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Study Protocol

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Assessing the neuroprotective efficacy of atorvastatin in traumatic brain injury: a systematic review protocol

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Abstract

Traumatic brain injury (TBI) is a significant public health threat, with an estimated 5.3 million people in the United States alone living with a disability related to TBI (1). The most common therapies for individuals with TBI at this time include supportive measures, direct monitoring and surgical interventions, but the treatment outcomes following TBI are still poor. Atorvastatin is one of 3-hydroxy–3-methylglutaryl coenzyme A reductase inhibitors commonly used for treatment reduction of low-density lipoprotein and relief of symptoms in cerebrovascular diseases, however, the recent randomized trials in animal models and human subjects have revealed a promising therapeutic effect for its use in the treatment of TBI that has shown a significant alleviation of neurological dysfunctions. Hence, this systematic review will streamline and provide a comprehensive avenue for understanding more about the dynamics of atorvastatin and its neuroprotective efficacy for the treatment of the severity of TBI and the improvement of functional outcomes. This systematic review will follow the 2020 PRISMA guidelines. Information sources will be obtained from electronic databases such as Pubmed, Cochrane Library, EMBASE and SCOPUS. All patients with TBI that received Atorvastatin will be included. The review will also include original peer-reviewed research articles addressing the efficacy of Atorvastatin in TBI in English. Ethical approval will not be required as there will be no human participant involvement in this study. The findings from this study will be disseminated at scientific conferences and published in a reputable peer-reviewed journal.

Strengths

- A wide range of study types will be included increasing the pool of information.
- Accuracy will be upheld as two to three reviewers will independently screen titles, abstracts and full texts.

Limitations

- Only studies in English will be included, hence studies in other languages that may be very informative will be excluded.

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INTRODUCTION

Rationale

Traumatic brain injury (TBI) is a significant public health threat, with an estimated 5.3 million people in the United States alone living with a disability related to TBI[1].

TBI is one of the common causes of long-term disabilities and mortality and each year, ~10 million worldwide die due to TBI[5].

TBI can cause long-term physical disability, and cognitive and psychological changes, leading to a significant burden on those affected and their families. This burden can include social and economic costs, such as lost wages, medical expenses and the need for long-term care. Individuals and society are heavily burdened financially by the costs associated with treating patients who suffered TBI.

TBI can also have a profound impact on the family of those affected, leading to increased stress and anxiety levels, as well as a need for more caregiver support. Furthermore, TBI can lead to a reduction in quality of life for those affected, as well as a disruption to their daily activities.

The most common therapies for individuals with TBI at this time include supportive measures, direct monitoring and surgical interventions, but the treatment outcomes following TBI are still poor. Cohort studies have suggested that patients with severe head injury (Glasgow Coma Scale [GCS] score ≤8) have approximately a 30% risk of death. Approximately 5–15% of patients with severe TBI are discharged from acute care in a vegetative state [2–4]. Over the years that follow, only 50% of these patients regain consciousness, and almost all of them continue to be severely disabled.

Atorvastatin is one of 3-hydroxy−3-methylglutaryl coenzyme A reductase inhibitors commonly used for treatment reduction of low-density lipoprotein and relief of symptoms in cerebrovascular diseases, however, the recent randomized trials in animal models and human subjects have revealed a promising therapeutic effect for its use in the treatment of TBI that has shown a significant alleviation of neurological dysfunctions. The primary effect of atorvastatin is thought to have anti-inflammatory, anti-apoptotic and angiogenic effects that reduce the severity of secondary brain damage and improve functional recovery. It reduces the cerebral edema and the volume of parenchymal hemorrhage that ultimately result in increased blood flow and angiogenesis relieving the neurological symptoms. To our knowledge, this systematic review will streamline and provide a comprehensive avenue for understanding more about the dynamics of atorvastatin and its neuroprotective efficacy for the treatment of severity of TBI and improvement of functional outcomes.

Therefore, we suggest that conducting a comprehensive evaluation of the neuroprotective efficacy of atorvastatin in TBI will provide an important step forward in understanding the treatment of this dismal for improvement of quality of care to our patients and provide adequate resources and support for those affected.

Primary objective

(i) To determine the neuroprotective pathways of Atorvastatin in TBI.

Secondary objectives

(i) To evaluate the pharmacodynamic pathways of Atorvastatin in TBI.
(ii) To assess the dosage efficacy and route of administration of Atorvastatin in TBI.
(iii) To evaluate the prognostic outcomes of TBI patients that received Atorvastatin.

MATERIALS AND METHODS

Protocol and registration

The review registration will be obtained from the PROSPERO registry and a research protocol will be submitted for publication to a reputable international journal of neurosurgery.

Eligibility criteria

Study design

This study will summarize results from randomized controlled trials, quasi-experimental studies and observational studies like cohort, case-control studies and case series as well as reports and conference abstracts. Only studies published in the English language will be included. The exclusion criteria will be systematic reviews, scoping reviews, book chapters and non-English pieces.

Population

All patients with TBI.

Intervention

Atorvastatin therapy.

Comparator

Demographics (age and gender), and location (continent and country).

Outcome

GCS, length of hospital stay, mortality rate.

Information sources

The literature articles for this review will be searched from major electronic databases including PubMed, Cochrane Library, EMBASE, SCOPUS, WOS and others including semantic scholar, google scholar.

Search strategy

The MeSH terms will be deployed, and the search string will be constructed using boolean operators such as AND and OR for synonym terms. Keywords such as 'atorvastatin*'[All Fields].

AND ('brain injuries, traumatic'[MeSH Terms] OR ('brain'[All Fields] AND 'injuries'[All Fields].

AND 'traumatic'[All Fields]) OR 'traumatic brain injuries'[All Fields] OR ('traumatic'[All Fields] AND 'brain'[All Fields] AND 'injury'[All Fields]) OR 'traumatic brain injury'[All Fields]) will be used. More detailed search keywords will be included in the appendices.

Study selection

Studies will be screened in two stages, title and abstract screening followed by full-text screening using the inclusion and exclusion criteria. To improve accuracy and ensure full coverage, each paper will be independently screened by two researchers. Any conflicts arising will be addressed by a discussion and if still unresolved, a 3rd reviewer will be called in to solve the conflict. The selection process will be piloted on a small sample of studies to ensure the feasibility of the eligibility criteria and the adequacy of collected data. Any necessary amendments will be made to the eligibility criteria after the pilot phase (Fig. 1).

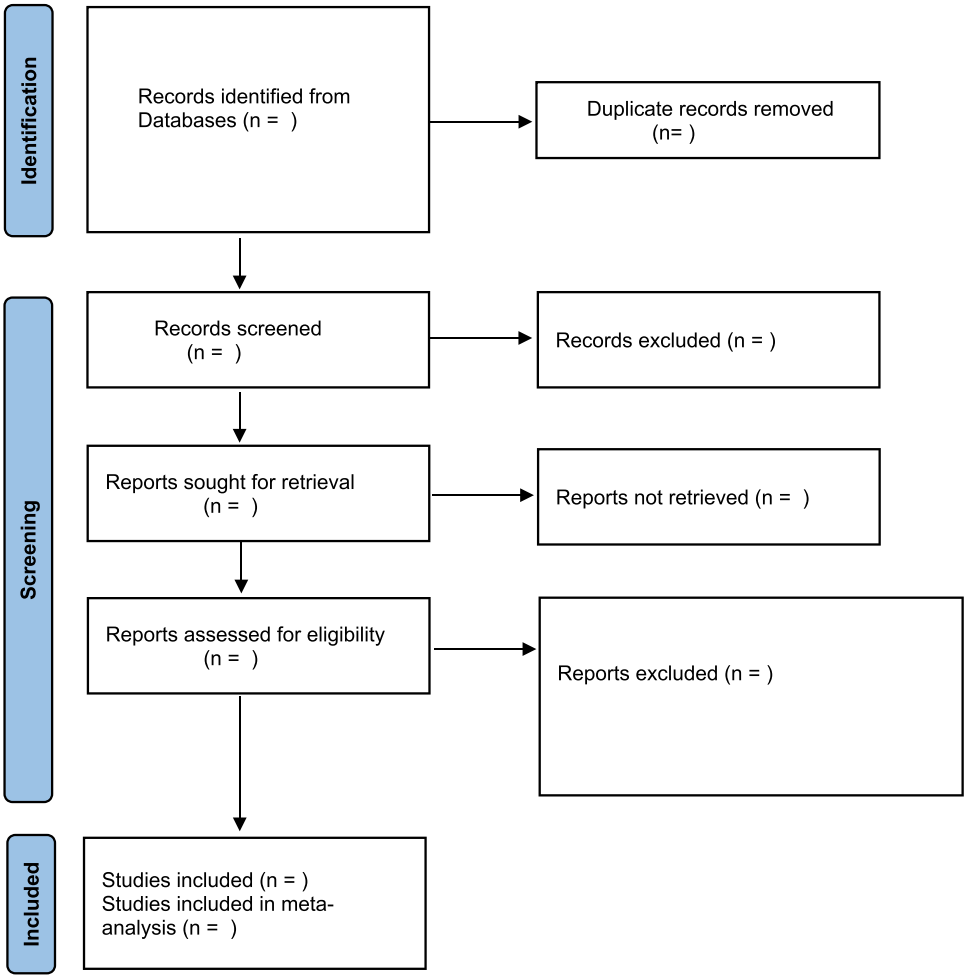

Figure 1. PRISMA flow diagram for study selection process.

Data extraction process

Data will be collected from full texts of articles selected after screening using the RevMan (Review Manager) feature of Cochrane, with each article having one reviewer. Each reviewer will extract data independently into an Excel spreadsheet consisting of study design, demographics, country of origin, dosages given, route of administration and patient outcomes. The data extraction sheet will undergo a pilot study of three studies per reviewer to improve the accuracy of the results. Any necessary amendments to the data extraction sheet will be made subsequent to the pilot study and implemented accordingly.

Data items

The data to be extracted will include the year of publication, country/setting, study design, duration of study, type of data analysis and demographics such as age and sex of study participants, and sample size from each study.

Also to be included is the dosage, route and frequency of administration of Atorvastatin and outcomes such as GCS score before and after the intervention.

Risk of bias in individual studies

The risk of bias for randomized controlled studies will be assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2) [6] whereas cohort studies will be assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool[7]. Different attributes of the studies will be assessed, including the rationale, study design, sampling criteria, selection bias, measurement of outcome of interest, statistical analysis, study findings and limitations. Eligible studies will be then graded according to the quality, as low, moderate or severe and critical risk of bias.

Summary measures

Data analysis was performed using R. Categorical data from the individual studies will be summarized as frequencies and percentages whereas numerical continuous data will be summarized as mean and standard deviation or median and interquartile range for parametric or non-parametric conditions, respectively. A random-effect model meta-analysis will be performed, and results will be presented as forest plots.

Sub-group analysis will be also performed for different age groups, gender, regional location, dosage of Atorvastatin therapy, GCS, length of hospital stay, mortality rate and quality of studies.

Synthesis of results

Extracted data will be tabulated into an excel spreadsheet reflecting the characteristics of each included study in a descriptive manner. This will consider the year of publication, country, study design, number and age of participants, dosage, route and frequency of administration of Atorvastatin and outcomes from each study. The dosages of Atorvastatin will be presented as total daily dosage in milligrams (mg) and route of administration as orally (PO), intravenously (IV) or intramuscularly (IM). The

primary outcomes of interest will include the GCS, while the secondary outcomes will include the length of hospital stay and mortality rate.

Risk of bias across studies

Egger's test and a funnel plot will be used to assess for bias across studies, and the trim-and-fill method will be used to eliminate the effects of any publication bias. A systematic narrative synthesis will be performed to complete the meta-analysis. A $P < 0.05$ will be considered statistically significant for all hypothesis testing.

Subgroup analysis

Sub-group analysis will be also performed for different age groups, gender, regional location, dosage of Atorvastatin therapy, GCS, length of hospital stay, mortality rate and quality of studies.

Sensitivity analysis

Sensitivity analysis will be used to evaluate how reliable the results are. Research with incomplete data and high risk of bias will be excluded and analysis run. To evaluate quality, the Cochrane risk of bias (C-ROB) tool will be used. The C-ROB utilizes a set of criteria to evaluate potential bias related to patient selection, randomization and treatment allocation.

Strength of body of evidence

The certainty of evidence will be assessed using five GRADE domains of risk of bias, consistency, precision, directness and publication bias. Ultimately, the strength of evidence will be rated in levels, as either high, moderate, low or very low.

Ethical consideration and dissemination

Ethical approval will not be required as there will be no human participant involvement in this study. The findings from this study will be disseminated at scientific conferences and published in a reputable peer-reviewed journal.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of Surgical Protocols and Research Methodologies* online.

AUTHORS' CONTRIBUTIONS

V.K and N.M designed and drafted the protocol. N.S, N.M, K.D, M.S, T.T, O.T, A.L, A.S, L.K, E.M, V.K, E.S, H.A, F.G, I.E, A.T drafted the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interest disclosure.

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