Review Article

A Study of the Therapeutic Effects of Progesterone in Patients with Traumatic Brain Injury: A Systematic Review and Meta-analysis

Rezvan Bazgir[1], Ali Siahposht-Khachaki[2,3], Esmaeil Akbari[2,3], Davood Farzin[4]

[1]Department of Physiology and Pharmacology, Ramsar Campus, Mazandaran University of Medical Sciences, [2]Immunogenetics Research Center, School of Medicine, Mazandaran University of Medical Sciences, Departments of [3]Physiology and [4]Pharmacology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

ORCID:

Rezvan Bazgir: 0000-0002-4849-018X
Ali Siahposht-Khachaki: 0000-0001-7505-3148
Esmail Akbari: 0000-0003-4161-0000
Davood Farzin: 0000-0002-9062-7610

Abstract

Background and Objectives: Traumatic brain injury (TBI) is one of the main causes of death and disability in affected people. Progesterone, an endogenous steroid hormone, is known to have a function in the central nervous system. The aim of this study was to investigate the therapeutic effects of progesterone in patients with severe TBIs through systematic review and meta-analysis of randomized clinical trials. **Methods:** This systematic review and meta-analysis was conducted based on the preferred reporting items for systematic reviews and meta-analyses guidelines for systematic reviews. A systematic search was conducted at PubMed, EMBASE, Web of Science, and Scopus. The keywords, including "progesterone," "progestin," "traumatic brain damage," "TBI," "head injury," and "stroke" were searched. There was no time or language limit. Inclusion criteria were as follows: (a) study type: randomized controlled trial; (b) participants: patients with acute TBI; (c) intervention: progesterone; and (d) outcomes: favorable outcome based on mortality rate. Exclusion criteria were as follows: (a) study types: case reports, case reviews, retrospective study, and cohort studies and (b) control: positive control. The data were then collected and analyzed using randomized pooled analysis of risk ratio (RR) for mortality. **Results:** In the study, 721 articles were selected. Finally, 11 studies were analyzed and entered into meta-analysis. All studies are classified as high quality (with a score of more than 7) and therefore no studies were evaluated based on quality assessment. The result of the fixed pooled analysis of RR for mortality was 0.95 with a *P* value of 0.495. **Conclusions:** The results of the present study suggest that progesterone does not decrease the mortality rate despite the various data, suggesting the positive effects of progesterone on the treatment of TBIs.

Keywords: Progesterone, systematic review and meta-analysis, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the main causes of death and disability in injured people.[1] About 1.5 million people die every year, and at least 10 million people are hospitalized or traumatized due to brain damage following trauma or death.[2] The cost of treating brain damage after trauma is significant. In the United States, it is estimated that the cost of acute treatment and rehabilitation for patients with brain damage is estimated at $2 billion a year.[3] Identifying effective, inexpensive, and usable treatments for brain damage is very important. No drug agent has been proven to improve TBI outcomes. Methylprednisolone was shown to be harmful

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Address for correspondence: Dr. Ali Siahposht-Khachaki, Department of Physiology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
E-mail: a.siahposht@mazums.ac.ir

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when used in the treatment,[4] and there is no evidence to support the use of magnesium in patients with acute TBI.[5] TBI is a progressive disorder in which initial damage causes a complex sequence of biochemical and metabolic changes that lead to tissue progression and cell death. These secondary events offer opportunities for therapeutic intervention. Multiple pathophysiologic mechanisms are involved in this complex disorder, such as disseminated axonal damage, bleeding, and systemic disorders in varying degrees.[6,7] It is important to consider protective neuromuscular and clinical drugs to prevent secondary brain damage after TBI, and progesterone has several properties that make it an appropriate drug for use in these patients. It has been proven that progesterone has central nervous properties in various animal species and in various types of neurological damage. The effects of several progesterone proteins include inhibiting inflammatory cytokines, reducing the level of factors associated with inflammation, preventing irritable toxicity, reducing apoptosis, and controlling vasogenic edema.[8-10] Progesterone, an endogenous steroid hormone, is known to have a function in the central nervous system. The neuroprotective effects of progesterone have recently been shown in various types of animals, including ischemic and damaged brain models.[11-15] The administration of progesterone in experimental models of head injury can provide significant protection against TBI brain edema.[16,17] Empirical evidence suggests that postsurgical treatment with progesterone reduces brain edema and damages radicals and reduces the degradation of the neural tissue in animal models of TBI.[18-20] Progesterone also reduces inflammatory response and nerve disorders after ischemic and spinal cord injury.[20-23] Over the past 10 years, several clinical trials have examined the therapeutic effects of progesterone in these patients. Given the numerous human studies that have been done in this area in recent years, and there is no consensus on this, we examined the therapeutic effects of progesterone in patients with TBI through a systematic review and meta-analysis.

Methods

Search strategy

Objectives were designed based on PICO: "P" included patients with TBI; "I," progesterone (synthetic or natural); "C," placebo; and "O," mortality. This study was conducted as a systematic review and meta-analysis. Three experts searched systematically in PubMed, EMBASE, Web of Science, and Scopus. The keywords "head injury", "stroke", "progesterone",

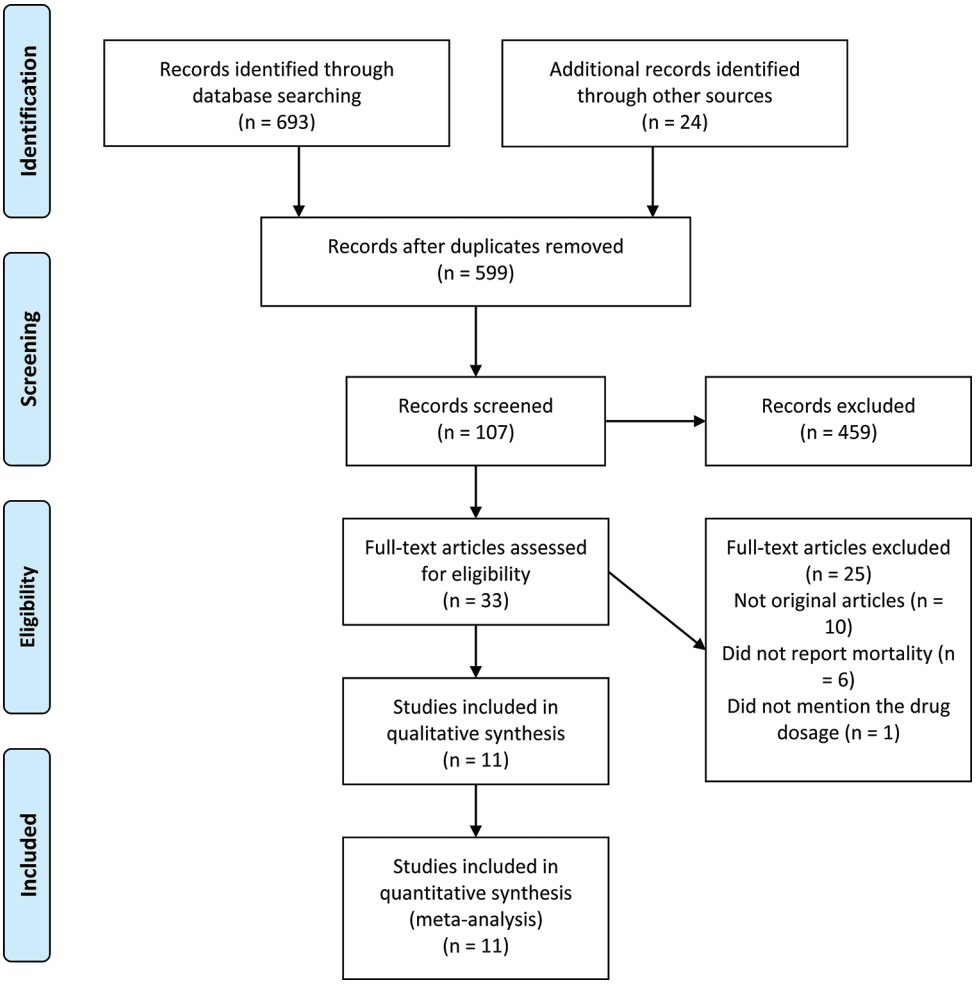

Figure 1: Flow diagram showing selection of studies for inclusion in this meta-analysis

"progestin", "TBI," and "traumatic brain damage" were searched. There was no time or language limit.

Study selection

Inclusion criteria were as follows: (a) study type: randomized controlled trial (RCT); (b) participants: patients with acute TBI; (c) intervention: progesterone; and (d) outcomes: favorable outcome based on mortality rate. Exclusion criteria were as follows: (a) study types: case reports, case reviews, retrospective study, and cohort studies and (b) control: positive control arms of studies. We carefully reviewed the titles, abstracts, and full text of all the articles in the search. The results mentioned in these articles were also examined. According to the preferred reporting items for systematic reviews and meta-analyses guidelines for systematic review, all articles were independently reviewed by three people at each screening level (title, summary, and full text).

Quality assessment

The quality of the included studies was assessed by three authors independently using the Newcastle–Ottawa scale, which is commonly used for observational studies in meta-analysis. On this scale, observational studies were divided into three categories: selection (up to 4 points), comparison (up to 2 points), and exposure or outcome of the participants in the study (maximum 3 points). Studies with a cumulative score of 7 or more are considered high quality, and studies with aggregate Grades 4–6 are defined as fair quality. The data were then collected and analyzed.

Data extraction

Data including author name, publication year, sample size, Glasgow coma scale (GCS), mortality, drug regimen, and follow-up time were extracted by two independent authors and exported to the Excel Software.

Data synthesis and analysis

Finally, risk ratio (RR) for mortality with 95% confidence intervals (CI) was pooled using a fixed effects model. Heterogeneity was examined by "I 2" index and was considered significant if "I 2" value was 50% and greater. The *P* value was used to compare the above parameters in subgroup analyses and

Table 1: Characteristics of the studies entered into the meta-analysis

Author/year	Study type	Country	Age (years)	Number of patients	Drug regimen	GCS	Follow up (months)	RR for mortality
Wright *et al*., 2007[24]	Clinical trial	USA	>18	100	Intravenously 0.71 mg/kg progesterone for the first hour and 0.5 mg/kg per hour for the next 71 h	4-12	1	0.46
Xiao *et al*., 2007[25]	Clinical trial	China	18-65	56	Intramuscularly 80 mg every 12 h for 5 days	4-12	3	0.82
Xiao *et al*., 2008[26]	Clinical trial	China	18-65	159	Intramuscularly 1.0 mg/kg progesterone every 12 h for 5 consecutive days	≤8	6	0.56
Aminmansour *et al*., 2012[27]	Clinical trial	Iran	Mean 27.87	40	Intramuscularly 1.0 mg/kg progesterone every 12 h for 5 consecutive days	≤8	3	0.50
Shakeri *et al*., 2013[28]	Clinical trial	Iran	18-60	76	Orally 1 mg/kg every 12 h for 5 days	3-8	3	0.86
Wright *et al*., 2014[29]	Clinical trial	USA	17-94	882	Intravenously 0.71 mg/kg progesterone for the first hour, 0.50 mg/kg for the next 71 h and tapered by 0.125 mg/kg every 8 h, for a total of 96 h	4-12	6	1.2
Skolnick *et al*., 2014[30]	Clinical trial	North and South America, Asia and Europe	16-70	1179	Intravenously 0.71 mg/kg progesterone for the first hour and 0.5 mg/kg per hour for the next 119 h	≤8	6	1.14
Soltani *et al*., 2016[31]	Clinical trial	Iran	18-60	44	Intramuscularly 1 mg/kg every 12 h to the case group, for 5 days	≤12	6	0.12
Sinha *et al*., 2017[32]	Clinical trial	India	18-65	46 42	progesterone at 1.0 mg/kg via an intramuscular injection and then once every 12 h for 5 consecutive days	4-8	6 12	0.64 0.61
Mofid *et al*., 2016[33]	Clinical trial	Iran	18-60	32	Intramuscularly 1 mg/kg progesterone every 12 h for 5 consecutive days	≤12	6	0.143
Aboukhabar *et al*., 2017[34]	Clinical trial	Egypt	Not mentioned	100	Intramuscularly 1 mg/kg progesterone every 12 h for 5 consecutive days	≤8	1	1.143

GCS: Glasgow Coma Scale

it was significant if ≤0.05. All statistical analyses were performed by the statistical software Comprehensive Meta-Analysis V3.

Results

Characteristics of the included studies

In this study, 721 articles were selected. Finally, 11 studies were analyzed and entered into the meta-analysis. Figure 1 shows the process of how the articles were selected. According to the study objectives, some data, including the GCS rate of the patients, treatment strategy, study design, and a follow-up period for the patients, were extracted from the studies, as detailed in Table 1.

Quality assessment

All studies were classified as high quality (with a score of more than 7), and therefore no studies were excluded based on the quality assessment. The risk of bias assessment and authors' judgments regarding each parameter for each included study are shown in Table 2.

Outcomes and evaluation

The RR for mortality in each study was calculated and collected. A total of 2714 patients were examined. The highest RR rate for mortality was 1.7 (95% CI: 0.85–1.62) in Wright *et al.*'s study in 2014, and the lowest RR rate was 0.11 (95% CI: 0.01–1.85) in Soltani *et al.*'s[24] study in 2016. Due to the low heterogeneity of the included studies (I^2 = 47%), the rate

Table 2: Risk of bias of the articles included in the meta-analysis

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Wright *et al.*, 2007[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xiao *et al.*, 2007[25]	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Xiao *et al.*, 2008[26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Aminmansour *et al.*, 2012[27]	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Shakeri *et al.*, 2013[28]	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Wright *et al.*, 2014[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Skolnick *et al.*, 2014[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Soltani *et al.*, 2016[31]	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Mofid *et al.*, 2016[33]	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Sinha *et al.*, 2017[32]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Unclear risk
Aboukhabar *et al.*, 2017[34]	High risk	High risk	High risk	High risk	Unclear risk	Unclear risk	Unclear risk

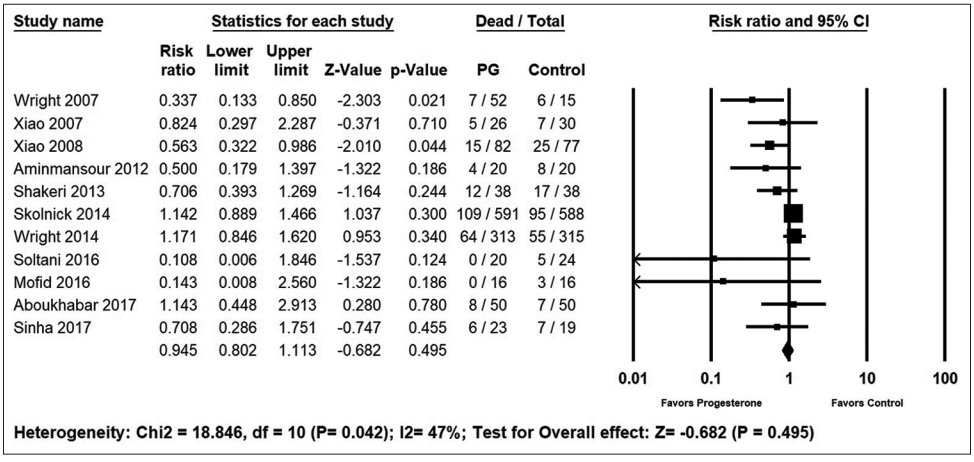

Figure 2: Meta-analysis of mortality rate between progesterone and control groups

of RR for mortality was analyzed using a fixed method. The fixed analysis of RR for mortality was 0.95 (95% CI: 0.8–1.11) with a *P* value of 0.495. Details of the meta-analysis are shown in Figure 2.

Discussion

The findings of this study suggest that progesterone treatment does not reduce mortality or improve neurological outcomes in patients with TBI. The results of this study, which is the largest meta-analysis performed in this field, are consistent with previous studies.

With the increasing use of motor vehicles, especially in developing countries, the prevalence of TBI worldwide increases.[35] However, unconsciously, due to the lack of appropriate treatment strategies, TBI-related mortality has not significantly decreased, and the result of TBI recovery has not been greatly improved over the past two decades.[36,37] To obtain the result of TBI patients, it is necessary to find a safe and effective treatment. Progesterone, a synthesized neurosteroid in the central nervous system, is one of the promising candidates for the treatment of acute TBI.[36] In many experimental studies, the effect of progesterone on the central nervous system has been studied with different animal models, and increasing evidence suggests that progesterone reduces brain vasodilation, protects and restores brain barrier, improves muscle survival, and limits cell necrosis and apoptosis after acute TBI.[28,38]

Early small RCTs revealed the potential benefits of progesterone in TBI-induced injury.[24-26] Consequently, with heightening hopes for the treatment of TBI, large studied were performed. In two large studies, with a low risk of bias, progesterone failed to produce any therapeutic efficacy.[29,30] Hence, researchers and clinicians were puzzled regarding the applicability of progesterone. Once again, small studies were conducted in this area, a significant therapeutic benefit was revealed.[31,32] Therefore, to avoid confusion, it seemed necessary to analyze the results of all studies in order to draw a conclusion.

In 2015, Zeng *et al*.[39] examined the effects of progesterone on acute cerebral hemorrhage in a study by systematic review and meta-analysis. In this study, 6 studies involving 2476 patients were studied. The results of this study showed that, despite some orientations, evidence suggests that progesterone is well tolerated but does not reduce the mortality or adverse outcomes of adolescents with acute TBI, as the RR cumulative mortality rate was equal to 0.83. In 2016, Lu *et al*.[40] examined the effects of progesterone on the treatment of patients with brain trauma in a systematic and meta-analysis study. In this study, 8 studies involving 2585 patients were studied, which was the largest meta-analysis performed to date for the determination of progesterone's therapeutic efficacy in TBI. The RR mortality rate in this study was 0.85. Both studies showed that progesterone is not effective in reducing mortality in post-TBI. In the present study, 2714 patients were evaluated. The highest RR for mortality was 1.17 in Wright *et al*.'s study in 2014, and the lowest was 0.11 in Soltani *et al*.'s study[31] in 2016. The RR for mortality was analyzed using the fixed analysis method in 11 studies. The result of the cumulative analysis of RR for mortality was 0.95 with a *P* value of 0.495. Similar to the abovementioned studies, our finding suggests that progesterone cannot reduce mortality post-TBI.

However, several limitations are posed to our study: (i) although our study includes the largest sample size, still the number of participants was very limited, which may result in a lack of precision and stability of current findings; (ii) Two studies from Iran and Egypt did not include their clinical registration information; therefore, the research quality was varied among the included studies; (iii) the language of the literature search was in English, which may lead to a language bias; (iv) the number of studies was limited, and each included only a few short- and long-term outcome indicators, which can alter the reliability and stability of findings; (v) most studies included individuals with moderate-to-severe (GCS ≤8) TBI; therefore, the effect of progesterone in milder cases remains to be elucidated; (vi) progesterone's dose and route of administration are varied in the included studies, and this can be an influencing factor in the mixed treatment effects observed in studies; (vii) progesterone is a sex-dependent hormone, andthe effect of progesterone can be variable among genders; however, no study separated two genders in their analysis, and hence, future studies are required to elucidate the therapeutic efficacy of progesterone in either sexes.

Conclusions

The results of the present study suggest that progesterone does not decrease the mortality rate despite the various data, suggesting the positive effects of progesterone on the treatment of TBIs.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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