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Research Article

The Neuroprotective Efficiency of Cysteinyl Leukotriene Receptor Antagonist (Montelukast) in TBI; A Systematic Review and Meta-Analysis Protocol

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Abstract

Background: Traumatic Brain Injury (TBI) is one of the leading causes of morbidity, disability, and mortality across all ages, with a global annual incidence between 27 to 69 million. The pathophysiology of TBI involves the over-production of reactive oxygen species. This systematic review aims to evaluate the efficacy of montelukast in patients with TBI.

Methodology: This systematic review aims to evaluate the neuroprotective efficacy of montelukast, a cysteinyl leukotriene receptor antagonist, in Traumatic Brain Injury (TBI) patients. The study will be conducted following the AMSTAR guidelines and reported according to PRIMA guidelines. A comprehensive literature search will be conducted in various databases, including Pubmed, Embase, Hinari, Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform, and clinicaltrials.gov, using keywords related to leukotriene receptor antagonists and TBI. The inclusion criteria for the studies will be randomized controlled trials in human subjects that compare montelukast with a placebo or montelukast with routine treatment. Two independent reviewers will screen the titles and abstracts of the studies identified by the search and obtain full-text articles for those that meet the inclusion criteria. The quality of the included studies will be evaluated using the Cochrane Risk of Bias tool or ROBIN. Data will be extracted from the studies using Eppi Reviewer or Microsoft Excel. A narrative synthesis of the data will be conducted, and a meta-analysis will be performed if appropriate.

Ethics and dissemination: This research will utilize previously collected data, and no individuals will be involved. Therefore, obtaining ethical clearance is not required. The findings of this study will be presented at national and international conferences and submitted for publication in a journal undergoing peer review.

Keywords: Traumatic brain injury; Montelukast; Cysteinyl leukotriene receptor antagonist; Neuroprotection; Randomized controlled trial; Secondary data analysis; Meta-analysis; Leukotriene receptor antagonist; TBI; Cochrane risk of bias tool

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Background

Traumatic brain injury.

Description of the condition

Traumatic Brain Injury (TBI) is physical injury to brain tissue that temporarily or permanently impairs brain function [1]. Causes include motor vehicle crashes and other transportation-related causes (eg. bicycle crashes, collisions with pedestrians), falls (especially in older adults and young children), assaults, and sports activities [1]. TBI has been one of the leading causes of morbidity, disability and mortality across all ages [2]. Globally, more than 50 million individuals suffer from TBIs each year. As of 2005, approximately 3.17 million TBI survivors experience post-traumatic complications ranging from neurological and psychosocial problems to long-term disability [3].

Death of resident cells of the Central Nervous System (CNS) has traditionally been accepted to take place in two phases: an early necrotic and an ongoing long-term apoptotic phase [4]. At the cellular level, the biphasic nature of the secondary injury is mediated by numerous disturbed pathways which include: (a) excitotoxicity caused by an excess of the neurotransmitter glutamate; (b) free radical generation by dysfunctional mitochondria, causing damage to proteins and phospholipid membranes of neurons and glia; and (c) the neuroinflammatory response which takes place due to both CNS and systemic immune activation [5]. Moreover, microglial activation within injured loci was observed within 6-48 hours post-injury [6]. Thus, diffuse brain injury-mediated immune responses, blood-brain barrier alterations and neuroinflammation seem to play an important role in the pathology [7].

Clinical manifestations vary markedly in severity and consequences. Damages of neuronal tissues associated with TBI fall into two categories: (i) primary injury, and (ii) secondary injury [8]. Primary brain injury refers to the unavoidable brain damage which occurs at the immediate moment of impact, resulting in the disruption of the brain parenchyma and cerebral blood vessels [9]. Secondary brain injury develops in minutes to months following the original insult; progressively contributing to the worsened neurological impairment suffered [10]. This complex phenomenon is defined by the various neurochemical cascades activated and the systemic physiological responses which manifest following the traumatic event [11].

Description of the intervention

Leukotrienes were initially described by Feldberg and Kellaway between 1938 and 1940 [12]. They are involved in various inflammatory processes from increased vascular permeability to being instrumental in airway constriction [13]. Leukotrienes can be found in various locations in the brain. Traumatic Brain Injury (TBI) is associated with acute neuronal injury and neuroinflammation through the upregulation of cysteine Leukotriene Receptors (CysLTR) which modulate the actions of cysteinyl leukotrienes. The diffuse axonal injury that results from TBI causes these receptors which have a high affinity for leukotriene LTD4 to be activated.

Subsequently, pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines (CCL2, CCL5, CXCL1) are released, gaining access through a permeable Blood-Brain Barrier (BBB) and these agents are involved in kick-starting the neuroinflammatory process [14]. This inflammatory process in its acute form is beneficial to the brain as it helps in the repair of damaged neurons, and neuroplasticity and further offers protection to intact neuronal tissues. When acute inflammation progresses to chronic, the priorities of proinflammatory cytokines which have now been produced in excess change as they are now more involved in the destruction of neurons which incites the pathway that eventually leads to degeneration [15].

How the intervention might work

Montelukast, a monocarboxylic acid with aliphatic sulphide belonging to the quinolone family, was approved by the FDA in 1998. It acts by inhibiting 5-LO, and CysLTR, and has been influential in the management of asthma, urticaria and allergic rhinitis [16]. Its bioavailability is 60%-70% with high plasma protein binding. Montelukast, an antagonist to CysLTR, offers neuroprotection through its anti-inflammatory activities and restoration of the damaged BBB [17]. Neurotoxicity is precipitated through the action of leukotrienes involved in chronic inflammation. Glutamate, an excitatory neurotransmitter, which is essential in neuro-signalling and transport, functions by encouraging calcium influx into neurons which then activates the AA pathways resulting in the production of leukotrienes. It has been discovered that montelukast possesses antagonistic abilities against NMDA-induced CysLTR expression. Thus, helping to mitigate the effects of LTD4-induced neuroinflammation [18].

Why it is important to carry out this review

So far, the precise role of montelukast in TBI has not been fully comprehensively described as compared to its role in asthmatic disorders and other related disorders. While some studies have reported its role in reducing brain oedema and stabilizing the blood-brain barrier [18]. Some other studies in animals have however shown its propensity to increase membrane permeability [13].

Systematic review studies have been done on this subject but to our knowledge, little to no current meta-analysis has been carried out on this subject. This paper, therefore, aims to evaluate the efficacy, adverse effects and mechanism of action of montelukast in patients with TBI.

Specific objectives

To evaluate the clinical-based therapeutic effects and adverse effects of montelukast in TBI patients. The specific objectives include:

1. To measure the effect of montelukast on TBI patients
2. To evaluate the severe adverse effects of montelukast in TBI patients
3. To determine the prognosis of patients with TBI treated with Montelukast.
4. To compare and contrast the mechanism of action of montelukast in TBI patients from various studies.

Methodology

Types of studies

Randomized Controlled Trials (RCTs) will be included in this study. Due to the paucity of studies on this subject, we will include the reports of both published and unpublished works and studies published in different languages will be included without any exceptions.

Study population

The study participants would involve people with TBI. There will be no restriction on age or sex. We will also include participants

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irrespective of the severity of the head injury.

Eligibility criteria

The studies will be included and excluded based on the following criteria:

Inclusion criteria: All RCTs studies published that discuss and report the effect and efficacy of cysteinyl leukotriene antagonist, montelukast will be included. There will be no restriction on language.

Exclusion criteria: The following study characteristics will not be considered

1. Studies that discuss another cysteinyl leukotriene antagonist aside from Montelukast
2. Studies that involve animal subjects
3. Articles on the role of montelukast in Asthma and Allergic rhinitis will be excluded.

Types of intervention

We will include RCTs that evaluate the efficacy of Montelukast, a cysteinyl leukotriene receptor antagonist in TBI patients. We will ensure that the participants in the included study both have almost equal care including any form of pharmacotherapy, non-pharmacotherapy such as rehabilitation, etc. The comparison will be made as follow:

- Montelukast versus the placebo.
- Montelukast plus routine treatment versus routine treatment alone.

Type of outcomes measure

The outcome will be divided into primary and secondary outcomes.

Primary outcome:

- Mortality
- Functional outcomes such as the number of days spent in the ICU, Number of days spent on mechanical ventilation, duration of coma, and disability will be measured.

Secondary outcome:

- Disability
- Mechanism of action of intervention
- The effective dose of intervention, route of administration, and side effects/adverse effects of the intervention.

Search strategy

The search will be conducted independently by two reviewers. An initial search will involve searching major databases such as Pubmed, Embase, Hinari, Cochrane Central Register of Controlled Trials in the Cochrane database, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and ClinicalTrials.gov. The titles and abstracts, index terms, and, and MeSH term keywords will be searched such as ('Montelukast' OR 'cysteinyl leukotriene receptor antagonist') AND ('traumatic brain injury' OR 'TBI' OR 'brain injury') (see Appendix I for a complete search strategy for MEDLINE *via* PubMed).

The searched strategies will include both published and unpublished studies. Publication in all languages will be eligible. Non-English studies will be translated into the English language before review. In addition to the databases above, we will also search specific other grey databases like Health Management Information Consortium database (HMIC), OpenGrey, google scholar and the National Technical Information Consortium database (NTIS). Studies found from these grey databases will also be included. We will also perform a secondary search to identify and include the reference lists of some of the included studies.

Study selection

The studies collected during the search will be entered into Rayyan [19]. This is web-based software for systematic review and meta-analysis. The initial review will involve screening titles and abstracts based on the eligibility criteria. Afterwards, the second screening will involve the review of the main text articles. During the screening processes, the blind will be turned on so as to allow the reviewers to screen each article independently and without any external influence.

At the end of the initial review, the blind will be turned off so as to allow any form of differences in opinion to be settled among the reviewers paired to screen a particular set of papers. The opinion of a third reviewer will be sought if two paired reviewers are not able to come to an agreement on their views. The second screening will also be done following the same procedure. The selection and exclusion of the papers will be illustrated using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [20] flow diagram as shown in Figure 1 below.

Quality assessment/risk of bias

Quality assessment or risk assessment will be done using the Cochrane collaboration tool for assessing the risk of bias [21]. This will be done independently by two review authors. The domains for judgment will include

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting

The judgment assessment criteria for each domain as outlined in the Cochrane book will be used. The risk will be grouped into 'Low risk' of bias, 'High risk' of bias or 'Unclear risk' of bias. In the end, disagreement in the decision will be resolved via a meeting and discussion between two reviewers. Risk will be categorized as 'Unclear risk of bias if there is no detailed information about what happened in the study and if the risk of bias in that particular study is not known

The measure of treatment effect

The effect of montelukast as compared to placebo/observation or to other treatments' analysis as stated in the intervention section will be done using survival data (i.e. time-to-event data). We will extract Hazard Ratios (HR) and their 95% Confidence Intervals (CI) from each study to achieve this. For binary data (such as toxicity), we will use Risk Ratios (RR) to describe the differences between experimental and comparator groups.

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Data extraction

Following the screening of full-text articles, the next step will be to read the articles identified for inclusion in the systematic review [22]. Each reviewer will be given about 3-5 papers depending on the number of articles selected to read through thoroughly and get the relevant data needed for inclusion in the study. After this, the relevant data will be extracted into Ms Excel forms. Data will be collected based on the following points (i) Study design (ii) Study demographics (iii) Country of origin (iv)Intervention with Montelukast (v) Control group outcome (vi) Barriers to Montelukast administration (Vii) patient outcome after the intervention. To ensure that valid and standardised data is collected, a short pilot that will involve assigning senior reviewers' articles to re-evaluate will be done.

Data analysis/synthesis

A meta-analysis will be done based on the intervention and the patient outcomes from the data extracted. We will ensure that the data is collected from studies on the same topic and ensure that it can be combined [23]. We will clearly define the Population, Intervention, Comparison and Outcomes (PICO) during the study selection as these are essential for evidence-based research. Meta-analysis will only be conducted when there is homogeneity in data collected among the various studies. The study's participants, methods, and outcomes will be examined critically. Chi-Squared and I2 statistics will be used. Heterogeneity will be said to be present and statistically significant when the p-value is <0.05. Subsequently, an I2 statistic value >50% will also be considered statistically significant. Sub-group analysis will be done on Low dose versus high dose; ICU admissions *vs.* Inpatient ward admissions and mild brain injury *vs.* moderate brain injury groups.

Limitation

This is a systematic review and meta-analysis study that will pool data from several studies. The possibility of bias in study selection cannot be totally ruled out and some important studies can be left out due to imprecision in search and study selection. Also, the selection of the study's outcome to be reported can be biased. The varying study methodology and differing heterogeneity can limit the inclusion of certain studies in the meta-analysis.

Conclusion

We will base our conclusion on the results from our meta-analysis and we will review areas of future research and give an appropriate recommendation.

Acknowledgement

We love to acknowledge every author for sparing time to participate in this systematic review.

Authors' Contributions

K.A., M. S. and O.T.A. contributed to the conceptualization and study design. M.N, C.I, A.N, E.O, and Z.Y.E, S.O.D contributed to the drafting of the different parts of the protocol, editing and revising.

Registration Number

This protocol will be registered on the International Prospective Register of Systematic Reviews (PROSPERO).

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