Article title: Paroxysmal sympathetic hyperactivity and the role of beta-blockers in moderate/severe traumatic brain injury: a scoping review protocol

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Research Protocol

Title: Paroxysmal sympathetic hyperactivity and the role of beta-blockers in moderate/severe traumatic brain injury: A Scoping Review

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BACKGROUND

In 1929, Dr Wilder Penfield mentioned for the first time a syndrome combining lacrimation, hypertension, diaphoresis and agitation which he named diencephalic seizures[1].

Later, electrophysiological investigations of this phenomenon did not show any electroencephalographic manifestations. Many names were attributed to this syndrome: dysautonomia, sympathetic storming, brainstem attacks, autonomic dysregulation and paroxysmal autonomic instability with dystonia[2]–[5]. In 2014 the International Brain Injury Association convened a consensus workgroup to clarify the nomenclature and diagnostic criteria for this entity. The proposed term from this consensus group was “paroxysmal sympathetic hyperactivity (PSH).”[6]

PSH traditionally occurs in severe acquired brain injuries such as: head trauma, stroke, anoxic brain injury, tumors, infections, spinal injuries, serotonin syndrome[7]. The prevalence of PSH is 8-33%[8] and 79.4% reported cases of PSH result from traumatic brain

injury (TBI)[9]. 80% of PSH have moderate to severe head trauma and for severe head trauma the prevalence is 15-33%[8].

The pathophysiology of PSH is poorly understood, there are a lot of theories and the dominant one suggests failures of central autonomic network including the insular cortex, amygdala, hypothalamus, medulla, periaqueductal gray matter, parabrachial complex, and nucleus of the tractus solitarius[7], [10]. Many pharmacological agents have been used alone or in combination to treat PSH. They include opiates, dopamine agonists, benzodiazepines, baclofen, and gabapentin[7].

Beta-blockers have a cardioprotective effect by reducing the heart rate, the perfusion volume and the mean arterial pressure, which limits myocardial oxygen consumption, thus preventing myocardial infarction. They also have a neuroprotective effect by reducing cerebral blood flow, which reduces the cerebral consumption of oxygen and glucose as metabolism is reduced. Non-selective beta receptor antagonists have a lipophilic property which allows them to cross the blood brain barrier. beta-blockers, diminish the effect of circulating catecholamines and attenuate the resting metabolism rate which is markedly increased in patients with severe acute brain injury[11]–[18]. propranolol is the most commonly used, labetalol has also been shown to be effective against PSH[19], [20].

The aim of our study is to collate existing evidence of the role of beta-blockers in the treatment of PSH.

REVIEW QUESTIONS

Primary:

What is the role of beta blockers in treatment of PSH?

Secondary:

1. Pharmacokinetics of beta-blockers and their potential role in post-TBI PSH
2. Which beta blockers are the best in PSH treatment?
3. Efficacy of beta-blockers in post-TBI PSH
4. Level of evidence of studies evaluating beta-blockers in post-TBI PSH

RESEARCH STRATEGY

An exhaustive scoping review of the following databases will be carried out: MEDLINE, Web of Science, EMBASE, Cochrane, and Google Scholar. No language or geographical restrictions will be applied. The search terms used (Appendix 1) will cover the following terms: “paroxysmal sympathetic hyperactivity”, “traumatic brain injury” and “beta-blockers.”

The results will be narrowed down first by deduplication, then two independent co-authors will screen the titles and abstracts of each article following predefined inclusion and exclusion criteria. If there is a conflict the two reviewers will find a mutual consensus and if they cannot a third co-author will decide. The reference lists of included documents will be examined using forward and backward citation analyses to identify any further relevant documents the initial search might have missed.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines will be used to write and report the findings.

INCLUSION CRITERIA:

Types of study to be included :

- Original research
- Systematic reviews
- Literature reviews
- Reports
- Expert opinion

Exclusion criteria :

- PSH treatment without beta-blockers
- Use of beta-blockers in non-TBI PSH

DATA EXTRACTION

Using a pre-designed and pre-piloted data extraction form (Google Forms), data from each included citation will be collected by two independent reviewers. Conflicts in data collection will be resolved by discussion.

DATA ANALYSIS

Simple descriptive data analyses will be performed and the results will be presented both in a narrative and tabular form.

TYPE AND METHOD OF REVIEW

Scoping review

ANTICIPATED OR ACTUAL START DATE

28/09/2020

ANTICIPATED COMPLETION DATE

01/11/2020

FUNDING SOURCES/ SPONSORS

Not applicable

CONFLICTS OF INTEREST

None

LANGUAGE

English, French, Italian, Spanish

STAGE OF REVIEW

Review Ongoing

Subject index terms status

Subject indexing assigned by SN

Subject index term

These are assigned by SN

REFERENCES

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APPENDIX S1

SEARCH TERMS:

- Paroxysmal sympathetic storm, paroxysmal sympathetic surge, diencephalic seizure, diencephalic storm, paroxysmal autonomic instability with dystonia, acute hypothalamic instability, dysautonomia, sympathetic storming, brainstem attacks, and autonomic dysregulation.
- Beta-adrenergic blockers, adrenergic beta antagonist, β -adrenergic blockers, β -blockers
- Traumatic brain injury, head injury, craniocerebral trauma

SEARCH STRINGS:

1. Pubmed

("Autonomic Nervous System Diseases"[MeSH Terms] OR "Paroxysmal sympathetic storm"[Text Word] OR "diencephalic seizure"[Text Word] OR "paroxysmal autonomic instability with dystonia"[Text Word] OR "acute hypothalamic instability"[Text Word]) AND ("adrenergic beta antagonists"[MeSH Terms] OR "beta-adrenergic blockers"[Text Word] OR "adrenergic beta antagonist"[Text Word] OR "beta-adrenergic blockers"[Text Word] OR "beta-blockers"[Text Word]) AND ("craniocerebral trauma"[MeSH Terms] OR ("craniocerebral"[All Fields] AND "trauma"[All Fields]) OR "craniocerebral trauma"[All Fields] OR ("head"[All Fields] AND "injury"[All Fields]) OR "head injury"[All Fields])

APPENDIX S2

DATA EXTRACTION FORM