en revanche influencée par de nombreux facteurs comme le niveau socio-économique des patients, leur niveau de stress et l'expérience des psychologues.
Ainsi, les résultats actuellement disponibles suggèrent que les structures d'urgences pourraient être un lieu privilégié pour repérer et prendre en charge des patients fragiles, à risque de développer des PCLS.
L'opportunité offerte par le passage aux urgences pourrait avoir un impact important en termes de santé publique et constituer un outil puissant de santé communautaire pour lutter contre les inégalités de santé.

Abstract : Worldwide, tens of millions of people suffer minor injuries and many are admitted to emergency departments (ED). This represents approximately 5 million ED admissions in France and nearly 40 million in Europe each year. For several years, studies have suggested that up to 20% of these patients will suffer for months from chronic symptoms initially described in mild traumatic brain injury (MTBI) and referred to as "post-concussion syndrome" (PCS). Today, these symptoms have been identified as non-specific to TCL and most authors use the term "Post-Concussion-Like Symptoms" (PCLS). Such a combination of symptoms can lead to a significant deterioration in the quality of social and family life or delay the return to work or school. In France, if the results described in the literature are representative of the entire population, up to one million people could be affected by this currently poorly identified public health problem.
The different objectives of this work were as follows:
- to identify the factors associated with the development of "Post-Concussion like symptoms" at a distance from an emergency room visit,
- to develop a tool to assess the level of risk of developing these symptoms for patients managed in emergency departments
- to identify interventions that could be offered to emergencies as a means of prevention.
- to assess the value of implementing interventions in the ED to prevent these symptoms from occurring.

We found in SOFTER 1 that PCLS were associated with stress at the ED discharge. Then, after creating a risk assessment tool, we showed that it is possible to conduct EMDR sessions during ED stay. The effectiveness of this intervention appeared to be influenced by many factors such as patients' socio-economic conditions, stress level and psychologists' experience.
Thus, results currently available suggested that ED could be a place to identify and manage fragile patients at risk of developing PCLS. The opportunity offered by ED visit could have a significant impact in terms of public health and could be a powerful community health tool to combat health inequalities.