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Review Article

Emerging therapies for immunomodulation in traumatic brain injury: A systematic review and meta-analysis

Abdulrahim Saleh Alrasheed[1], Mohammed Abdullah Alqadhibi[2], Rammaz Hussam Khoja[3], Abdulaziz Saad Alayyaf[4], Duaa Saleh Alhumoudi[5], Mubarak Ibrahim Aldawlan[6], Bedoor Obidallah Alghanmi[7], Fahad Salman Almutairi[8], Mohammed Ali Bin-Mahfooz[9], Lina Abdulrahim Altalhi[10], Saud Nayef Aldanyowi[1], Abdulsalam Mohammed Aleid[1], Awn Abdulmohsen Alessa[11]

[1]Department of Surgery, College of Medicine, King Faisal University, AlAhsa, [2]Department of Surgery, College of Medicine, Majmaah University, Majmaah, [3]Department of Surgery, College of Medicine, Taibah University, Madinah, [4]Department of Surgery, College of Medicine, Prince Sattam bin Abdulaziz University, [5]Department of Surgery, College of Medicine, King Saud University, Riyadh, [6]Department of Surgery, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, [7]Department of Surgery, College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, [8]Department of Surgery, Royal College of Surgeons in Ireland, Dublin, Ireland, [9]Department of Surgery, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [10]Department of Surgery, College of Medicine and Medical Science, Arabian Gulf University, Manama, Bahrain, [11]Department of Neurosurgery, King Fahad Hospital, AlAhsa, Saudi Arabia.

E-mail: Abdulrahim Saleh Alrasheed - 221414880@student.kfu.edu.sa; Mohammed Abdullah Alqadhibi - 391100322@s.mu.edu.sa; Rammaz Hussam Khoja - tu4251379@taibahu.edu.sa; Abdulaziz Saad Alayyaf - 439050015@std.psau.edu.sa; Duaa Saleh Alhumoudi - duaaalhumoudi@gmail.com; Mubarak Ibrahim Aldawlan - Maldawlan@gmail.com; Bedoor Obidallah Alghanmi - bhussainalghanmi@stu.kau.edu.sa; Fahad Salman Almutairi - fahad.fahad10606@gmail.com; Mohammed Ali Bin-Mahfooz - mohammedbinmz@outlook.com;Lina Abdulrahim Altalhi - linaaltalhi1@gmail.com; *Saud Nayef Aldanyowi - saldanyowi@kfu.edu.sa; Abdulsalam Mohammed Aleid - 225094489@student.kfu.edu.sa; Awn Abdulmohsen Alessa - awabalessa@moh.gov.sa

***Corresponding author:**
Saud Nayef Aldanyowi,
Department of Surgery, College of Medicine, King Faisal University, AlAhsa, Saudi Arabia.

saldanyowi@kfu.edu.sa

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ABSTRACT

Background: Traumatic brain injury (TBI) represents a significant global health burden, often leading to significant morbidity and mortality. Mounting evidence underscores the intricate involvement of dysregulated immune responses in TBI pathophysiology, highlighting the potential for immunomodulatory interventions to mitigate secondary injury cascades and enhance patient outcomes. Despite advancements in treatment modalities, optimizing therapeutic strategies remains a critical challenge in TBI management. To address this gap, this systematic review and meta-analysis aimed to rigorously evaluate the efficacy and safety of emerging immunomodulatory therapies in the context of TBI.

Methods: We searched electronic databases such as PubMed, Scopus, Web of Science and CENTRAL for relevant studies investigating the efficacy of immunomodulatory therapies in TBI that were meticulously selected for inclusion. Two independent reviewers meticulously performed data extraction and quality assessment, adhering to predefined criteria. Both randomized controlled trials (RCTs) and observational studies reporting clinically relevant outcomes, such as mortality rates, the Glasgow coma scale, and adverse events, were meticulously scrutinized. Meta-analysis techniques were employed to assess treatment effects across studies quantitatively and analyzed using the Review Manager software (version 5.2).

Results: Fourteen studies (n = 1 observational and n = 13 RCTs) were included in our study. Meta-analysis showed no significant overall mortality difference, but erythropoietin (EPO) significantly reduced mortality (odds ratio = 0.49; 95% confidence interval: 0.31–0.78, P = 0.002). The adverse event meta-analysis revealed no significant differences.

Conclusion: Immunomodulatory therapies did not significantly affect overall mortality, but EPO demonstrated promising results. Adverse events did not significantly differ from controls. Further research is warranted to refine TBI treatment protocols.

Keywords: Erythropoietin, Immunomodulatory therapies, Traumatic brain injury, Treatment outcomes

INTRODUCTION

Traumatic brain injury (TBI) can be defined as the disruption in brain function or other evidence of brain pathology caused by an external physical force. The yearly incidence of TBI is estimated at 50 million cases worldwide; thus, approximately half of the global population will have an episode of TBI in their life.[14,15-27] In the UK, it is the most common cause of death and disability in those aged under 40 years.[23,26] Moreover, even higher rates of morbidity and mortality are seen in low-income and middle-income countries. Yearly, TBI costs the global economy approximately 400 billion US dollars, representing 0.5% of the gross world product.[14]

A large number of TBI patients are living with lifelong motor, cognitive, and other disabilities. In addition, TBI increases the incidence of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, among survivors.[35] So far, there is no effective pharmacological treatment to reduce brain injury or promote brain repair after TBI.

The severity of a TBI does not depend solely on the direct initial injury. The acute primary insult to the brain elicits a cascade of immune responses in the lesioned brain, which may induce secondary injuries and expand brain lesion size at the subacute stage of TBI. Indeed, prolonged immune responses could be observed in human and mouse brains years after TBI.[3,5,6,25,34,35] The severity of immune responses is associated with brain lesion size and neurologic deficits.[34] As the first line of defense in the central nervous system (CNS), microglia, as well as invaded macrophages, play an essential role in immunoregulation after TBI.[12] In the acute phase of TBI, microglia and macrophages secrete a large number of anti-inflammatory factors, including interleukin IL-4, IL-10, and transforming growth factor-beta, to limit brain damage. However, persistent microglia and macrophage activation in the subacute phase results in excessive production of proinflammatory factors such as IL-6, IL-1β, tumor necrosis factor-alpha, and interferon gamma, which can aggravate brain injury.[2,4,5,8,10,12,22] Shifting microglia and macrophage responses to an anti-inflammatory modality that favors brain preservation and repair may, therefore, represent a legitimate therapy for TBI.[8,12]

Immunomodulation is the process of modifying the immune response to achieve a therapeutic effect. In the context of TBI, immunomodulation is used to reduce the damaging inflammatory response that occurs after the initial injury. One promising approach to achieve immunomodulation in TBI is through the use of mesenchymal stem cells (MSCs). MSCs have been shown to reduce secondary neurodegeneration and neuroinflammation, promote neurogenesis and angiogenesis, and improve functional outcomes in animal models of TBI.[3,6,7,10,39] The beneficial effects of MSC therapy are thought to be due to the immunomodulatory properties of the molecular factors secreted by MSCs rather than cell engraftment. Several emerging therapies for immunomodulation in TBI have been investigated, including B-cell treatment, mesenchymal stromal cells, and human umbilical cord blood cells.[6,12]

Researchers have shown substantial interest in understanding the use of anti-inflammatory drugs to address the robust inflammatory response observed during the acute phase of TBI. This inflammatory response has been shown to exacerbate secondary injury progression. Various categories of anti-inflammatory medications, such as non-steroidal anti-inflammatory drugs, corticosteroids, and minocycline, have been subject to scrutiny for their potential efficacy in managing TBI.[4,13,16,39]

Erythropoietin (EPO) was investigated as a potential treatment modality for TBI due to its neuroprotective properties. EPO is a glycoprotein hormone that regulates red blood cell production and has been shown to protect tissues in addition to its hematopoietic function. Research suggests that EPO may exert neuroprotective effects by reducing inflammation, preventing neuronal damage, promoting neurogenesis, and enhancing angiogenesis. These mechanisms could potentially help mitigate the secondary injury cascade that occurs following TBI, thereby improving outcomes for patients.[2,21,33]

The immunomodulation target therapies are showing great potential in managing TBI; as a result, we present a comprehensive systematic review and meta-analysis aimed at determining the efficacy and safety of emerging immunomodulation therapies in TBI. We aimed to better understand the impact of immunomodulatory interventions on key outcomes such as neurological function, mortality rates, and adverse events by systematically synthesizing data from relevant clinical studies.

MATERIALS AND METHODS

This study was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. The current study was prospectively registered into the International Prospective Register of Systematic Reviews (PROSPERO) under the following protocol number: [CRD42024523787].

Study selection

Literature search strategy

We searched electronic databases such as PubMed, CENTRAL, Scopus, and Web of Science for relevant studies. We used the following search strategy: (Traumatic Brain Injury OR TBI) AND (Stem Cell OR Cyclosporin OR Erythropoietin OR Progesterone OR Immunomodulation OR Immunomodulatory Therapy).

Eligibility criteria

Studies were eligible for inclusion if they met the following criteria:

- Studies published in English
- **Population:** Adult patients (≥18 years) were diagnosed with TBI
- **Intervention:** Immunomodulation therapies
- **Comparator:** Placebo
- **Outcome:** Studies reporting at least the mortality rate
- Study design: All randomized controlled trials (RCTs) and observational studies, either case–control or cohort studies.

Reviews, case reports, editorial letters, conference abstracts and study protocols, animal and phantom studies were excluded from the study.

Study selection process

Two independent reviewers screened the titles and abstracts of the retrieved articles to identify potentially relevant studies. Full-text articles were then reviewed for eligibility based on the inclusion and exclusion criteria. Discrepancies between reviewers were resolved through consensus or consultation with a third reviewer.

Data extraction

A standardized data extraction sheet was developed to capture relevant information from the included studies using Microsoft Excel. Each author extracted the following data from included studies: name of the first author, publication year, type of study, number of enrolled patients, sex ratio, period of the study, inclusion criteria, average ages, intervention details, adverse events, and outcomes. Two senior authors reviewed the extracted data. Any disagreements were resolved by group discussion.

Quality assessment

The methodological quality and risk of bias (ROB) of the included studies were assessed using appropriate tools based on the study design. For RCTs, the Cochrane ROB Tool was used to evaluate random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case–control studies.[22]

Data synthesis and analysis

Meta-analysis was conducted to pool data from included studies using appropriate statistical methods using the Review Manager software 5.1.4, provided by Cochrane Collaboration. Effect sizes were calculated for relevant outcomes, such as mortality rates, Glasgow coma scale (GCS), and adverse events. Random-effect models were used to account for heterogeneity between studies. Subgroup analyses were conducted to investigate potential sources of variability in the study outcomes, with a focus on the different types of immunomodulatory therapies utilized and the GCS scores as indicators of injury severity. The funnel plot and Egger regression test were used to assess potential publication bias [Figure 1].

RESULTS

Literature search

The initial database search yielded a total of 12561 articles. 4816 records were screened by titles and abstracts, and 150 articles were identified as potentially relevant for full-text review. Following a thorough assessment of eligibility criteria, 13 studies were included in the final analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart, shown in Figure 2, illustrates the selection process of the study.

Characteristics of the included studies

There were 13 randomized controlled trials (RCTs) and one cohort study that included patients older than 18 years with TBI. These interventions included progesterone, EPO, and cyclosporine, with seven studies assessing progesterone. The general characteristics of the included studies are summarized in Table 1, while extracted data of the baseline characteristics of the participants are outlined in Table 2.

Quality assessment

Overall, one included observational study had a good quality in NOS assessment.[20] While in the ROB-2 assessment of

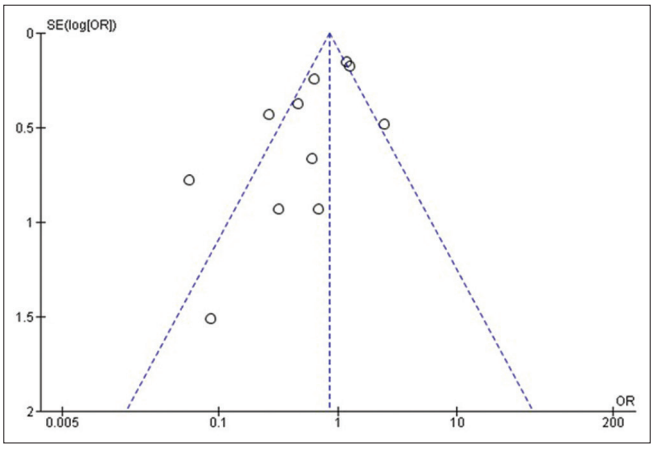

Figure 1: Funnel plot of mortality.

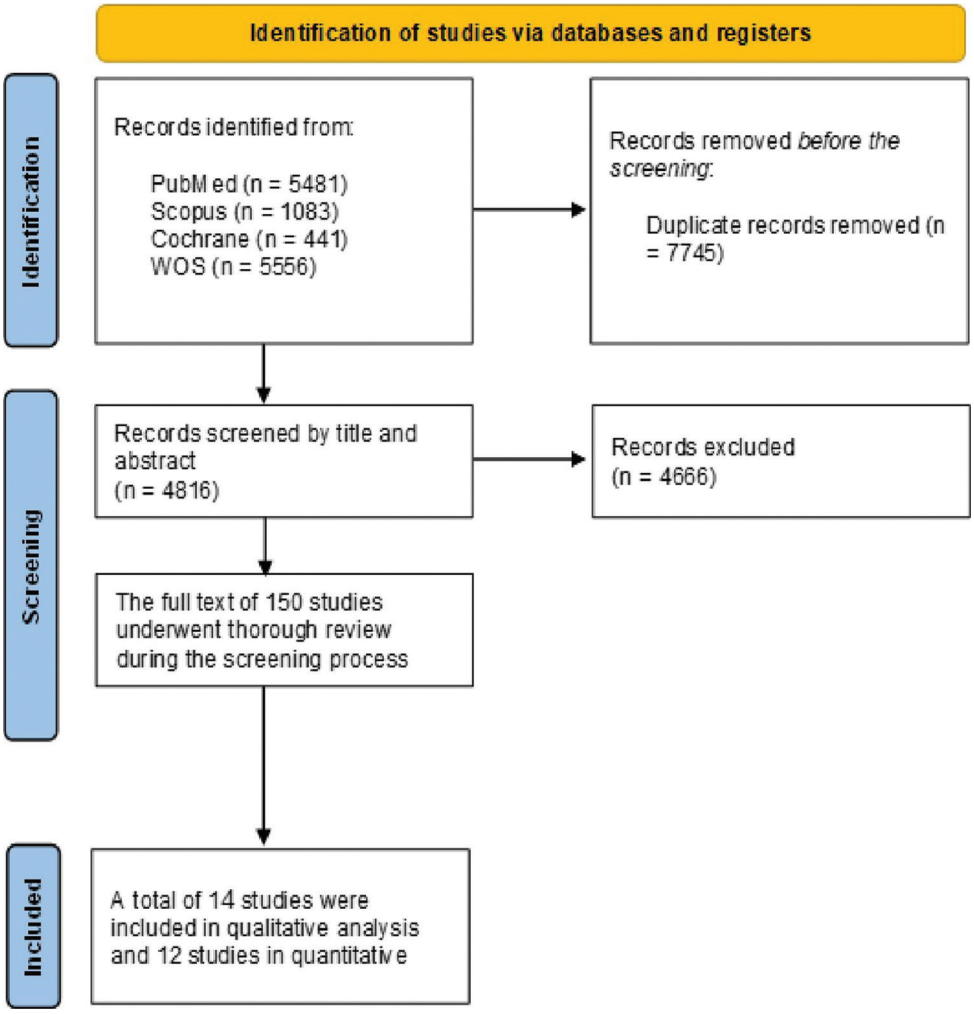

Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the included studies. 150 articles were considered for full-text review; 14 articles were included in our qualitative review, and 12 were considered for quantitative analysis.

randomized controlled trials (RCTs), seven studies revealed a low ROB,[11,24,30-32,37,38] three out of 13 had a high ROB.[1,2,18] The other three RCTs showed fair quality.[9,28,36] ROB-2 assessments are illustrated in Figures 3 and 4.

Outcomes

Mortality

A meta-analysis was conducted to compare the mortality rates between the intervention and control groups for TBI. Eleven studies[1,11,18,24,25,30-33,36-38] with a total of 3537 participants were included in the analysis. The pooled odds ratio (OR) was estimated to be 0.85 (95% confidence interval [CI]: 0.71–1.01), which indicates that there is no statistically significant difference in mortality between the two groups. Significant heterogeneity was observed among the included studies, with $I^2 = 75\%$, so a random effect model was used [Figure 5].

We found that heterogeneity was minimized in the subgroup of EPO ($I^2 = 13\%$) and reduced among the progesterone group ($I^2 = 81\%$). Furthermore, we noticed that there was no statistically significant difference between the two groups in progesterone studies (OR = 0.74; 95% CI: 0.39–1.39, $P = 0.35$) and a statistically significant difference in the EPO intervention group (OR = 0.49; 95% CI: 0.31–0.78, $P = 0.002$) [Figure 6].

Efficacy of immunomodulators on neurological recovery

The neurological outcomes of TBI patients were evaluated in the included studies[2,11,18,24,30-33,36,38] by the GCS showing different level of consciousness and overall function. A favorable outcome (GCS >8) was found among various studies, which revealed that immunomodulators showed a significant favorable neurological recovery (RR = 1.21, 95% CI: 1.01–1.46; $P = 0.04$). However, the control group was associated with an unfavorable neurological function

Table 1: Baseline characteristics of the included studies.

Study ID	No. of patients	Condition	Intervention	Age (mean±SD)	Sex (male %)	Mechanism of injury
Bai and Gao, 2018	120	Severe TBI	Recombinant human EPO versus Placebo	44.5±11.4 versus 43.1±10.9	68.3 versus 73.3	Vehicle accident: 60.0%, Fall: 30.0%, Others
Liu *et al*., 2011	84	TBI	Endothelial Progenitor Cells	42.92±16.24 versus 40.45±18.05	75.7 versus 75	-
Hatton *et al*., 2008	40	Severe TBI	Cyclosporin versus Placebo	29.5±11.7 versus 6±6.6	78.125 versus 100	-
Aloizos *et al*., 2015	42	Severe closed TBI	EPO versus Placebo	29.4±1.3 versus 46.5±4.5	95.8 versus 88	-
Goldstein *et al*., 2017	-	Moderate to severe TBI	Progesterone versus Placebo	42.33±43.9 versus 43.66±49.9	74.5 versus 71.7	-
Li *et al*., 2016	146	Severe TBI	Recombinant human EPO versus Placebo	43.4±10.1 versus 41.1±9.6	65.3 versus 57.7	-
Nichol *et al*., 2015	603	Severe to moderate TBI	EPO versus Placebo	33.46±18.69 versus 33.9±18.9	36 versus 33	Motor vehicle accident: 37%, Fall/jump: 24%, Others
Shakeri *et al*., 2013	76	-	Progesterone versus Placebo	33.97±12.48 versus 34.68±12.87	50	-
Skolnick *et al*., 2014	1179	Severe TBI	Progesterone versus Placebo	36.33±20.8 versus 36±19.32	78.5 versus 78.7	Motor vehicle or motorcycle accident: 62.4%, Fall: 21%, Others
Soltani *et al*., 2017	48	Moderate to Severe TBI	Progesterone versus Placebo	27.85±1.44 versus 30.37±2.51	-	Motor vehicle: 20%, Others
Wright *et al*., 2007	100	Acute TBI	Progesterone versus Placebo	35.3±14.3 versus 37.4±17.4	71 versus 70	Motor vehicle: 74%, Fall: 6%, Others
Xiao *et al*., 2008	159	Acute Severe TBI	Progesterone versus Placebo	30±11 versus 31±9	70 versus 74	Motor vehicle: 80%, Fall: 10%, Assault: 8%, Others
Wright *et al*., 2014	882	Acute TBI	Progesterone versus Placebo	49±57.26 versus 48±56.25	73.3 versus 74.1	Motor vehicle accident: 36%, Motorcycle: 17.6%, Others
Robertson *et al*., 2014	400	-	EPO 1 regimen, EPO 2 regimen, Placebo, Transfusion Threshold	-	-	Assault: 5.3%, Automobile accident: 50%, Others

TBI: Traumatic brain injury, EPO: Erythropoietin

(GCS <8) (RR = 0.78, 95% CI: 0.36–0.95; $P = 0.01$). A random effect model was conducted [Figure 7].

Adverse events

Thromboembolic events

A meta-analysis of six studies[2,18,24,33,36,37] was conducted to compare the incidence of thromboembolic events between both groups. We found that there is no statistically significant difference between the two groups; the OR was 1.29 (95% CI, 0.82–2.03, $P = 0.27$). There is no heterogeneity found among the included studies with $I^2 = 0\%$ [Figure 8].

Gastrointestinal tract disturbances

A meta-analysis of three[2,24,31] was conducted to compare the incidence of gastrointestinal problems between both groups.

Table 2: Summary of the included studies.

Study ID	Study design	Country	Duration of the study (Months)	Eligibility criteria	Key findings
Bai and Gao, 2018	RCT	China	April 2013–March 2016	Patients with severe TBI (GCS <8), <24 h since the injury, aged 18–70	Recombinant human EPO did not enhance neurological outcomes or reduce mortality in short-term severe TBI cases
Liu *et al*., 2011	Cohort	China	April 2006–March 2007	Patients with complex trauma and TBI	Changes in circulating were EPCs correlated with GCS, indicating potential as a prognostic marker in TBI
Hatton *et al*., 2008	RCT	Kentucky	3 years	Patients aged 16–65 with GCS of 4–8, hemodynamic stability, positive CT findings, and intraventricular catheter placement	Cyclosporine administration was safe and may mitigate cognitive and physical impairments in TBI.
Aloizos *et al*., 2015	RCT	Greece	-	Patients with blunt head trauma, GCS <9 or hypotension, aged >18 years, admitted to the ICU within 6 h of injury.	EPO therapy showed lower mortality and better neurological outcomes, suggesting its potential use in TBI treatment
Goldstein *et al*., 2017	RCT	-	Within 6 months post-injury	Patients with GOAT scores ≥75	Neuropsychological assessment showed no significant effect of progesterone on outcomes in moderate-to-severe TBI patients.
Li *et al*., 2016	RCT	China	July 2010–July 2014	Patients with severe TBI	Recombinant human EPO improved functional recovery without increasing thromboembolic events or severe infections in severe TBI patients.
Nichol *et al*., 2015	RCT	Seven countries	May 2010–May 2015	Patients with moderate or severe TBI	EPO did not reduce severe neurological dysfunction or increase deep venous thrombosis, with uncertain effects on mortality
Shakeri *et al*., 2013	RCT	Iran	17 months (2010–2011)	Male patients with head trauma and diagnosed with DAI, GCS ≤8, admitted within 8 h of injury.	Progesterone administration improved neurological outcomes in traumatic patients with DAI and GCS≤8 without significant side effects.
Skolnick *et al*., 2014	RCT	-	July 2010–September 2013	Patients with severe non-penetrating TBI	Progesterone did not show clinical benefit in severe TBI patients compared to placebo.
Soltani *et al*., 2017	RCT	Iran	May 2013–December 2015	Patients aged 18–60 with moderate to severe TBI and pure DAI demonstrated on CT scan, with a GCS ≤12, were treated within 4 h post-injury	Early administration of progesterone may offer neuroprotection in moderate-to-severe DAI cases, warranting further investigation.
Wright *et al*., 2007	RCT	Georgia	-	Adult blunt trauma victims arriving at Grady Memorial Hospital within 11 hours of injury with a post-resuscitation GCS score of 4–12	Progesterone showed no harm and possible benefit to blunt trauma victims.
Xiao *et al*., 2008	RCT	China	-	Patients with acute severe TBI (GCS ≤8)	Progesterone administration improved neurological outcomes in acute-severe TBI patients up to 6 months post-injury

(Contd...)

Table 2: *(Continued)*.

Study ID	Study design	Country	Duration of the study (Months)	Eligibility criteria	Key findings
Wright *et al*., 2014	RCT	United States	-	Adults with severe, moderate-to-severe, or moderate TBI with GCS of 4–12 due to blunt mechanism	Progesterone did not improve outcomes in acute TBI patients compared to placebo.
Robertson *et al*., 2014	RCT	Houston	-	Patients with a closed head injury who were unable to follow commands within 6 h of injury	EPO administration or maintaining hemoglobin concentration did not improve neurological outcomes in closed-head injury patients

RCT: Randomized controlled trial, GCS: Glasgow coma scale, TBI: Traumatic brain injury, DAI: Diffuse axonal injury, EPO: Erythropoietin, EPCs: Endothelial progenitor cells, GOAT: Galveston orientation and amnesia test, ICU: Intensive care units, CT: Computed tomography

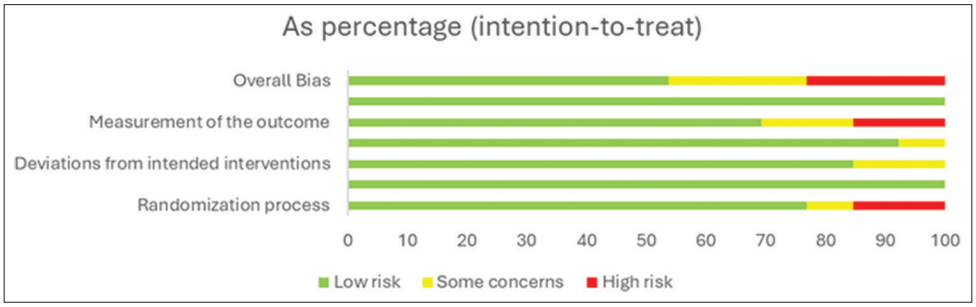

Figure 3: Risk of bias graph for the included RCTs (Randomized controlled trials).

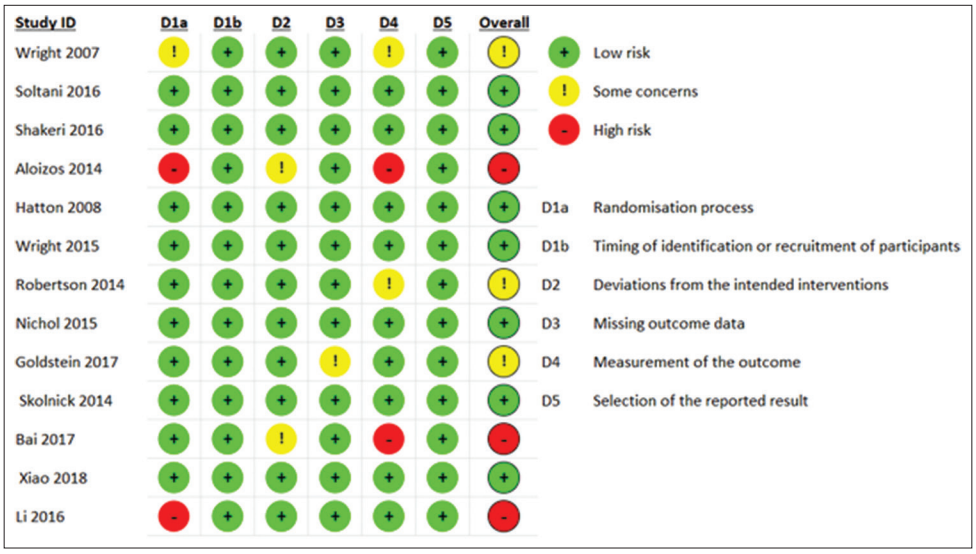

Figure 4: Risk of bias summary for the included RCTs (Randomized controlled trials).

We found that there is no statistically significant difference between the two groups; the OR was 1.11 (95% CI, 0.68–1.82, $P = 0.68$). There is minimal heterogeneity found among the included studies, with $I^2 = 15\%$ [Figure 9].

Cardiac problems

A meta-analysis of five studies[2,24,31,37,38] was conducted to compare the incidence of cardiac problems between both groups. We found that there is no statistically significant difference between the two groups; the OR was 0.99 (95% CI, 0.77–1.27, $P = 0.92$). There is no heterogeneity found among the included studies, with $I^2 = 0\%$ [Figure 10].

Sepsis

A meta-analysis of seven studies[2,19,24,31,33,37,38] was conducted to compare the incidence of sepsis between both groups.

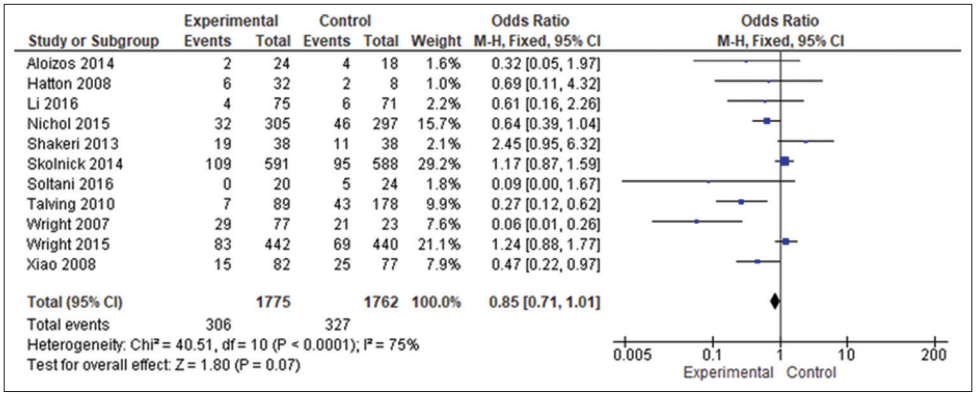

Figure 5: Meta-analysis of mortality shown as a forest plot. CI: Confidence interval.

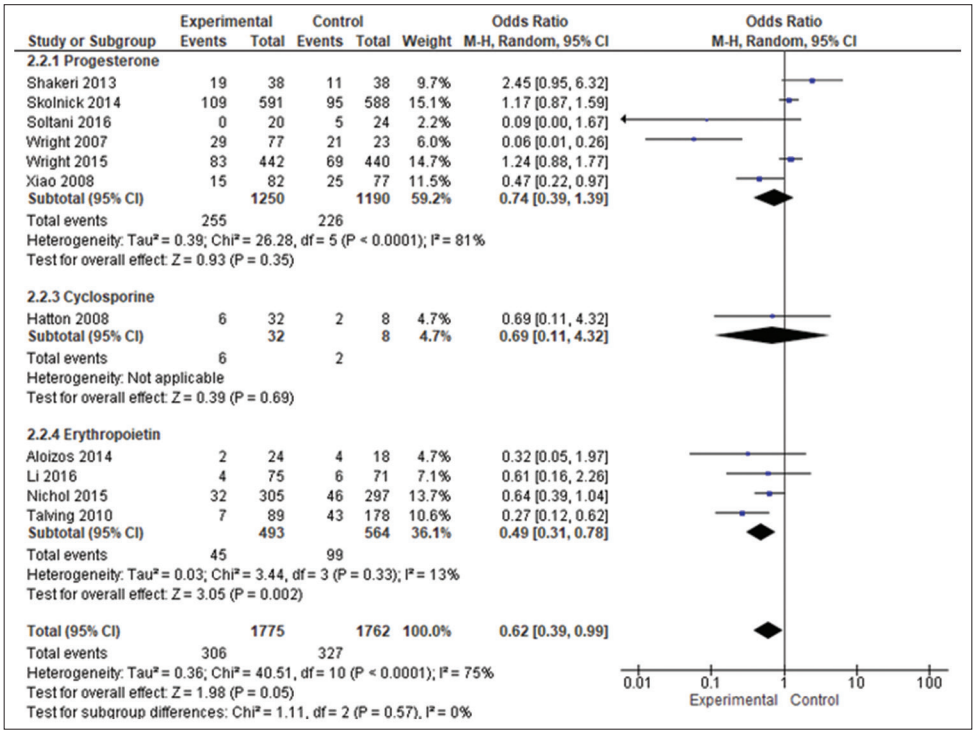

Figure 6: Subgroup analysis of mortality rate based on the type of the therapy. CI: Confidence interval.

We found that there is no statistically significant difference between the two groups; the OR was 1.16 (95% CI, 0.84–1.60, P = 0.37). There is no heterogeneity found among the included studies, with I^2 = 0% [Figure 11].

CNS disturbances

A meta-analysis of five studies[2,24,31,36,37] was conducted to compare the incidence of central nervous system disturbances between both groups. We found that there is no statistically significant difference between the two groups; the OR was 1.01 (95% CI, 0.79–1.29, P = 0.91). There is minimal heterogeneity found among the included studies, with I^2 = 3% [Figure 12].

Pneumonia

A meta-analysis of five studies[2,18,31,33,38] was conducted to compare the incidence of pneumonia between both groups. We found that there is no statistically significant difference between the two groups; the OR was 0.95 (95% CI, 0.80–1.13, P = 0.56). There is no heterogeneity found among the included studies, with I^2 = 0% [Figure 13].

DISCUSSION

TBI remains a significant public health concern worldwide, with substantial morbidity, mortality, and economic burden.[27] Despite advances in medical science, there are

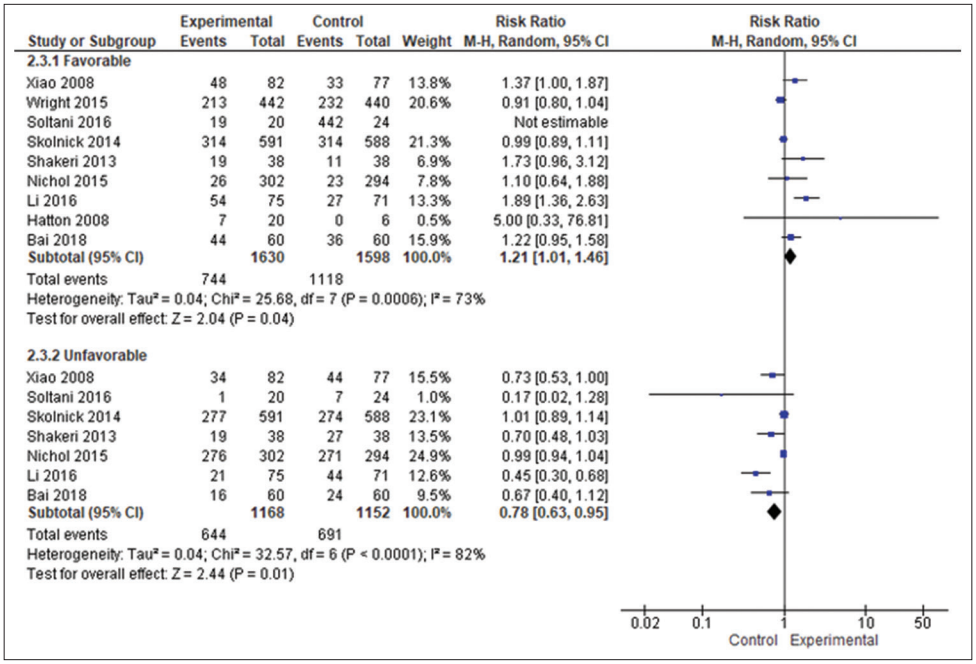

Figure 7: Meta-analysis of the neurological outcomes of the patients after therapies. *Favorable Glasgow coma scale (GCS) refers to a score greater than 8, indicating a likelihood of good to moderate outcomes. **Unfavorable GCS means GCS indicates a score lower than 8, suggesting a higher risk of severe disabilities or poor prognosis. CI: Confidence interval.

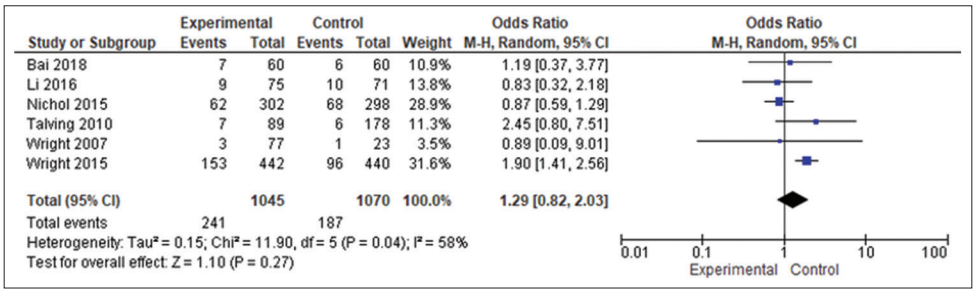

Figure 8: Meta-analysis of thromboembolic events. CI: Confidence interval

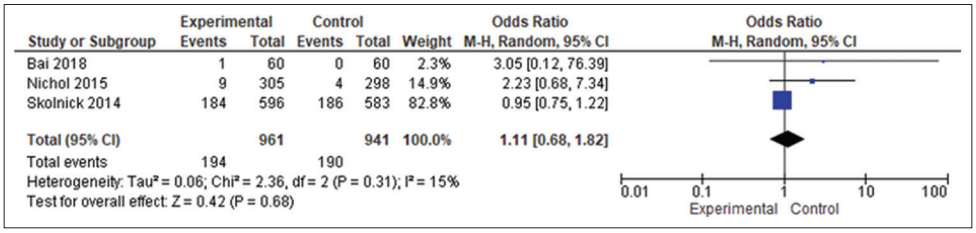

Figure 9: Meta-analysis of gastrointestinal disturbances. CI: Confidence interval

no effective pharmacological interventions to mitigate brain injury and promote recovery after TBI. Immunomodulation has emerged as a promising therapeutic approach to address the damaging inflammatory responses that occur after TBI, aiming to limit secondary neurodegeneration and enhance neuroregeneration. Several studies have highlighted the potential of immune modulation to reduce cerebral and systemic inflammatory reactions in the early phase of TBI, restore peripheral immune functions to avoid secondary infections, and limit chronic cerebral inflammation and neurologic dysfunction in the late phase.[5,27,39] Our study's findings provide valuable insights into the effectiveness of

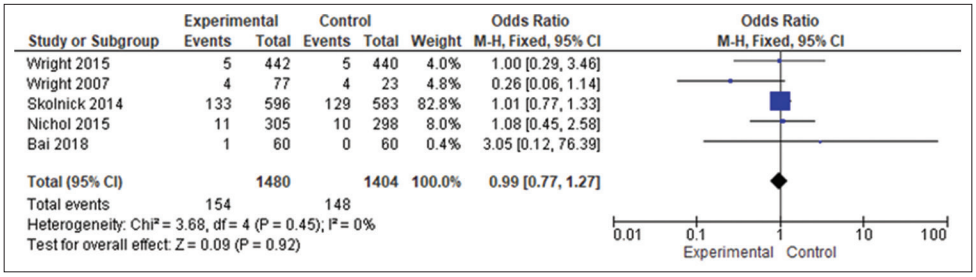

Figure 10: Meta-analysis of the incidence of cardiovascular disturbances. CI: Confidence interval

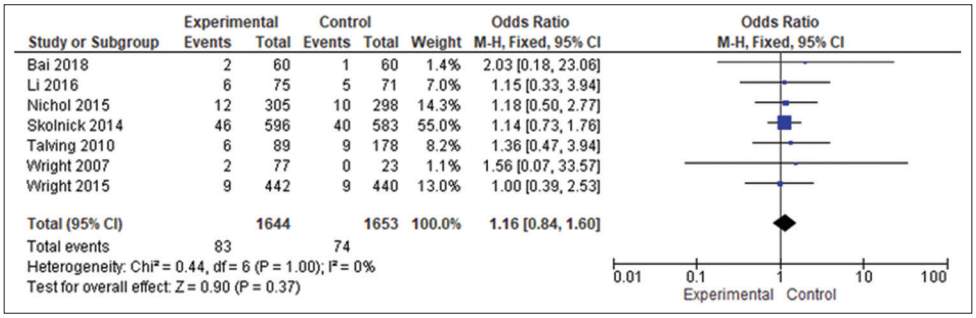

Figure 11: Meta-analysis of sepsis incidence. CI: Confidence interval

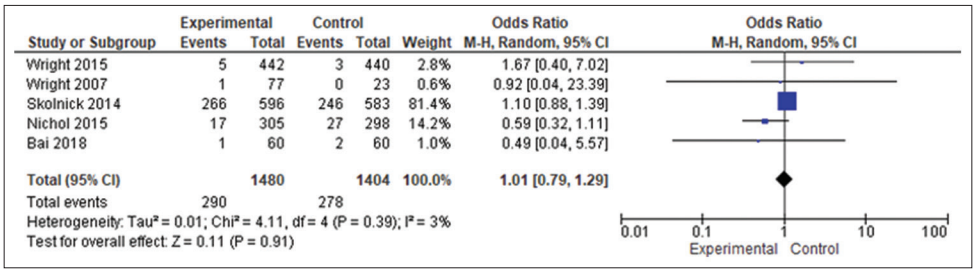

Figure 12: Meta-analysis of the incidence of central nervous system disturbances. CI: Confidence interval

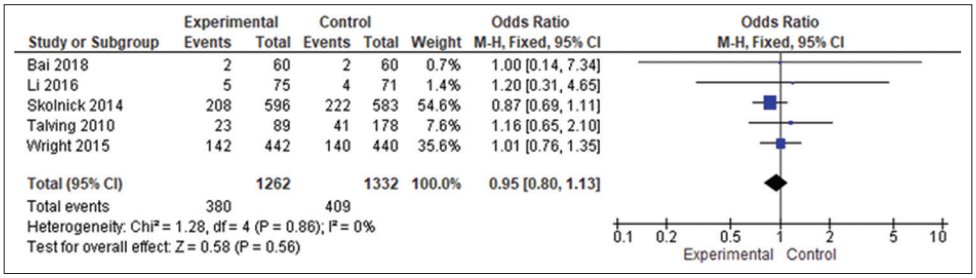

Figure 13: Meta-analysis of the incidence of pneumonia. CI: Confidence interval

different immunomodulators and their adverse events in TBI patients.

The impact of EPO on TBI is a topic of significant interest and investigation within the medical research community. EPO, a hormone primarily known for its role in stimulating red blood cell production, has shown potential therapeutic benefits beyond its hematopoietic function, particularly in neuroprotection and neuroregeneration following TBI.[21,28,29]

Our meta-analysis demonstrates that there is no OS benefit of administration of included immunomodulators such as progesterone, EPO, and cyclosporin for managing TBI patients. However, the overall mortality in the EPO group indicated a significant statistical difference between the intervention and control groups. A meta-analysis conducted in 2020 reported that treatment with EPO is associated with improved functional recovery in patients who sustained

severe TBI.[17] On the contrary, Liu *et al*.'s meta-analysis of EPO in TBI patients found that the administration of EPO did not influence acute hospital mortality within a 10-week timeframe, nor did it impact short-term mortality from 10 weeks to 3 months post-treatment, and did not lead to an increase in adverse events, including thrombotic and cardiovascular complications. In addition, there was no significant effect observed on the improvement of neurological function following the EPO intervention.[21]

Moreover, in our meta-analysis, progesterone did not show a significant improvement in mortality rates among the included research articles, as shown in Figure 6. A meta-analysis of RCTs published in 2014 evaluated the efficacy of progesterone for moderate to severe TBI. The study found that progesterone treatment was associated with a significant reduction in mortality and an improvement in functional outcomes.[19] A recent network pharmacology and molecular-docking technology was to explore the potential mechanisms of progesterone in treating TBI. The study suggested that progesterone can treat TBI through anti-inflammatory action, repairing damaged cell membranes, stabilizing the structure of the blood-brain barrier, and promoting neurological function recovery by regulating nerve cell autophagy.[40]

The neurological outcome was assessed through our meta-analysis. By collecting the GCS, we collected all the patients in the included studies who had a GCS of more than eight in one category, as this cut point reveals a good overall function of the patient. We found that many studies revealed a favorable outcome in patients managed by different immunomodulatory therapies. Many studies revealed similar results, as shown in recent meta-analyses.[2,17,19,21,28]

The adverse events of immunomodulatory therapies, including progesterone and EPO, have been the subject of investigation.[3] We assessed the adverse events in our meta-analysis, revealing that there are no differences between the included immunomodulatory therapies and the control groups in the incidence of pneumonia, sepsis, cardiac events, CNS disturbances, and gastrointestinal disturbances. Our meta-analysis included all the immunomodulatory therapies in one study to assess their efficacy in managing TBI, while the recent meta-analyses included one therapy only. There are several limitations that we faced. First, the heterogeneity among the included studies is due to several factors, such as the type of therapy, severity of the condition, dose, time to receive the therapy, and study design. We included only one study about cyclosporine, which is not sufficient to prove its efficacy in managing TBI. We found sufficient studies about other immunomodulation therapies, such as stem cells, glucocorticoids, target therapies, and anti-inflammatory agents, which limit our study from giving a comprehensive point of view about the efficacy of immunomodulators in managing TBI. Another limitation of our meta-analysis is the inclusion of two studies with a high ROB, which may impact the reliability and validity of our findings.[1,2] Studies with a high ROB are more prone to systematic errors or flaws in study design, conduct, or analysis, which can introduce bias and affect the accuracy of the results. In our meta-analysis, the inclusion of these studies may lead to an overestimation or underestimation of the true effect size of the interventions being evaluated. Furthermore, there were different evaluating time points in the included studies at 3, 6, and 12 months. We included the last evaluated results, which may be an important factor in assessing the efficacy of each one along with time. However, we recommend more trials to assess the efficacy of immunomodulatory drugs, compare them together, and evaluate the long-term effects of the interventions.

CONCLUSION

While immunomodulatory therapies for TBI did not demonstrate a significant overall impact on mortality rates, subgroup analysis revealed promising outcomes with EPO intervention. In addition, these therapies did not significantly increase the risk of adverse events compared to conventional treatments. Future research should focus on further elucidating the efficacy of specific immunomodulatory agents and refining treatment protocols to optimize outcomes for TBI patients.

Ethical approval

The Institutional Review Board has waived the ethical approval for this study.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the

writing or editing of the manuscript and no images were manipulated using AI.

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