Update on the prevalence of persistent post-traumatic headache in adult civilian traumatic brain injury: protocol for a systematic review and meta-analysis

Caroline Arbour, Yasmine Bouferguene, Roxanne Beauregard, Gilles Lavigne, Alberto Herrero Babiloni

Introduction

Traumatic brain injury (TBI) is a major public health concern. Persistent post-traumatic headache (PTH) is a common consequence of TBI affecting productivity and quality of life. The only review providing information about headache prevalence after TBI was published in 2008, combined data from civilian and military TBI, and was strictly derived from Medline database. Due to recent changes in TBI diagnosis and trauma epidemiology, the aim of the current study is to perform a systematic review and meta-analysis to derive updated prevalence estimates of persistent PTH in adult civilian TBI.

Methods and analysis

The methods have been defined following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies published from 2008 to 2019 will be identified searching the electronic databases Medline, Embase, Cochrane, Google Scholar, Directory of Open Access Journals and Web of Science. Retrieved records will be independently screened by two authors and relevant data will be extracted from studies reporting data on persistent PTH prevalence among civilian TBI individuals (>16 years). The pooled prevalence estimates of any form of headache will be computed applying random-effects meta-analysis. Heterogeneity will be assessed using the I² statistic and explored through subgroup analyses considering TBI severity (mild vs moderate/severe). Estimations of risk of bias will be performed using the Risk of Bias Tool for Prevalence Studies.

Ethics and dissemination

The result of this systematic review will be published in a peer-reviewed journal and disseminated at relevant conferences presentations. Formal ethical approval is not required because we will search and evaluate only existing sources of literature. By focusing on studies conducted in the last decade, this review will provide the most up-to-date information about the global prevalence of persistent PTH after TBI. Considering the economical and social burden of persistent PTH after TBI, accurate estimates of this problematic disorder is of utmost importance for planning, implementing and evaluating prevention interventions.

Strengths and limitations of this study

- This systematic review will yield solid and updated estimates on the prevalence of persistent post-traumatic headache in adult traumatic brain injury (TBI) populations.
- Unlike previous prevalence estimates on pain after head trauma, data included in this review will be restricted to civilian TBI and exclude studies conducted in a military context, as differences between the two groups have been documented in terms of premorbid characteristics and patterns of recovery.
- Data of persistent post-traumatic headache after TBI will first be pooled to provide a global prevalence estimate of this problematic disorder, then analysed separately in mild and moderate/severe cases.
- The increased reliance in TBI research on self-report information to confirm the history of head trauma is likely to reduce the comparability with studies using the classical clinician’s assessment approach to TBI diagnostic.
- Regarding the development of persistent post-traumatic headache after TBI, heterogeneity in prevalence estimates might be caused by multiple features including psychiatric disorders comorbidity and time elapsed since injury. Those elements will be thoroughly documented.

BACKGROUND

Traumatic brain injury (TBI) occurs when an external force is applied to the head leading to permanent or temporary disabilities. TBI can be considered mild, moderate or severe depending on changes in cognitive and executive processes. TBI is a major threat to global health as 69 million individuals worldwide are estimated to sustain such injury each year. In the European Union, more than 1.4 million individuals are hospitalised for TBI annually. In the USA, 2.8 million individuals seek medical attention for TBI each year.
with an estimated annual cost of over US$76 billion.\textsuperscript{5,6} Incidence of TBI is also on the rise in low-income and middle-income countries, mainly due to the increased use of motor vehicles.\textsuperscript{7–9} While sport and military-related TBI have received considerable media attention in the last decade, the highest combined incidence of TBI-related emergency department visits, hospitalisations and deaths occurs in civilians.\textsuperscript{10}

Chronic pain is a common consequence of TBI.\textsuperscript{11} To date, post-traumatic headache (PTH) following TBI has been the focus of several studies and reports on the topic.\textsuperscript{12–14} According to the International Headache Society, persistent PTH attributed to head trauma is defined as a headache developing within 7 days following the impact and persisting more than 3 months after.\textsuperscript{15–16} Persistent PTH after TBI has no defining clinical features, and it is classified as a secondary headache disorder because of the close temporal relation to another disorder known to cause headache (in this case TBI).\textsuperscript{15} This remains true even when the headache has the characteristics of a primary headache (migraine, tension-type headache, cluster headache or one of the other primary headaches). In terms of recovery, persistent PTH after TBI has been associated to higher rates of anxiety and depression symptoms and reduced quality of life.\textsuperscript{17} In TBI adults, the odds of returning to work successfully are more than cut in half for each unit increase in PTH intensity.\textsuperscript{18}

The only available estimates of headache in adult TBI date back to 2008 when chronic pain prevalence data were pooled from 23 studies (from 1951 to 2008) yielding a global prevalence of 57.8% for persistent PTH, with surprising higher rates in mild TBI (75.3%) when compared with moderate/severe TBI (32.1%).\textsuperscript{19} In the last decade, several factors may have led to significant changes in chronic headache epidemiology after TBI including the revision of mild TBI diagnosis criteria to make it more inclusive and an historic peak of TBI in the elderly attributed to the ageing population.\textsuperscript{20–22} In addition, the above-mentioned systematic review conducted by Nampiaparampil\textsuperscript{19} combined epidemiological data from civilian TBI and military-related TBI, reducing the comparability between eligible studies. Moreover, the review did not account for the presence of psychiatric disorders comorbidity, which would have been important as we now know these elements may contribute to pain chronicity after TBI.\textsuperscript{23} For all the aforementioned reasons, updating the prevalence estimate of persistent PTH in adult civilian TBI becomes especially relevant.

OBJECTIVES
The aim of the current study is to carry out a systematic review and meta-analysis to derive updated estimates on global and severity-specific prevalence of persistent PTH in adult civilian TBI. The proposed review will address two main questions:
1. What is the updated global prevalence of persistent PTH in adult civilian TBI?
2. What is the specific prevalence of persistent PTH in adult civilians with mild TBI versus moderate/severe TBI?

Considering the increased reliance on self-report and screening measures to validate the occurrence of events leading to TBI in recent years, we expect an increase in persistent PTH prevalence in adult civilian TBI.\textsuperscript{24} These updated data will inform the planning, implementation and evaluation of chronic pain prevention intervention in trauma care, and potentially, contribute to reduce its morbidity after TBI.

METHODS/DESIGN
The methods for this systematic review have been defined in advance following the Prepared Items for Systematic Reviews and Meta-Analyses (PRISMA).\textsuperscript{25} The protocol was developed according to the PRISMA-Protocols checklist\textsuperscript{26} (see online supplementary Appendix 1).

Eligibility criteria
Studies will be selected according to the criteria outlined below.

Study designs
Studies will be considered for inclusion based on their relevance to answer the review questions. For review question 1, any form of observational studies investigating the prevalence of persistent PTH after civilian TBI, or from which prevalence estimates can be derived and that meet the eligibility criteria will be considered. More specifically, prevalence estimates for persistent PTH occurring within 7 days after TBI will be derived from either: (1) the general population (ie, from population prevalence surveys), (2) patient registries or primary care practices’ databases, (3) hospital-based populations or (4) screening programmes. For review question 2, studies eligible for question 1, in which prevalence estimates are presented based on TBI severity will be considered. Studies will not be restricted by language. However, all will have to report original data and be peer reviewed. Expert opinion letters or editorials, conference summaries or reviews will be excluded. Intervention studies (including randomised control trials) will also be excluded on the basis that they are not deemed appropriate to help answer the review questions.

Population
The population of interest consists of individuals (18 years or older) from the general population who have sustained a mild, moderate or severe TBI. Considering teenagers aged 16 years and older are often treated in adult trauma units, studies including 16 and 17 years old individuals in their sampling procedures will also be considered for inclusion. Mixed patient population studies will also be considered for inclusion if the analyses of results are stratified according to patients’ diagnosis and mechanism of injury, allowing the review team to discern findings specific to the civilian TBI group. Studies about persistent...
PTH following military TBI will not be considered in this study as differences compared with civilian TBI in terms of premorbid characteristics and patterns of recovery have been documented. For similar reasons, pain studies using animal models of TBI will be excluded. Consistent with Nampiaparampil, only studies using a clearly defined operational definition for the diagnosis of TBI will be considered for inclusion. Recognised criteria for the diagnosis of TBI include either: (1) a period of unconsciousness and/or post-traumatic amnesia, (2) clinician’s confirmation of the initial Glasgow Coma Scale score at hospital admission or (3) a self-professed experience of transient neuropsychological dysfunction following injury to the head.

Outcomes
The primary outcome will be the global prevalence of persistent PTH following TBI. In order to be considered ‘persistent’, headache will have to occur for longer than 3 months after initial onset to fulfil the criteria of the International Classification of Headache Disorders -third edition (ICHD-3). The secondary outcome will be a better understanding of the associations between persistent PTH and TBI severity. The latest could potentially help to identify which type of TBI patients are most likely to benefit from systematic screening and preventative interventions for headache disorders during acute recovery.

Timing
Considering the latest estimates of persistent PTH prevalence after TBI are based on studies published from 1951 to February 2008, only studies published from March 2008 to 2019 will be considered for inclusion.

Setting
As TBI is a serious public health problem around the world, no geographical limitations will be applied.

Information sources
The following databases will be searched: Medline, Embase, Cochrane Library, Google Scholar and Directory of Open Access Journals. For search optimisation, we will scan the reference lists of included studies. We will also search the authors’ personal bibliography on Web of Science to make sure that all relevant material has been captured.

Search strategy
The specific search strategies will be created by a Health Sciences Librarian with expertise in systematic reviews using the Peer Review for Electronic Search Strategies checklist. To date, a first search strategy has been developed by the librarian and peer reviewed by a member of the review team (YB) in Medline using Medical Subject Headings (MeSH) combined with free-text terms around the three search components ‘TBI’, ‘headaches’ and ‘prevalence’. A draft Medline search strategy is included in online supplementary appendix 2. The search strategy will eventually be adapted by the librarian for its use in the other databases.

Study records
Data management
An initial literature search will be performed by one member of the review team (YB) and entirely reviewed by a second member (AHB). The citation abstract and full-text article of all references identified will be uploaded to EndNote (EndNote 2017, Clarative Analytics). The search results from the different electronic databases will be combined in a single EndNote library to facilitate collaboration among the review team members (YB and AHB) during the study selection process. No training in relation to the literature search is planned at this stage as both reviewers are already familiar with EndNote and the content area of the review.

Selection process
Titles and abstracts of studies generated from the initial search will be screened independently by two members of the review team (YB and AHB). The full text will be retrieved and independently assessed by both authors for eligibility based on the inclusion/exclusion criteria mentioned previously. The full text of remaining articles will be independently examined by the same reviewers to reach a final list of articles. Disagreements at either screening stage will be resolved through discussion with a third reviewer (CA). The reasons for study exclusion will be documented. For duplicated references, and data that has been published more than once, the most complete study will be chosen for inclusion in the library while the others will be removed. A PRISMA flow diagram of the study selection procedure will be prepared to provide an overview of the decisions that are made in the data collection process.

Data collection process
Consistent with Nampiaparampil, the prevalence in this review is defined as the estimate of the total amount of persistent PTH at a time point or period interval in a certain sample of adult civilian TBI. Based on this definition, data will be extracted from the included studies using a standardised data extraction spreadsheet. The data extraction spreadsheet will be pretested by two members of the review team (YB and RB) on 10 randomly selected publications and modified accordingly. Using the same data extraction spreadsheet, the reviewers (YB and RB) will independently extract and manage the data for each of the included studies. Disagreements will be resolved by discussion between the two authors; if no agreement can be reached, consensus will be sought through discussions with a third author (CA). Authors of the included studies will be contacted in case clarifications or further data are needed (up to three attempts by email over a period of 8 weeks). Data will be extracted on the following:

<table>
<thead>
<tr>
<th>Data Elements</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI Type</td>
<td>Military vs Civilian</td>
</tr>
<tr>
<td>PTH Type</td>
<td>Persistent</td>
</tr>
<tr>
<td>Study Design</td>
<td>Observational vs Randomised</td>
</tr>
<tr>
<td>Setting</td>
<td>Military vs Civilian</td>
</tr>
<tr>
<td>Outcome</td>
<td>Global Prevalence</td>
</tr>
<tr>
<td>Data Source</td>
<td>Medline, Embase, Cochrane Library, Google Scholar, Open Access Journals</td>
</tr>
<tr>
<td>Search Strategy</td>
<td>Medline, Medical Subject Headings (MeSH)</td>
</tr>
<tr>
<td></td>
<td>Free-text terms</td>
</tr>
<tr>
<td></td>
<td>TBI, headaches, prevalence</td>
</tr>
</tbody>
</table>

Table 1  TBI severity classification inspired by the Mayo Clinic classification system

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/severe TBI (definite)</td>
<td>- Death</td>
</tr>
<tr>
<td></td>
<td>- Loss of consciousness &gt;30 min</td>
</tr>
<tr>
<td></td>
<td>- Antegrade amnesia &gt;24 hours</td>
</tr>
<tr>
<td></td>
<td>- Glasgow Coma Scale score &lt;13 in the initial 24 hours</td>
</tr>
<tr>
<td></td>
<td>- Intracerebral, subdural, epidural or subarachnoid haemorrhages;</td>
</tr>
<tr>
<td></td>
<td>cerebral or haemorrhagic contusion, penetrating TBI or brainstem injury</td>
</tr>
<tr>
<td>Mild TBI (probable)</td>
<td>- Loss of consciousness—momentarily to &lt;30 min</td>
</tr>
<tr>
<td></td>
<td>- Post-traumatic antegrade amnesia—momentarily to &lt;2-4 hours</td>
</tr>
<tr>
<td></td>
<td>- Depressed basilar or linear skull fracture (dura intact)</td>
</tr>
<tr>
<td>Symptomatic (possible mild TBI)</td>
<td>- A history of head trauma is reported by the patient</td>
</tr>
<tr>
<td></td>
<td>- One or more of the following symptoms are reported:</td>
</tr>
<tr>
<td></td>
<td>- blurred vision, confusion (changes in mental status), dizziness,</td>
</tr>
<tr>
<td></td>
<td>headache, nausea or focal neurological symptoms</td>
</tr>
</tbody>
</table>

TBI, traumatic brain injury.

1. Publication details: title, journal, author, year, city and country, in which the study was conducted, type of publication and source of funding.
2. Design: type of study (cohort, case–control and so on), method of data collection, response rate, recruitment and sampling methods and eligibility (inclusion and exclusion criteria).
3. Study participant details: number of persons interviewed or surveyed, population characteristics including setting, age, sex and premorbid characteristics including pre-existing primary headache disorders. Information about TBI severity will be rigorously extracted with respect to the clinical features and classification methods widely used (see table 1).
4. Data for outcome measures: prevalence of persistent PTH after TBI in general or according to TBI severity, characteristics of the headache (migraine, tension-type headache, cluster headache or one of the other primary headaches), time period referenced in assessment of the condition and factors (mainly comorbidities) found to be related significantly to the development of headaches after TBI.
5. Missing data: considering there are no standardised time points for the assessment of persistent PTH after TBI, prospective multiple assessments can be expected in some studies. This may potentially result in missing data. Reasons for missing data will be recorded from the original articles. If the original articles did not include this detail, we will try our best to obtain requisite information by contacting the corresponding author of the referenced articles for the missing data. The potential impact of the effect of missing data on the final findings of the review will be addressed in the discussion.

Risk of bias
Risk of bias of included studies will be independently evaluated by two members of the review team (YB and RB) using the Risk of Bias Tool for Prevalence Studies developed by Hoy et al (see online supplementary appendix 3). Individual items will be rated as ‘yes’ if the criterion is fulfilled. Otherwise, if the design of the study is not applicable or if there is insufficient information in the study to permit a judgement for a particular criterion, it will be noted as ‘no’. In the event that a full consensus cannot be reached between the two reviewers, the opinion of a third reviewer (CA) will be obtained, and the proceeding majority consensus will be taken.

Data analysis and synthesis
We will perform descriptive analysis and report the characteristics of included studies in summary tables and narrative text. Limitations of the studies will be discussed in detail.

As we anticipate variability between included studies (mainly in the time points considered for the screening of headache disorders), the pooled prevalence estimate of persistent PTH will be computed applying random-effects meta-analysis models (rather than assuming a single true value in a fixed-effect approach) using the MetaXL (www.epigear.com) add-in for Microsoft Excel. A pooled prevalence figure will be calculated with 95% CI. Meta-analysis will be limited to studies with at least 100 participants allowing an acceptable margin of error of ≤10% in the prevalence estimates of headache. Heterogeneity within included studies will be assessed through the utilisation of the I² statistics, with I² values of 25%, 50% and 75% being considered low, moderate and high, respectively. Depending on data availability, we plan to account for heterogeneity conducting meta-regressions and subgroup analysis considering the following covariates: time elapsed since TBI and TBI severity. Sensitivity analysis will be carried out considering only studies of the highest methodological quality using the Risk of Bias Tool for Prevalence Studies checklist.

Ethics and dissemination
As this will be a review of published data, patients will not be primarily involved in any stage of the study. Data will be collected from published studies available in the previously mentioned electronic databases. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal and present the results at conferences.
DISCUSSION

To date, the only systematic review providing information about chronic headache following TBI was published in 2008,19 and no new review is underway based on PROSPERO. Considering the recent changes in TBI diagnosis and epidemiology, there is a strong rationale for updating current evidence on persistent PTH prevalence in adult civilian TBI.

The systematic review and meta-analysis plan we come to carry out builds on the methodology applied previously,19 but reducing its limitations. Indeed, the previous review on the topic was performed solely through a MEDLINE search.40 41 The exclusion of other databases in which many journals are not indexed and the restriction of publications in other languages than English may have limited the findings and contributed to the confusion about the influence of TBI severity of headache prevalence. We believe that the use of additional sources of data aside from Medline will provide rigorous and updated estimates on prevalence of chronic headache in TBI. Moreover, differently from Nampiaparampil,19 we will limit the review to studies about non-military TBI as the highest combined incidence of TBI-related emergency department visits, hospitalisations and deaths occurs in civilians. In terms of research, pooling of such data is necessary to monitor trends in comorbidities among individuals who sustained TBI and to contribute to the design of further outcome studies. Another point that will differ from Nampiaparampil’s work is the use of ICHD-3 operative criteria for the definition of persistent PTH. As shown in a recent systematic review of PTH in children,42 use of a standardised definition helps to make distinction between the prevalence of non-specific persistent PTH and prevalence of persistent PTH as defined by recognised organisations. Last but not the least, we will include, in a separate section of the review, data about the prevalence of persistent PTH after TBI based on TBI severity.

To our knowledge, this is the first systematic review and meta-analysis protocol addressing the important need to update the prevalence estimates of persistent PTH in adult civilian TBI. Some limitations can be anticipated due to missing data and heterogeneity of the studies. Aside from variations in persistent PTH definition, another aspect that could contribute to study heterogeneity is the fact that depressed skull fractures with intact dura have only been recently recognised as mild TBI. Thus, studies performed before 2017 may not have included these cases in their estimates of persistent PTH after mild TBI. Despite these limitations, we anticipated our data will still be important to inform the planning, implementation and evaluation of chronic pain prevention intervention in trauma care, and potentially, contribute to reduce its morbidity after TBI.

REFERENCES

7 Adeleye AO, Ogun MI. Clinical epidemiology of head injury from road-traffic trauma in a developing country in the current era. Front Neurol 2017;8:695.


