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Review Article

The efficacy and safety of progesterone for traumatic brain injury: a systematic review and meta-analysis of randomized controlled trials

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Abstract: Objective: The objective of this meta-analysis is to assess the efficacy and safety of progesterone (PG) for traumatic brain injury (TBI). Methods: The databases Cochrane Library, OvidSP, Web of Science, PubMed, CNKI, WFSD, and CBM were systematically searched from their inception dates to August 1, 2019, using the keywords traumatic brain injury/traumatic encephalopathy and progesterone/pregnenedione. A pooled analysis of the relevant data was conducted using RevMan 5.3 software. The outcome measures included good functional outcomes (GFO) and mortality, related indicators (RIs), and adverse events (AEs). Subgroup analyses were performed according to the type of injury, the level of consciousness, and the route of administration. Results: A total of 14 randomized controlled trials (RCTs) involving 2908 participants were included in this meta-analysis. The meta-analysis findings indicated that statistically significant differences were found in terms of GFO (RR 1.28, 95% CI 1.09~1.51, P=0.002), mortality (intramuscular administration) (RR 0.64, 95% CI 0.45~0.92, P=0.01), and RIs (at some time points) between the PG and control groups. Furthermore, compared with the control groups, PG may increase the incidence of phlebitis and decrease the incidence of hyperkalemia, but other AEs were not statistically significant. Subgroup analyses demonstrated that the level of consciousness and the route of administration were the influencing factors for PG improving GFO, and type of injury and route of administration were the influencing factors for PG reducing mortality. Conclusions: We firmly believe that PG via intramuscular administration is a potentially promising protocol for TBI. But the conclusion still requires high-quality clinical studies for further validation.

Keywords: Progesterone, traumatic brain injury, good functional outcomes, mortality, meta-analysis

Introduction

Traumatic brain injury (TBI) is defined as an alteration in brain function or other evidence of brain pathology caused by an external force [1]. According to whether the brain tissue is connected to the outside after injury, TBI can be divided into open and closed brain injury. According to whether the brain damage occurs immediately when the violence acts on the head, it is divided into primary brain injury and secondary brain injury. TBI is not just a violent injury (primary brain injury). On this basis, the brain damage caused by the pathophysiological process is called secondary brain injury. Most scholars believe that the pathophysiological process of secondary brain injury is a complex cascade of molecular and biochemical events that occur after the onset of injury. Several studies found that neuronal excitotoxicity [2, 3], intracellular Ca^{2+} influx [4], free radicals, and lipid peroxidation [5, 6] exacerbate the inflammatory response [7, 8] and that the subsequent neuronal cell death via necrosis and apoptosis [9, 10] may be part of the cause of secondary brain injury. With the rapid development of the economy, motor vehicles have proliferated, accompanied by a surge in the number of car accidents, particularly in developing countries. TBI is a leading cause of morbidity and mortality in young adults, resulting in a large direct and indirect social loss [11, 12]. It is urgent to develop a safe and effective therapy protocol to improve the outcomes of TBI patients. However, so far, scientists have not found a combination of one

or several drugs that can effectively improve the long-term neurological prognosis of patients with TBI [13]. Fortunately, progesterone (PG) appears to be a potentially promising drug for TBI. PG, although still widely considered primarily a sex hormone, is an important agent affecting many central nervous system functions. Several studies have reported that females tend to recover better than males following a TBI [14]. Stein et al. investigated the possibility that this effect might have a hormonal basis [14]. Since then, several studies of PG in the treatment of TBI have been completed. There is growing evidence that this hormone may be a safe and effective treatment for TBI [15]. The studies indicate that PG appears to protect the rebuilding of the blood-brain barrier (BBB), reduces cerebral edema, downregulates the inflammatory cascade, and reduces apoptosis [16]. Studies by Sinha et al. [17] and Wu et al. [18] indicate that PG may be useful in limiting disability and improving neurological function outcomes following traumatic brain injury. However, studies by Wright et al. [19] and Skolnick et al. [20] demonstrated that PG does not appear to be effective at improving neurological function outcomes in patients with TBI. Furthermore, studies by Wright et al. [21] and Xiao et al. [22] found that PG can effectively reduce the mortality rate in patients with TBI, but studies such as Wright et al. [19] and Skolnick et al. [20] showed that PG cannot effectively reduce mortality in patients with TBI. The evidence for the use of PG for TBI in clinical settings is currently inconclusive, as results from human trials are conflicting. Therefore, this meta-analysis was performed to further investigate the clinical significance of PG for TBI.

Methods

Search strategy

To identify eligible studies, the main searching was conducted in the electronic databases Cochrane Library, OvidSP, Web of Science, PubMed, CNKI, WFSD, and CBM from their inception dates to August 1, 2019, using various combinations of Medical Subject Headings (MeSH) (traumatic brain injury and progesterone) and non-MeSH (traumatic encephalopathy and pregnenedione) terms. Specific retrieval strategies were adjusted according to different databases. The procedure was concluded by: (i) the perusal of the reference sections of all relevant studies; (ii) a manual search of key journals and abstracts from the major annual meetings in the field of PG for TBI; and (iii) contact with experts. The main searching was completed independently by the investigators. If there were any disagreements, a corresponding author (L.D.) was consulted, and a consensus was reached by discussion. If a consensus could not be reached, two members of the team were randomly selected to express their opinions and then a consensus was reached through discussion.

Inclusion criteria

1) Participants: patients >16 years old and clinically diagnosed with TBI; 2) Intervention: PG versus no PG or placebo; 3) Outcomes: as a minimum, the outcome indicators had to include one of the following: the Glasgow Outcome Scale (GOS)/the extended Glasgow Outcome Scale (GOS-E)/mortality/related indicators (RIs)/adverse events (AEs); 4) Study design: published randomized controlled trials (RCTs).

Exclusion criteria

1) Randomized trials without a placebo or treatment groups; 2) Studies lacking original data; 3) Patients with penetrating trauma, pregnancy, life-threatening systemic injuries, cardiac arrest, or severe pre-existing disease.

Quality assessment

Two independent reviewers (J.Z. and H.-L.W.) assessed the risk of bias of the included studies following the *Cochrane Handbook for Systematic Reviews of Interventions* [23]. We analyzed the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcomes assessment, incomplete outcome data, selective outcome reporting, and other bias, of which, random sequence generation, the blinding of participants, and personnel, and the blinding of outcomes assessment were the most concerning. We determined the risk of bias of each domain as low, unclear, or high risk, according to the methods used to ensure the minimization of each form of bias. Individual studies

were categorized as being based on a low, high, or unclear risk of bias. We used the following methods: 1) low risk of bias (plausible bias unlikely to seriously alter the results) if all the domains are at a low risk of bias; 2) unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains have an unclear risk of bias; or 3) high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at a high risk of bias. If there was any disagreement, a corresponding author (L.D.) was consulted and a consensus was reached by discussion. If a consensus could not be reached, two members of the team were randomly selected to express their opinions and then a consensus was reached by discussion.

Data extraction

Two reviewers (J.Z. and Y.-P.L.) extracted the data independently using a predefined data extraction form. Disagreements were resolved by discussion or consensus with a corresponding author (L.D.) and/or team members. The data extracted included the first author, the study characteristics (i.e., year, duration, setting, and design), the participant characteristics (i.e., age, sample size, and systemic therapy), and the GOS/GOS-E/mortality/RIs/AEs of the PG and control groups. We define good functional outcomes (GFO) as a patient being able to care for him/herself, corresponding to a GOS of 4 or 5, and a GOS-E of 5-8. For studies with insufficient information, the reviewers contacted the primary authors, when possible, to acquire and verify the data.

Statistical analysis

Dichotomous data were analyzed by using the risk ratios (RRs) with 95% confidence intervals (CIs). Continuous outcomes measured on the same scale were expressed as a mean value and standard deviation and were analyzed using weighted mean differences (WMDs) or standard mean differences (SMDs) with 95% CIs when the result unit or measurement method was inconsistent. We calculated the 95% CIs using the Mantel-Haenszel statistical method. I-square (I^2) statistics and Q tests were performed to assess the impact of the study heterogeneity on the results of the meta-analysis. According to the Cochrane review guidelines [23], if severe heterogeneity was present at ($P<0.1$ or $I^2>50\%$), the randomized effect models were chosen, otherwise the fixed effect models were used. Moreover, the sensitivity analysis was conducted by removing each study individually to evaluate the quality and consistency of the results. A visual inspection of the funnel plot was done to assess the publication bias. A subgroup analysis were performed according to the type of injury, level of consciousness, and route of administration.

Results

Search results and the characteristics of the included studies

According to the retrieval strategy given above, a total of 1499 related articles were retrieved, and after 382 duplicates were excluded, 1117 articles remained. 1077 studies that did not meet the inclusion criteria were excluded after we read the titles and abstracts. Of the remaining 47 articles, which were evaluated for their applicability to the full text, 33 were ruled out by the exclusion criteria, leaving 14 studies (RCTs). The flow diagram of the literature screening is shown in **Figure 1**. In addition, the papers' publication time trend is depicted in **Figure 2**. Two articles were published in 2007. There was 1 study published in 2008. In 2012, 3 studies were published. There was 1 paper published in 2013. Two studies were published 2014 and two in 2016. In 2017, there were 4 articles published. The age distribution of the participants in these studies was roughly 16-94 years old. The studies mainly reported the number of GOS/GOS-E, mortality, RIs, and AEs. The specific basic characteristics of the included studies are shown in **Table 1**.

Quality assessment

The quality of the included RCTs was assessed according to the *Cochrane Handbook* [23] (**Figure 3**). 14 studies were low risk on random sequence generation. There were 6 articles with sufficient allocation concealment, but the allocation and concealment schemes of the other 5 articles were not clear. 4 studies were low risk on double-blind. There were 7 studies with sufficient detection bias, but the other 6 articles were not clear. The incomplete data of 11 articles were all rated as low risk. The risk of selective reporting was low risk in 12 articles.

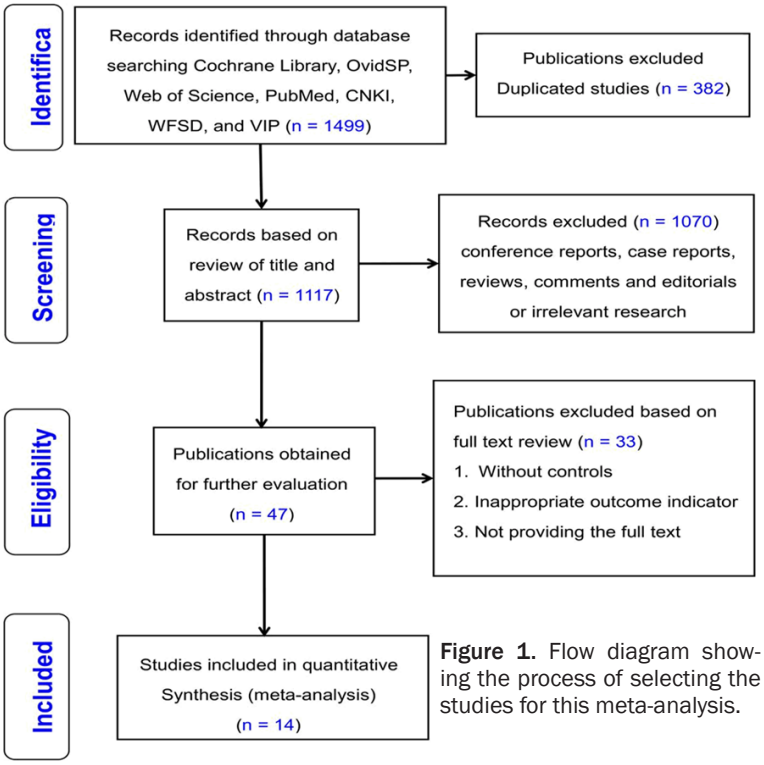

Figure 1. Flow diagram showing the process of selecting the studies for this meta-analysis.

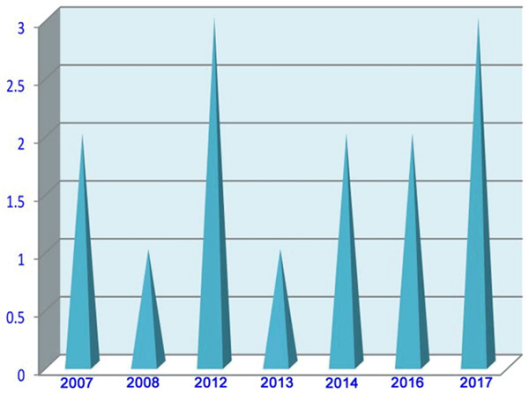

Figure 2. Paper publication time trend.

There were 13 studies with a low risk of other bias. In conclusion, the quality assessment of the 14 included studies was all high.

Meta-analysis findings

Primary outcome

Comparison of the GFO incidence between the PG groups and the control groups

Eleven studies [17-22, 24-28] reported GOS or GOS-E data between the PG groups and the control groups (n=722 in the PG groups vs. 662 in the control groups). The RR was used to estimate for GFO rate between the two groups. The result of the pooled RR is represented in **Figure 4**. There was significant heterogeneity among the studies (Chi^2= 28.01, I^2=64%, P=0.002), so the random-effects model was used. The pooled RR was 1.28 (95% CI=1.09~1.51, P=0.002<0.05), implying that PG (non-single route of administration) could improve the neurological prognosis in patients with TBI.

Secondary outcome

Comparison of the mortality incidence between the PG groups and the control groups

There were thirteen studies [17-22, 24-30] presenting mortality data in both groups (n=263 in the PG groups and 269 in the control groups). We applied the RR to estimate the mortality rates in both groups. The finding of the pooled RR is shown in **Figure 5**. The heterogeneity test showed only slight differences between the studies (Chi^2=20.94, I^2=43%, P=0.05), so the fixed-effects model was applied. The pooled RR was 0.94 (95% CI=0.80~1.09, P=0.39>0.05), suggesting PG did not reduce mortality in the patients with TBI compared with the control groups.

Comparison of the RIs levels between the PG groups and the control groups

Comparison of the serum PG levels in both groups: Three studies [27, 29, 31] presented the serum PG levels at 1 day in both groups (PG groups and control groups). There was substantial evidence of heterogeneity (I^2= 98%), so the random-effects model was applied. Since the mean difference between those two trials was high, SMD was applied. The pooled SMD was 7.09 (95% CI=0.70~13.49, P=0.03<0.05). There were two papers reporting the serum PG levels (at 5 days [30, 31] and 6 days [27, 29]) in the PG groups and

Table 1. Specific basic characteristics of the included studies

Study&year	Design	Follow-up	Age		Number		Intervention	AEs	NFO	Mortality	
			PGG	CG	PGG	CG				PGG	CG
Sinha, 2017	RCT	12 m	33.7±10	33.9±11.2	26	27	Intramuscular injection, PG (1 mg kg^{-1}), per 12 h, for 5 d	R	GOS	5	7 at 6 m
										6	7 at 12 m
Soltani, 2016	RCT	6 m	27.85±1.44	30.37±2.5	20	24	Intramuscular injection, PG (1 mg kg^{-1}), per 12 h, for 5 d	NR	GOS-E	0	5 at 6 m
Mofid, 2016	RCT	6 m	28.44±1.74	30.75±3.4	16	16	Intramuscular injection, PG (1 mg kg^{-1}), per 12 h, for 5 d	NR	GOS-E	0	3 at 6 m
Skolnick, 2014	RCT	6 m	23-51	24-50	591	588	Intravenous injection, PG (0.71 mg kg^{-1}) at first h, 0.5 mg kg^{-1} at 1-120 h	R	GOS	109	95 at 6 m
Wright, 2014	RCT	6 m	17-94	17-93	442	440	Intravenous injection, 14.3 ml per h for 1 h and then at 10 ml per h for 71 h; the dose was then tapered by 2.5 ml per h every 8 h, for a total treatment duration of 96 h	R	GOS-E	83	69 at 6 m
Shakeri, 2013	RCT	3 m	33.97±12.48	34.68±12.87	38	38	Nasogastric tube, PG (1 mg kg^{-1}), per 12 h, for 5 d	NR	GOS	12	17 at 3 m
Abokhabar, 2012	RCT	1 m	26.72±18.43	27.76±15.22	50	50	Intramuscular injection, PG (1 mg kg^{-1}), per 12 h, for 5 d	NR	GOS	8	7 at 1 m
Aminmansour, 2012	RCT	3 m	28±7.43	31.45±8.17	20	20	Intramuscular injection, PG (1 mg kg^{-1}), q 12 h, for 5 d	NR	GOS	4	8 at 3 m
Xiao, 2008	RCT	6 m	30±11	30±9	82	77	Intramuscular injection, PG (1 mg kg^{-1}), per 12 h, for 5 d	R	GOS	15	25 at 6 m
Xiao, 2007	RCT	3 m	31±9	31±9	26	30	Intramuscular injection, PG (80 mg), per 12 h, for 5 d	NR	GOS	5	7 at 3 m
Wright, 2007	RCT	1 m	35.3±14.3	37.1±17.4	77	23	Intravenous injection, 0.71 (mg kg^{-1}) of PG at 14 mL/h for the first h. Then, the infusion was reduced to 10 mL/h to deliver 0.5 (mg kg^{-1}) per h for the next 11 h. Five additional 12-h maintenance infusions were delivered at the standard rate of 10 mL/h, for a total of 3 d of treatment	R	GOS-E	5	7 at 1 m
Wu, 2017	RCT	6 m	41.0±16.0	42.6±16.4	43	40	Intravenous injection, PG (1.0 mg kg^{-1}), per 24 h, for 5 d	NR	GOS	8	14 at 6 m
Lu, 2017	RCT	-	45.36±19.14	45.36±19.14	20	19	Intramuscular injection, PG (20 mg), per 24 h, for 14 d	R	NR	NR	
Lu, 2012	RCT	3 m	43.20±12.31		32	33	Intravenous injection, PG (1.0 mg kg^{-1}), per 24 h, for 3 d	NR	GOS	3	5 at 3 m

PGG: Progesterone groups; CG: Control groups; NFO: Neurological function outcome; m: Month; h: Hours; d: Days; R: Report; NR: No report.

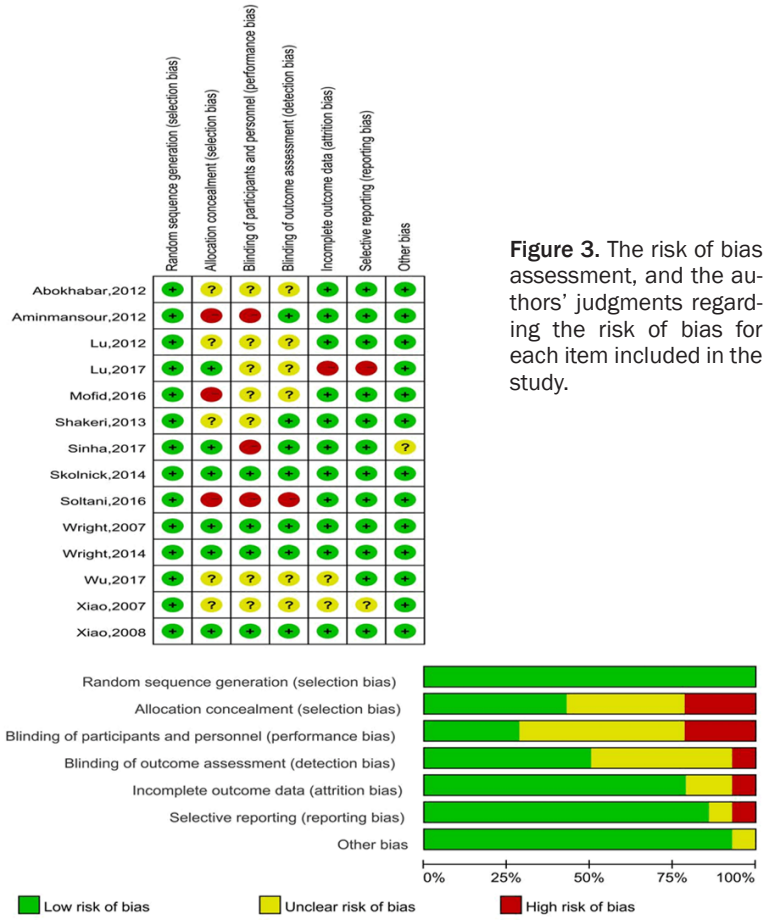

Figure 3. The risk of bias assessment, and the authors' judgments regarding the risk of bias for each item included in the study.

the control groups. The heterogeneity test showed only slight differences between the studies (I^2=0% at 5 days and 0% at 6 days), so the fixed-effect model was used. The pooled SMD were 1.34 (95% CI=0.89~1.79, P<0.00001) at 5 days and 14.36 (95% CI= 11.90~16.82, P<0.00001) at 6 days. The above results demonstrate that the PG group's serum PG levels at 1, 5, and 6 d were higher than they were in the control groups (**Table 2**).

Comparison of the intracranial pressure (ICP) levels in both groups: There were two studies [18, 22] reporting ICP at 1 day; 2 papers [18, 22] showing data at 3 days; and 2 studies [18, 22] reporting data at 7 days from the PG groups and the control groups. The heterogeneity test showed only slight differences between the studies (I^2=0% at 1 day) and significant differences between the studies (I^2=74% at 3 days and 58% at 7 days), so the random-effects model was applied. In addition, the mean difference between those two trials was high, so the SMD was used. The pooled SMD were -0.29 (95% CI=-0.61~ 0.02, P=0.07>0.05) at 1 day; -0.61 (95% CI=-1.24~0.02, P=0.06>0.05) at 3 days; and -0.53 (95% CI=-1.02~-0.04, P=0.03<0.05) at 7 days (**Table 2**). The above pooled findings of ICP suggest that PG can effectively reduce the ICP of TBI patients at the 7th day.

Comparison of the S-100B levels in both groups: Two studies [18, 29] presented S-100B at 1 day in both groups; 1 paper [18] reported S-100B at 5 days, and one article [29] reported S-100B at 6 days in both groups (the PG groups and the control groups). We used the SMD to estimate the S-100B levels in both groups. Significant heterogeneity was observed between the studies (I^2= 94%), so the random-effects model was applied (**Table 2**). The pooled SMD were -1.87 (95% CI=-4.18~-0.45, P=0.11>0.05) at 1 day; -4.52 (95% CI=-5.35~-3.70, P< 0.00001) at 5 days; and -3.05 (95% CI= -4.11~-1.99, P<0.00001) at 6 days. The pooled results demonstrated that compared with the control groups, PG can effectively reduce serum S-100B at 5 and 6 days.

Comparison of the interleukin-1 (IL-1β) levels in both groups: There were 3 studies [18, 26, 29] reporting serum IL-1β at day 1. 1 article [26] showed the data at 3 days. There were 2 studies [18, 26] reporting at 5 days in both groups. Since the mean difference between those two trials was high, SMD was applied. The heterogeneity test showed significant differences between the studies (I^2=93% at 1 day and 92% at 5 days), so the random-effects model was applied. The pooled SMD were -1.25 (95% CI=-2.25~0.02, P=0.05) at 1 day; -0.91 (95% CI=-1.42~-0.39, P=0.0005<0.05) at 3 days; and -1.07 (95% CI=-2.30~0.17, P=0.09>0.05) at 5 days (**Table 2**). The above pooled results of serum IL-1β showed that PG can reduce the serum IL-1β at 1 day and 5 days.

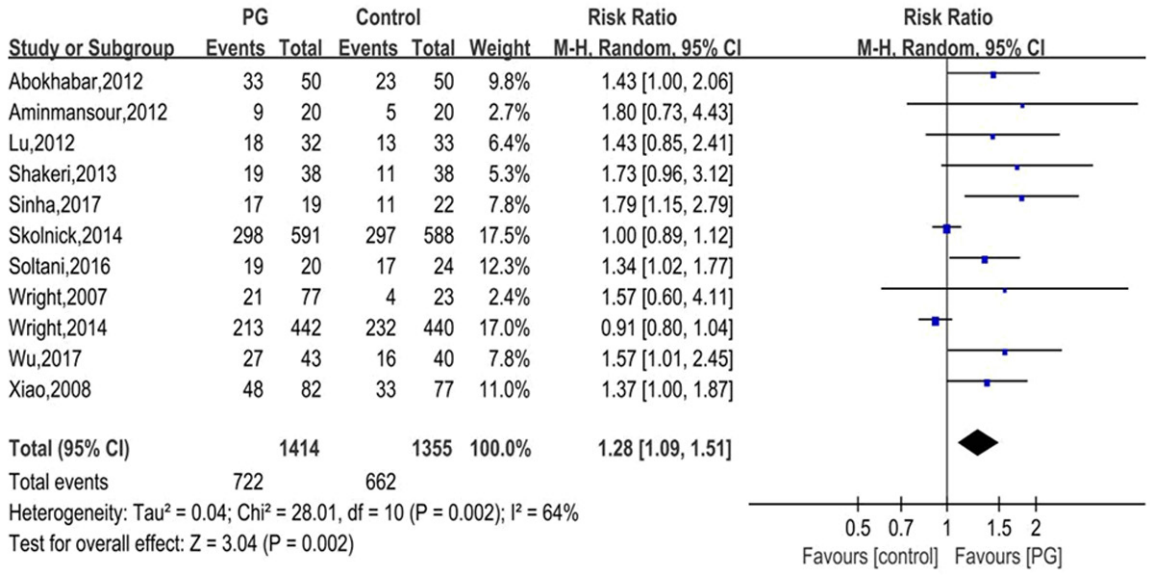

Figure 4. A meta-analysis of the GFO between the PG groups and the control groups.

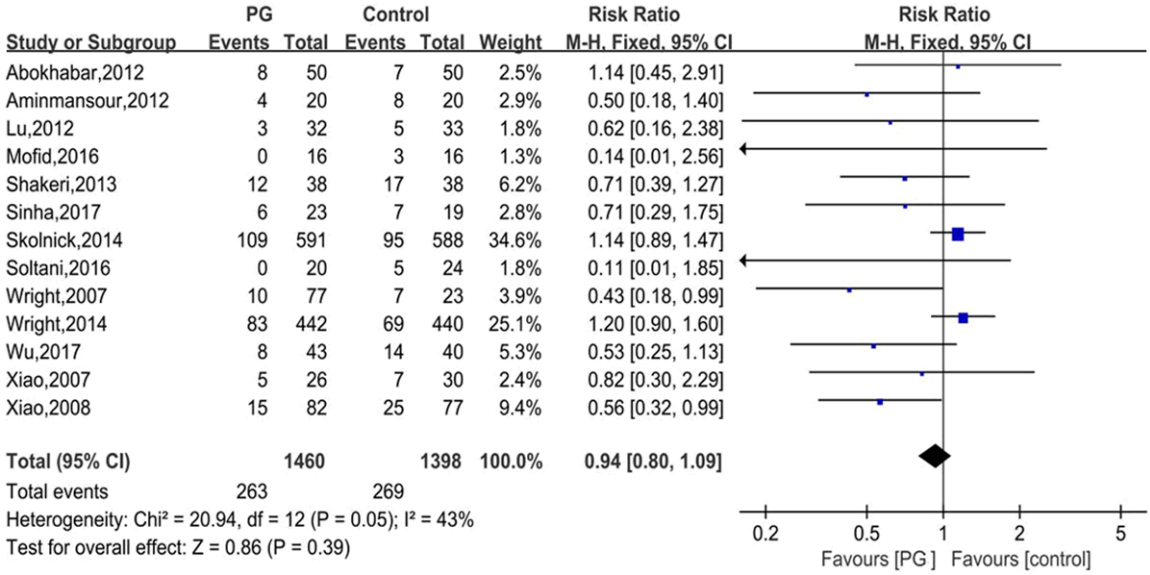

Figure 5. A meta-analysis of the mortality rates in the PG groups and the control groups.

Comparison of the tumor necrosis factor (TNF-α) levels in both groups: One study [26] reported serum TNF-α at 1 day; two papers [26, 30] presented it at 5 days, and one article [30] reported it at 10 days (**Table 3**). There was no substantial evidence of heterogeneity (I^2=49%), so the fixed-effects model was used. We used SMD to estimate the S-100B levels in both groups. The pooled SMD were -0.17 (95% CI=-0.65~0.32, P=0.50>0.05) at one day; -2.36 (95% CI=-2.83~-1.89, P<0.00001) at 5 days; and -0.73 (95% CI=-1.28~-0.19, P=0.008< 0.05) at 10 days. The pooled findings demonstrated that PG can reduce serum TNF-α at 5 and 10 days compared with the control groups.

Comparison of the incidence of AEs in the PG groups and the control groups

There was one study (Wright, 2014) [19] reporting data on phlebitis and thrombophlebitis in both groups (n=76 in the PG groups vs. n=25

Table 2. Meta-analysis of the related indicators: (serum PG, ICP, serum S-100B, serum IL-1, and serum TNF-α) in both groups

RIs	Date	Pooled		Results	
	SMD	CI (95%)	P	I^2 (%)	N
Serum PG					
1 d	7.09	[0.70, 13.49]	0.03	98	3
5 d	1.34	[0.89, 1.79]	<0.00001	0	2
6 d	14.36	[11.90, 16.82]	<0.00001	0	2
ICP					
1 d	-0.29	[-0.61, 0.02]	0.07	0	2
3 d	-0.61	[-1.24, 0.02]	0.06	74	2
7 d	-0.53	[-1.02, -0.04]	0.03	58	2
Serum S-100B					
1 d	-1.87	[-4.18, 0.45]	0.11	94	2
5 d	-4.52	[-5.35, -3.70]	<0.00001	-	1
6 d	-3.05	[-4.11, -1.99]	<0.00001	-	1
Serum IL-1β					
1 d	-1.25	[-2.52, 0.02]	0.05	93	3
3 d	-0.91	[-1.42, -0.39]	0.0005	-	1
5 d	-1.07	[-2.30, 0.17]	0.09	92	2
Serum TNF-α					
1 d	-0.17	[-0.65, 0.32]	0.50	-	1
5 d	-2.36	[-2.83, -1.89]	<0.00001	49	2
10 d	-0.73	[-1.28, -0.19]	0.008	-	1

N: Number.

in the control groups). We applied the RR to estimate the AEs rate in the two groups. The pooled RR was 3.03 (95% CI=1.96~4.66, P<0.00001) (**Table 3**). By carefully reading the study of Wright et al. [19], we found that the PG of the experimental groups was administered using an intravenous route. The result of the meta-analysis demonstrated that the intravenous injection of PG may increase the risk of phlebitis or thrombophlebitis. In addition, a study by Sinha et al. [17] reported data on hyperkalemia and hypokalemia in the PG groups and the control groups. The pooled RR were 0.09 (95% CI=0.02~0.35, P=0.0004< 0.05) on hyperkalemia and 0.88 (95% CI= 0.48~1.59, P=0.67>0.05) on hypokalemia, suggesting PG can reduce the incidence of hyperkalemia, which was basically not at the expense of increasing the incidence of hypokalemia (**Table 3**). The meta-analysis findings indicated that there were no statistical differences in terms of seizures, nervous system disorders, cardiac disorders, thromboembolic disease, gastrointestinal disorders, unexplained increased liver-enzyme levels, urinary complications, endocrine disorders, blood or lymphatic system disorders, sepsis, infections, or hyperglycemia in both groups (**Table 3**).

Subgroup

The subgroup analysis was performed to explore the heterogeneity source and the impact of type of injury, level of consciousness, and route of administration on the GFO and mortality.

The influence of type of injury on the GFO

Two studies [27, 28] reported GOS/GOS-E data in the patients with diffuse axonal injury (DAI) in the PG groups and the control groups (n=38 in the PG groups vs. n=28 in the control groups) (**Figure 6**). No statistically significant heterogeneity was observed between the studies (Chi^2= 0.86, I^2=0, P=0.35). The GFO rates of the PG groups and the control groups were 65.5% and 45.2%, respectively. The pooled RR was 1.40 (95% CI=1.09~ 1.80, P=0.008<0.05), suggesting that PG can effectively improve the GFO rate in patients with DAI. 9 studies [17-22, 24-26] presented GOS or GOS-E data in patients with non-diffuse axonal injury (non-DAI) in both groups (**Figure 6**). The heterogeneity test showed moderate differences between the studies (Chi^2=22.66, I^2=65%, P=0.004), indicating the heterogeneity of DAI and non-DAI, so the random-effects model was applied. The experimental groups' GFO rate was 50.4%, and the control groups' was 49.0%. The pooled RR was 1.25 (95% CI=1.05~1.49, P=0.02<0.05), suggesting that PG may not significantly or effectively improve the GFO in patients with non-DAI. In summary, the subgroup analysis of the included studies demonstrated that PG tended to result in a more favorable GFO in patients with DAI than the non-PG.

The influence of the level of consciousness on GFO

Three studies [19, 21, 27] presented GFO data in patients with the Glasgow Coma Scale (GCS)≤12 (**Figure 7**). Substantial heterogen-

Table 3. Meta-analysis of the AEs between the PG groups and the control groups

AEs	Date	Pooled		Results	
	RR	CI (95%)	P	I^2 (%)	N
Seizure	1.76	[0.60, 5.16]	0.31	0	2
Nervous system disorders	1.02	[0.95, 1.10]	0.55	0	3
Pneumonia	0.97	[0.86, 1.09]	0.59	0	4
Cardiac disorders	1.02	[0.83, 1.25]	0.84	0	3
Phlebitis or thrombophlebitis	3.03	[1.96, 4.66]	<0.00001	-	1
Thromboembolic disease	1.23	[0.84, 1.82]	0.29	0	2
Gastrointestinal disorders	0.99	[0.84, 1.17]	0.92	0	2
Unexplained increased liver-enzyme levels	1.28	[0.64, 2.54]	0.48	-	1
Urinary complications	0.76	[0.49, 1.17]	0.21	0	2
Endocrine disorders	0.84	[0.58, 1.24]	0.38	0	2
Blood or lymphatic system disorders	0.91	[0.78, 1.07]	0.27	-	1
Sepsis	1.12	[0.79, 1.57]	0.52	0	4
Infections	0.97	[0.89, 1.05]	0.42	-	1
Hyperkalemia	0.09	[0.02, 0.35]	0.0004	-	1
Hypokalemia	0.88	[0.48, 1.59]	0.67	-	1
Hyperglycemia	1.01	[0.62, 1.65]	0.96	0	2

N: Number.

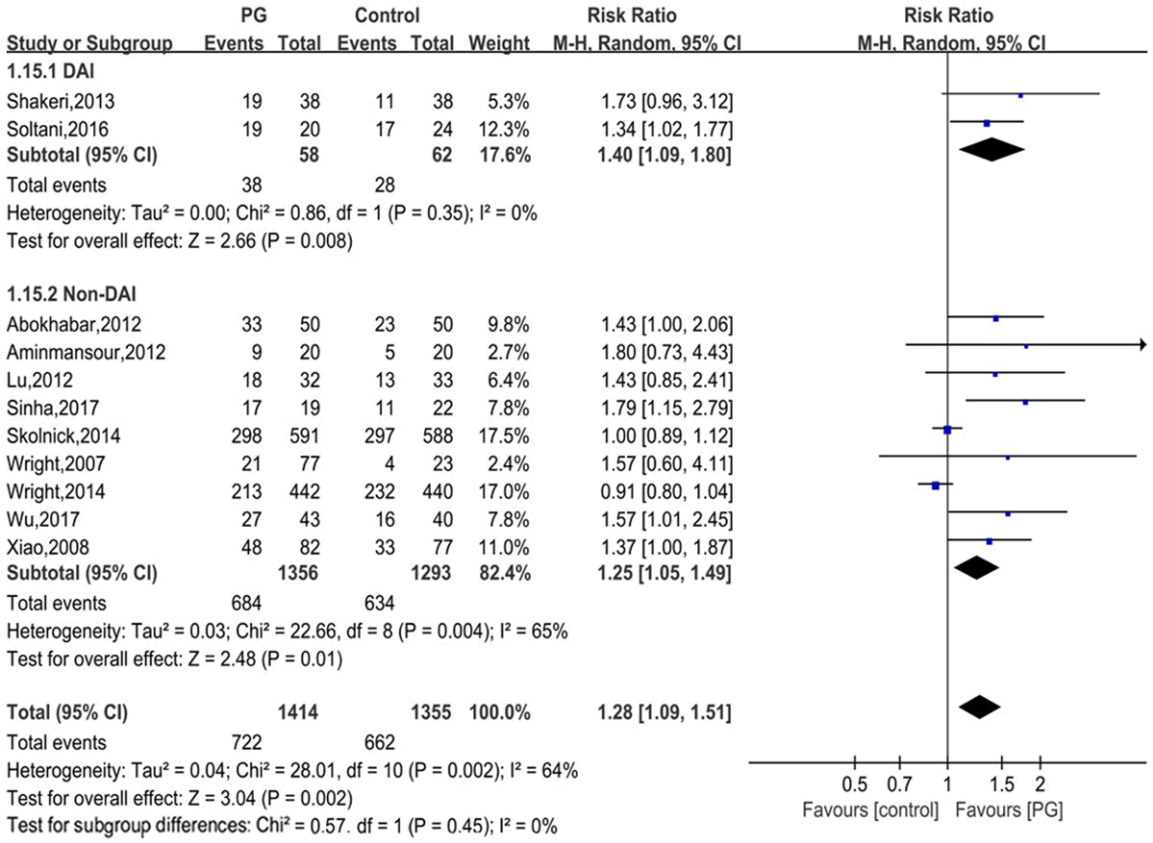

Figure 6. A subgroup analysis (DAI and non-DAI) of the GFOs in both groups.

eity was observed among the studies (Chi^2= 7.26, I^2=72%, P=0.03). The pooled RR was 1.13 (95% CI=0.80~1.60, P=0.50>0.05). In addition, there was 8 studies [17, 18, 20, 22,

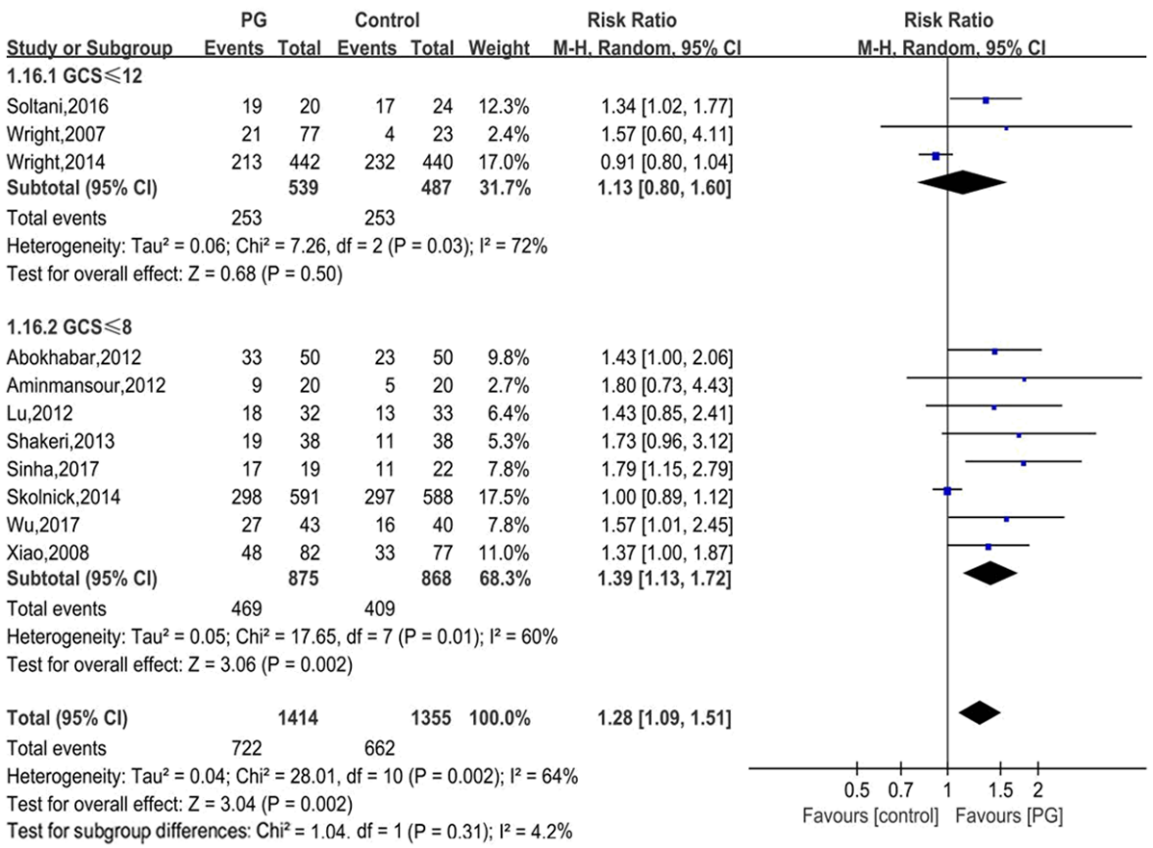

Figure 7. A subgroup analysis (GCS≤12 and 8) of the GFOs in both groups.

24-26, 28, 32] reporting GFO data in patients with Glasgow Coma Scale (GCS)≤8 in both groups (**Figure 7**). There was significant evidence of heterogeneity (Chi^2=17.65, I^2=60%, P=0.01), and the heterogeneity of GCS≤12 and GCS≤8, so the random-effects model was used. The GFO rates of the PG groups and the control groups were 53.6% and 47.1%, respectively. The pooled RR was 1.39 (95% CI=1.13~1.72, P=0.002<0.05), with a statistical difference between the two groups. The above two results suggested that the level of consciousness could be the influencing factor for the GFO.

The influence of route of administration on the GFO

There were 4 studies [18-21] reporting GFO data after the intravenous injection of PG and 6 papers [17, 22, 24-27] showing data after the intramuscular injection of PG. One paper [28] reported the GFO data after the nasogastric tube administration of PG in both groups (**Figure 8**). The heterogeneity test showed significant differences between the studies (Chi^2=6.45, I^2=53%, P=0.09 using intravenously injection) and no difference between studies (Chi^2=1.53, I^2=0, P=0.91 using intramuscular injection), so the random-effects model was applied. The pooled RR were 1.02 (95% CI=0.87~1.20, P=0.79>0.05) using intravenously injection; 1.43 (95% CI= 1.23~1.68, P<0.00001) using intramuscular injection; and 1.73 (95% CI=0.96~3.12, P=0.07>0.05) using nasogastric tube. The above subgroup analysis of the GFO demonstrated that the intramuscular injection of PG tended to result in a more favorable improvement to the GFO rate than intravenous injection and nasogastric tube. Furthermore, there was significant inter-group heterogeneity (Chi^2=9.99, I^2=80%, P=0.007) among the three groups (the intravenous injection, intramuscular injection, and nasogastric tube groups). The subgroup heterogeneity results indicated that intravenous injection and nasogastric tube administration protocols may be one of the causes of the heterogeneity of the GFO.

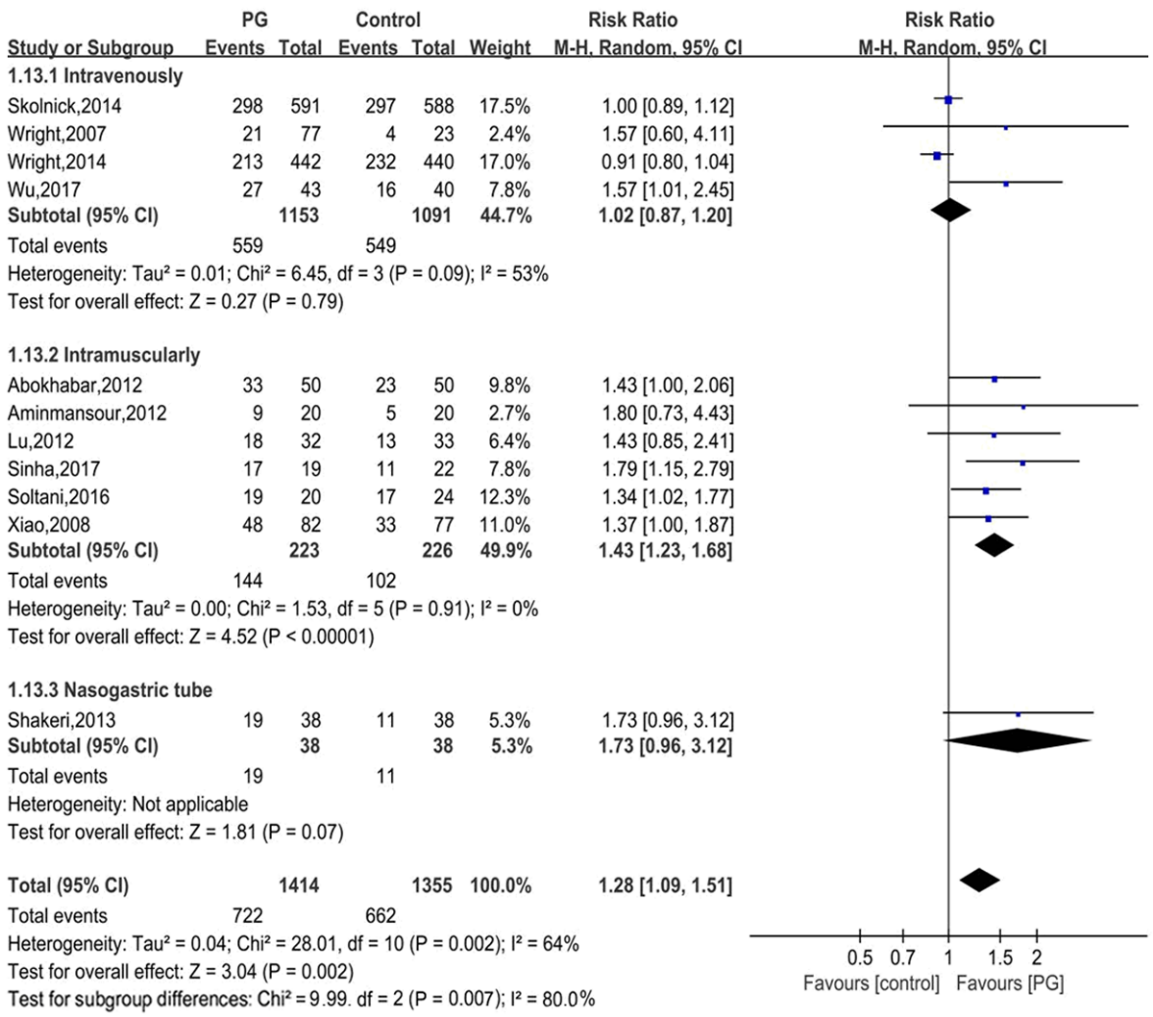

Figure 8. A subgroup analysis (intravenous injection, intramuscular injection, and nasogastric tube) of the GFOs in both groups.

The influence of type of injury on mortality

Three studies [27-29] reported mortality data in patients with DAI in the PG groups and the control groups (n=12 in the PG groups vs. n= 25 in the control groups) (**Figure 9**). Little statistically significant heterogeneity was observed among the studies (Chi^2=3.06, I^2= 35%, P=0.22). The mortality rates of the PG groups and the control groups were 16.2% and 32.1%. The pooled RR was 0.51 (95% CI=0.29~0.90, P=0.02<0.05), suggesting that PG can effectively reduce the mortality risk in patients with DAI. 10 studies [17-22, 24-26, 30] presented the mortality rates of patients with non-DAI in both groups (**Figure 9**). The heterogeneity test showed only slight differences between the studies (Chi^2=16.05, I^2=44%, P=0.07), indicating the heterogeneity of DAI and non-DAI, so the random-effects model was applied. The PG groups' mortality rate was 18.1% and the control groups' was 18.5%. The pooled RR was 0.94 (95% CI=0.80~1.15, P=0.79>0.05), indicating PG may not effectively reduce the mortality rate in patients with non-DAI. In addition, there was significant inter-group heterogeneity (Chi^2=4.69, I^2=78.7%, P=0.03) between the two groups (DAI and non-DAI). The subgroup heterogeneity results demonstrated that type of injury (non-DAI) may be one of the causes of the heterogeneity of the GFO.

The influence of level of consciousness on mortality

Four studies [19, 21, 27, 29] presented mortality data in patients with Glasgow Coma Scale

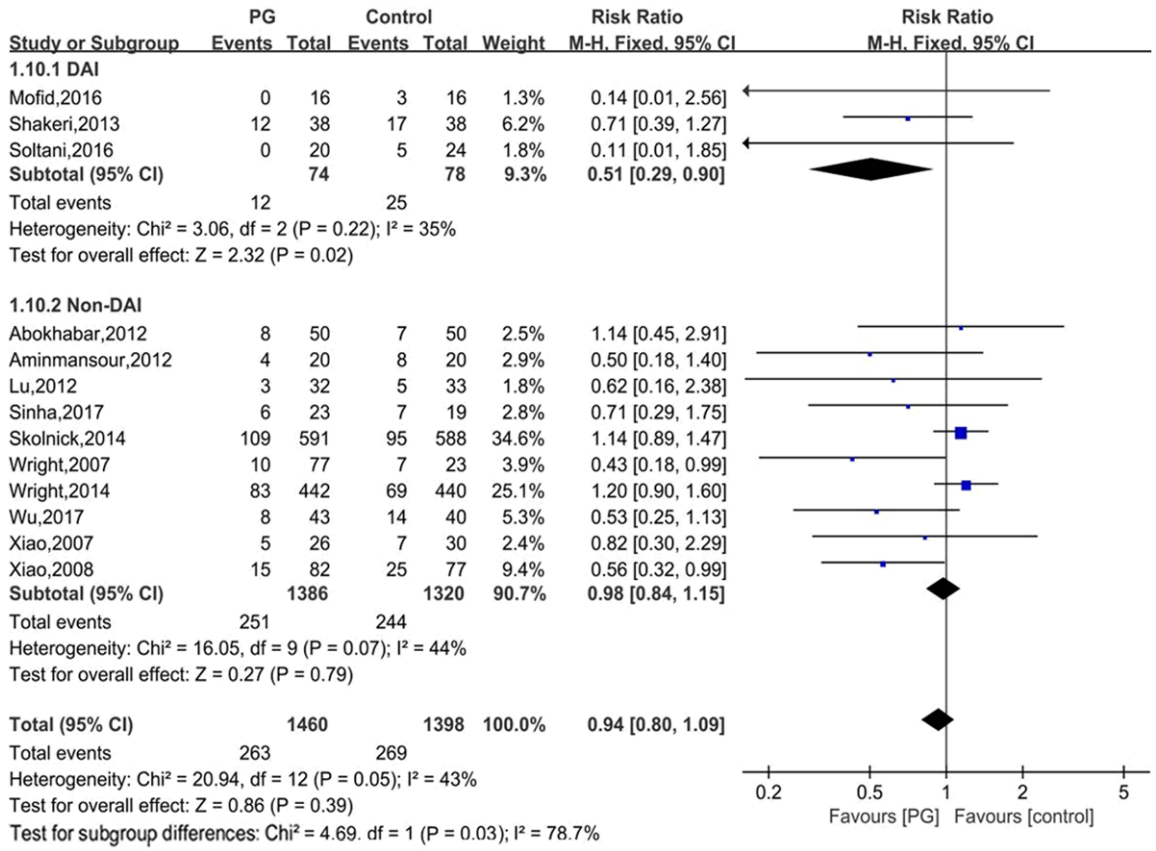

Figure 9. A subgroup analysis (DAI and non-DAI) of the mortality rates in both groups.

(GCS)≤12 (**Figure 10**). Substantial heterogeneity was observed among the studies (Chi^2= 9.47, I^2=68%, P=0.02). The pooled RR was 0.53 (95% CI=0.19~1.47, P=0.22>0.05). In addition, there was 9 studies [17, 18, 20, 22, 24-26, 28, 30] reporting mortality data in patients with Glasgow Coma Scale (GCS)≤8 in both groups (the PG groups and control groups) (**Figure 10**). There was little evidence of heterogeneity (Chi^2=10.80, I^2=26%, P= 0.21), and the heterogeneity of GCS≤12 and GCS≤8, so the random-effects model was used. The pooled RR was 0.79 (95% CI= 0.61~1.03, P=0.08>0.05), with no statistical differences between the two groups. The above two results suggest that PG does not reduce the mortality risk at the two different level of consciousness (GCS≤12 and 8).

The influence of the route of administration on mortality

There were 5 studies [18-21, 26] reporting mortality data after the intravenous injection of PG; 7 papers [17, 22, 24, 25, 27, 29, 30] showing data after the intramuscular injection of PG. One paper [28] reported mortality data after the use of a nasogastric tube to administer PG in both groups (**Figure 11**). The heterogeneity test showed obvious differences between the studies (Chi^2=9.29, I^2=57%, P=0.05 via intravenously injection) and no difference between studies (Chi^2=4.82, I^2=0, P=0.57 via intramuscular injection), so the random-effects model was applied. The pooled RR were 0.89 (95% CI=0.63~1.26, P= 0.52>0.05) using an intravenous injection; 0.64 (95% CI=0.45~0.92, P=0.01<0.05) using an intramuscular injection; and 0.71 (95% CI=0.39~1.27, P=0.24>0.05) using a nasogastric tube. The above subgroup analysis of GFO indicated that the intramuscular injection of PG tended to result in a more favorable reduction in the mortality rate than an intravenous injection or a nasogastric tube. Furthermore, there was significant inter-group heterogeneity (Chi^2=9.99, I^2=80%, P=0.007) among the three groups (the intravenous in-

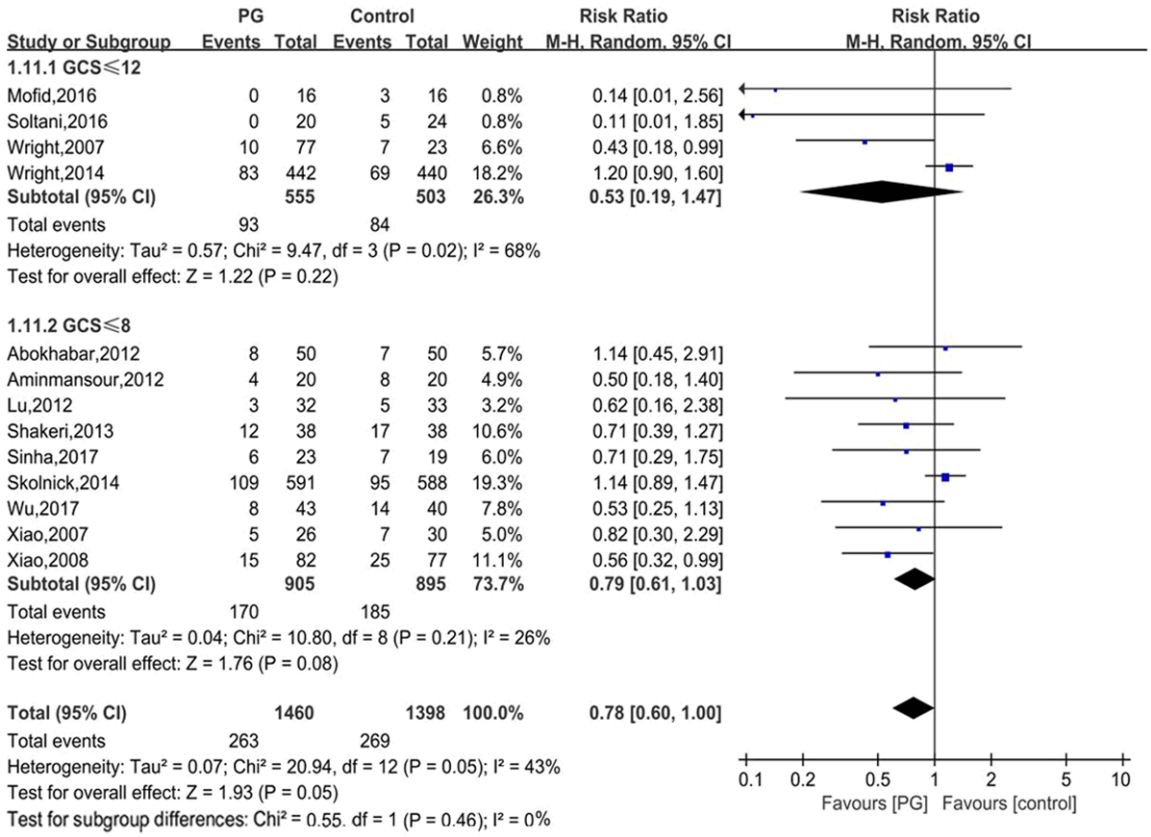

Figure 10. A subgroup analysis (GCS≤12 and 8) of the mortality in both groups.

jection, intramuscular injection, and nasogastric tube groups). The subgroup heterogeneity results demonstrated that the intravenous injection and nasogastric tube administration protocols may be one of the reasons for the GFO's heterogeneity.

Sensitivity analysis and publication bias

We evaluated the effect of each study on the GFO and mortality rate by removing a single study, sequentially. The pooled RR of the GFO fluctuation range was 1.23 to 1.38 and the mortality fluctuation range was 0.83 to 0.97. The *P* value of the pooled GFO data fluctuated from 0.0005 to 0.009, and the mortality data fluctuated from 0.05 to 0.74 (**Table 4**). The sensitivity analysis of the GFO results show that the stability of results did not undergo a significant change, which validated the rationality and the stability. However, a sensitivity analysis of the mortality results demonstrated that the pooled data results were unstable. This occurred because the *P* value was changed to 0.05 and the statistical significance may be reversed, when we removed the study by Skolnick et al. [20]. The funnel plot of the GFO and the mortality rate are shown in **Figure 12**. The moderate publication bias was obtained through a visual distribution of the funnel plot.

Discussion

A total of 1499 articles were searched, and 14 studies were finally included according to the inclusion and exclusion criteria. The paper publication trend indicated that studies on PG to treat TBI peaked in 2012 and 2017 (the number of publications was three). This meta-analysis mainly reports GFO, mortality, RIs, and AEs. Furthermore, a subgroup analysis of GFO and mortality was performed to investigate the effects of type of injury (DAI and non-DAI), the degree of coma (GCS≤12 and GCS≤8), and the route of administration (intravenous injection, intramuscular injection, and the nasogastric tube route) on GFO and mortality. The meta-analysis results showed that: 1) Compared with the control groups, the differ-

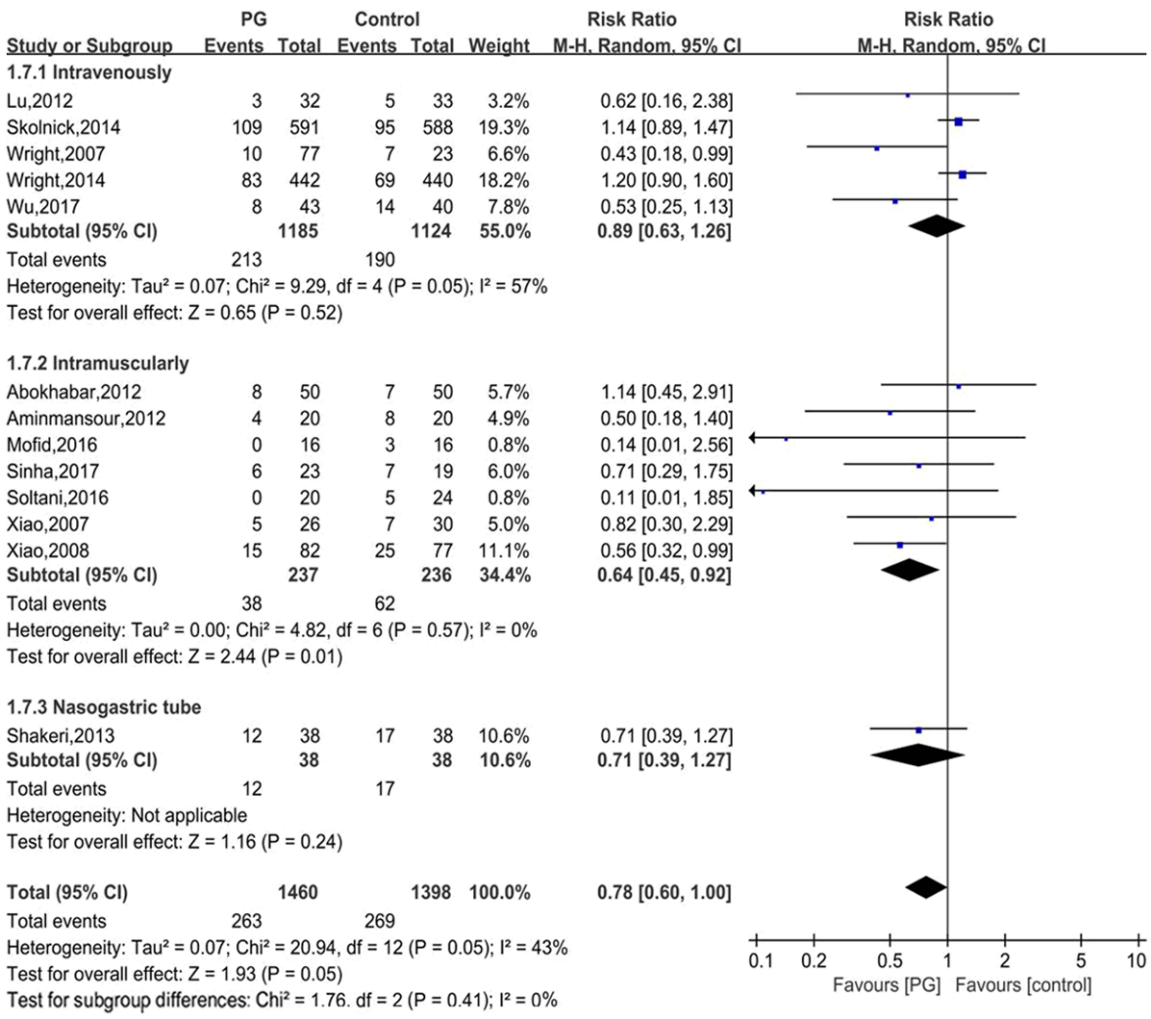

Figure 11. A subgroup analysis (intravenous injection, intramuscular injection, and nasogastric tube) of the mortality in both groups.

ences in the GFO were statistically significant in the PG groups (P=0.002); however, PG seems to only slightly increase the GFO rate in patients with TBI (51.1% in the PG groups vs. 48.9% in the control groups); 2) There was no statistical significance in the mortality between the two groups (P=0.39); 3) Compared with the control groups, the trial groups' serum PG levels were statistically significantly different on the first, fifth, and sixth days after the injury; there was no statistically significant difference in ICP between the first day and the third day after the injury, and the difference was statistically significant on the 7th day; there was no statistically significant difference in the serum S-100B levels on the first day after the injury, and the difference was statistically significant on the 5th and 6th days; there was no statistically significant difference in the serum IL-1β levels between the first day and the fifth days after the injury, and the difference was statistically significant on the third day. 4) The PG groups appeared to have an increase in the incidence of phlebitis or thrombophlebitis compared with the control groups. In addition, the experimental groups appeared to have a reduction in the incidence of hyperkalemia but not at the expense of increasing the incidence of hypokalemia. The difference in the other adverse events (seizures, nervous system, disorders, pneumonia, cardiac disorders, thromboembolic diseases, gastrointestinal disorders, unexplained increased liver-enzyme levels, urinary complications, endocrine disorders, blood or lymphatic system disorders, sepsis, infection, and hyper-

Table 4. Sensitivity analysis of GFO and mortality

Removing single study sequentially	GFO				Mortality			
	RR	CI (95%)	P	I^2 (%)	RR	CI (95%)	P	I^2 (%)
Not exclude	1.28	[1.09, 1.51]	0.002	64	0.94	[0.80, 1.09]	0.39	43
Abokhabar, 2012 excluded	1.27	[1.07, 1.50]	0.006	65	0.93	[0.80, 1.08]	0.35	47
Aminmansour, 2012 excluded	1.27	[1.08, 1.50]	0.004	66	0.95	[0.81, 1.11]	0.50	44
Lu, 2012 excluded	1.28	[1.08, 1.51]	0.004	67	0.94	[0.81, 1.10]	0.44	47
Shakeri, 2013 excluded	1.26	[1.07, 1.48]	0.006	65	0.95	[0.81, 1.11]	0.43	45
Sinha, 2017 excluded	1.23	[1.05, 1.44]	0.009	61	0.94	[0.81, 1.10]	0.45	47
Skolnick, 2014 excluded	1.38	[1.13, 1.69]	0.002	64	0.83	[0.68, 1.00]	0.05	35
Soltani, 2016 excluded	1.28	[1.07, 1.52]	0.006	64	0.95	[0.82, 1.11]	0.51	45
Wright, 2007 excluded	1.28	[1.08, 1.51]	0.003	67	0.96	[0.82, 1.12]	0.57	37
Wright, 2014 excluded	1.37	[1.15, 1.64]	0.0005	53	0.85	[0.71, 1.01]	0.07	36
Wu, 2017 excluded	1.26	[1.07, 1.48]	0.006	64	0.96	[0.82, 1.12]	0.59	41
Xiao, 2008 excluded	1.28	[1.07, 1.51]	0.006	65	0.97	[0.83, 1.14]	0.74	37
Xiao, 2007 excluded	-	-	-	-	0.94	[0.80, 1.09]	0.41	47
Mofid, 2014 excluded	-	-	-	-	0.95	[0.81, 1.10]	0.47	43

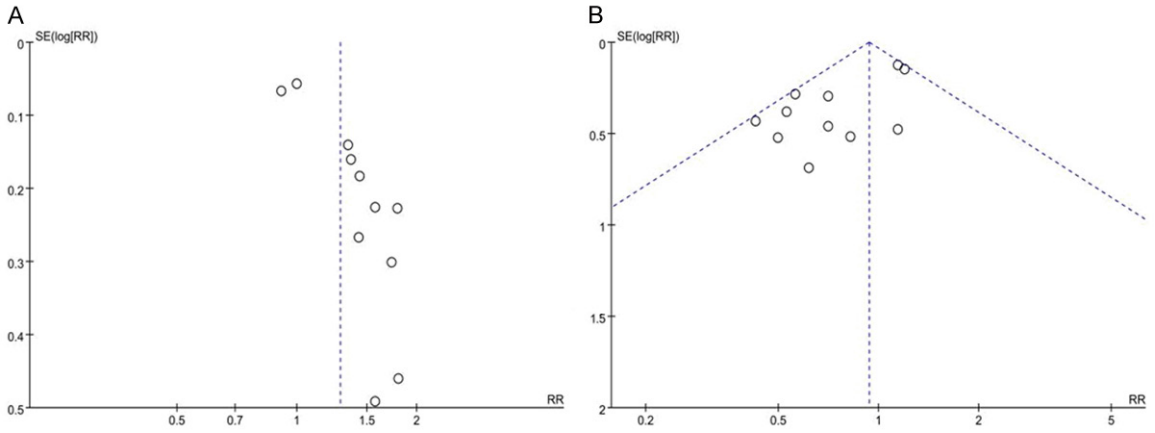

Figure 12. A funnel plot of the GFO (A) and the mortality rate (B).

glycemia) were not statistically significant in both groups. 5) The subgroup analysis indicated that the type of damage (DAI and non-DAI) does not appear to be a major factors affecting the PG improving GFO. The degree of coma (GCS≤8 and GCS≤12) and the route of administration (intravenous injection, intramuscular injection, and nasogastric tube route) may be one of the factors affecting PG improving GFO. 6) A subgroup analysis of mortality showed that type of injury and route of administration may be factors influencing PG reducing mortality. The degree of coma does not seem to significantly affect PG to reduce mortality. A sensitivity analysis showed lower GFO sensitivity and higher mortality rate sensitivity (when the study by Skolnick [20] was removed, the *P* value was 0.05 after the data were pooled using RR. 7) The publication bias test finding showed significant publication bias.

PG is a potentially promising drug for TBI. Our study indicated that PG slightly increased the GFO rate in patients with TBI, although the differences between the groups were small (51.1% in the PG groups vs. 48.9% in the control groups). We believe that there were three reasons for the small differences between the groups. First: Compared to traditional therapies, adding PG may not be as effective as we expected. Second: there are some differences in the treatment protocol (surgery or not, surgical protocol, type of drug, dosage, whether there is mild hypothermia treatment, and

whether there is a tracheotomy, etc.) between the different studies. In addition, to some extent, the level of health care, family economic conditions, family attitudes, patient physique, and other confounding factors will also affect the GFO rate between the groups. Third: PG has the potential to improve GFO, simply because the above conclusions are based on the appropriate routes of administration. Fortunately, a subgroup analysis of the route of administration seems to prove this view. Furthermore, the basic research conclusions by Candolfi et al. [33] seem to support our finding, showing that the intramuscular injection of PG can effectively improve the neurological prognostic outcomes in TBI mice. Meanwhile, the clinical trials by Xiao et al. [22] indicated that the intramuscular injection of 1 mg/kg PG every 12 hours for 5 days seemed to be effective. The meta-analysis by Pan et al. [34] demonstrated that PG has the potential to improve the GFO rate within 3 months. However, a meta-analysis by Lu et al. found the opposite [35]. By comparing our meta-analysis with their meta-analysis, it was found that there were some limitations (only 8 studies were included) in the study by Lu et al. Furthermore, we found that compared with the study by Pan et al. the research by Lu et al. did not perform a subgroup analysis on the route of administration.

The study by Wright (2014) et al. [19] demonstrated that PG is not effective in reducing patient mortality. However, the study by Wright (2007) et al. [21] found that PG can effectively reduce mortality in patients with TBI. We compared the two studies and found that there are large differences in the dosing protocols, which may be one of the root causes of the differences in their conclusions. Our pooled findings indicated that PG is not effective in reducing mortality in TBI patients. However, a subgroup analysis on the route of administration demonstrated that administering PG using an intramuscular injection can be effective in reducing mortality (16.0% in the PG groups vs. 26.3% in the control groups). This conclusion was consistent with the meta-analysis by Pan et al. [34]. Taking into account the above discussion on the GFO and mortality, we cautiously believe that intramuscular injection seems to be a better route of administration, because it not only can improve the neurological prognosis outcomes, but it can also effectively reduce mortality. Unfortunately, due to the limitations of the study data, we were unable to perform a subgroup analysis of the dosage and dosing time windows. This limits our chances of developing a reasonable administration protocol. Therefore, we hope, in the future, that more high-quality studies will be performed on PG administration protocols, because our research seems to suggest that the administration protocol (dosage, route of the administration, time window of the administration) can influence the PG therapeutic effect.

Several studies showed that the PG brain protection occurred through multi-mechanisms, which can be summarized as follows: 1) Reduce excitotoxicity by decreasing the effects of glutamate and boosting the effects of GABA; 2) Reduce lipid peroxidation; 3) Inhibit inflammation; 4) Inhibit neuronal apoptosis; 5) Promote neuroprotective factor expression and provide neurotrophic; 6) Reduce brain edema; 7) Promote the repair of the BBB [15, 32, 36-43]. Furthermore, our research on RIs also verifies this.

A subgroup analysis of the GFO on the injury types (DAI and Non-DAI) showed that the injury types were not an influencing factors of PG improving GFO. There was no heterogeneity between the subgroups (I^2=0), suggesting that the type of injury may not be the cause of the heterogeneity between the studies. In addition, the subgroup analysis of the coma score (GCS≤8 and GCS≤12) demonstrated that, compared with the patients with GCS≤12, PG can effectively improve the GFO of patients with GCS≤8, indicating that the degree of coma affects PG improving GFO. We believe that compared with the patients with GCS≤8, the TBI patients with GCS 9-12 can basically reach GFO using the traditional treatment protocol. This kind of good effect has basically reached the boundary of the patient's ability to recover in the traditional treatment protocol, so the additional use of PG seems to be sympathetic but has no ability to improve a patient's condition. The subgroup analysis of the GFO on the routes of administration demonstrated that intravenous administration and nasogastric tube administration cannot effectively improve the GFO in patients with TBI. However, the intramuscular injection of PG can significantly increase the GFO rate in patients with TBI

(64.6% in the PG groups vs. 45.1% in the control groups). Furthermore, the subgroup heterogeneity test findings suggested that the different routes of administration may be a source of heterogeneity (I^2=80%).

The subgroup analysis of the type of injury (DAI and non-DAI), level of consciousness (GCS≤8 and GCS≤12), and the route of administration (intravenous administration, intramuscular administration, and nasogastric tube) demonstrated that the type of injury and the route of administration may be the factors that affect PG reducing mortality and not the level of consciousness. The studies indicated that different types of injury will produce different degrees of trauma, intracranial hemorrhage, intracranial inflammation, and intracranial edema, and there will be differences in the degree of damage to the body, so the existence of the differences in body damage will lead to an inconsistency in mortality. However, the level of consciousness is mainly used to measure the patients' state of consciousness. It may be only moderately associated with mortality in TBI patients. Moreover, the subgroup heterogeneity test results (I^2=78.8%) indicated that the type of injury may be one of the reasons for the heterogeneity among the studies.

TBI is a serious public health issue worldwide, with a high mortality and disability rate, making it a leading cause of loss of human potential [44, 45]. Improving and predicting TBI patients' prognosis has always been a goal of neurologists [46]. Fortunately, our pooled findings suggested that PG (intramuscular administration) is a potentially promising drug for TBI. In addition, the safety of PG also deserves further clarification. Wright et al. [19] reported on phlebitis or thrombophlebitis events in the treatment of TBI with PG. We analyzed their research methods and found that they mainly administered PG intravenously. We believe that repeated intravenous administration may be the leading cause of phlebitis or thrombophlebitis. Moreover, the study also reported on hyperkalemia and hypokalemia. The data pooling results indicated that PG seems to be effective at reducing the incidence of hyperkalemia but not at the expense of increasing the risk of hypokalemia. In addition, the data pooling findings also showed that there was no statistically significant difference in terms of seizures, nervous system disorders, cardiac disorders, thromboembolic disease, gastrointestinal disorders, unexplained increased liver-enzyme levels, urinary complications, endocrine disorders, blood or lymphatic system disorders, sepsis, infections, or hyperglycemia.

The meta-analysis has the following limitations. 1) The sensitivity analysis of the mortality was not satisfactory. When we removed the study by Skolnick, 2014 [20], the pooled *P* values changed from 0.74 to 0.05. This forced us to re-analyze their study. We found that the PG was administered intravenously, indicating that intravenous injection not only increases the incidence of phlebitis, but it also increases the risk of mortality; 2) Moderate publication bias makes us question the stability of the results; 3) Significant heterogeneity poses a challenge to the scientific nature of the findings, although some heterogeneous sources have been discovered by the subgroup analysis, but the hidden confounding factors cannot be ignored; 4) There was significant heterogeneity in the data pooling results of the RIs and AEs; 5) The included papers only were limited to English (71.4%) and Chinese (28.6%) language studies, which could create the conditions for language bias; 6) Although PG via intramuscular injection for TBI may be safe and effective, this conclusion still needs a high-quality clinical study for further validation.

Conclusion

We firmly believe that PG via intramuscular administration is a potentially promising protocol for TBI. But this conclusion still requires a high-quality clinical study for further validation.

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Disclosure of conflict of interest

None.

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References

[1] Menon DK, Schwab K, Wright DW and Maas AI; Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil 2010; 91: 1637-40.

[2] McIntosh TK, Smith DH, Meaney DF, Kotapka MJ, Gennarelli TA and Graham DI. Neuropathological sequelae of traumatic brain injury: relationship to neurochemical and biomechanical mechanisms. Lab Invest 1996; 74: 315-42.

[3] Yi JH and Hazell AS. Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. Neurochem Int 2006; 48: 394-403.

[4] Faden AI, Demediuk P, Panter SS and Vink R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. Science 1989; 244: 798-800.

[5] Lewen A, Matz P and Chan PH. Free radical pathways in CNS injury. J Neurotrauma 2000; 17: 871-890.

[6] Tyurin VA, Tyurina YY, Borisenko GG, Sokolova TV, Ritov VB, Quinn PJ, Rose M, Kochanek P, Graham SH and Kagan VE. Oxidative stress following traumatic brain injury inrats: quantitation of biomarkers and detection of free radical intermediates. J Neurochem 2000; 75: 2178-2189.

[7] Frugier T, Morganti-Kossmann MC, O'Reilly D and McLean C. In situ detection of inflammatory mediators in post mortem human brain tissue after traumatic injury. J Neurotrauma 2010; 27: 497-507.

[8] Ghirnikar RS, Lee YL and Eng LF. Inflammation in traumatic brain injury: role of cytokines and chemokines. Neurochem Res 1998; 23: 329-340.

[9] Donkin JJ and Vink R. Mechanisms of cerebral edema in traumatic brain injury: therapeutic developments. Curr Opin Neurol 2010; 23: 293-299.

[10] Raghupathi R. Cell death mechanisms following traumatic brain injury. Brain Pathol 2004; 14: 215-222.

[11] Roozenbeek B, Maas AI and Menon DK. Changing patterms in the epidemiology of traumatic brain injury. Nat Rev Neurol 2013; 9: 231-236.

[12] Andriessen TM, Horn J, Franschman G, van der Naalt J, Haitsma I, Jacobs B, Steyerberg EW and Vos PE. Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. J Neurotrauma 2011; 28: 2019-2031.

[13] Alderson P and Roberts I. Corticosteroids for acute traumatic brain injury. Cochrane Database Syst Rev 2005; 2005: CD000196.

[14] Attella MJ, Nattinville A and Stein DG. Hormonal state affects recovery from frontal cortex lesions in adult female rats. Behav Neural Biol 1987; 48: 352-367.

[15] Stein DG. Embracing failure: what the phase II progesterone studies can teach about TBI clinical trials. Brain Injury 2015; 29: 1259-1272.

[16] Guo Q, Sayeed I, Baronne LM, Hoffman SW, Guennoun R and Stein DG. Progesterone administration modulates AQP4 expression and edema after traumatic brain injury in male rats. Exp Neurol 2006; 198: 469-478.

[17] Sinha S, Raheja A, Samson N, Goyal K, Bhoi S, Selvi A, Sharma P and Sharma BS. A randomized placebo-controlled trial of progesterone with or without hypothermia in patients with acute severe traumatic brain injury. Neurol India 2017; 65: 1304-1311.

[18] Wu J, Jiang DJ, Li Y, Chen J and Wang CQ. Effects of progesterone on serum markers, intracranial pressure and prognosis in patients with acute severe craniocerebral injury. Neural Injury and Functional Reconstruction 2017; 12: 581-582. (In Chinese)

[19] Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, Goldstein FC, Caveney AF, Howlett-Smith H, Bengelink EM, Manley GT, Merck LH, Janis LS and Barsan WG; NETT Investigators. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med 2014; 371: 2457-2466.

[20] Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, Ward JD, Nelson NR and Stocchetti N. A clinical trial of progesterone for severe traumatic brain injury. N Engl J Med 2014; 371: 2467-2476.

[21] Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, Goldstein FC, Salomone JP, Dent LL, Harris OA, Ander DS, Lowery DW, Patel MM, Denson DD, Gordon AB, Wald MM, Gupta S, Hoffman SW and Stein DG. ProTECT: a randomized clinical trial of progester-one for acute traumatic brain injury. Ann Emerg Med 2007; 49: 391-402, 402, e1-2.

[22] Xiao G, Wei J, Yan W, Wang W and Lu Z. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. Crit Care 2008; 12: R61.

[23] Higgins JPT and Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011.

[24] Abokhabar H, Abouelela A and Mousa S. Impact of progesterone administration on out-

come of patients with severe traumatic brain injury. Intens Care Med 2012; 38: 84-89.
[25] Aminmansour B, Nikbakht H, Ghorbani A, Rezvani M, Rahmani P, Torkashvand M, Nourian M, and Moradi M. Comparison of the administration of progesterone versus progesterone and vitamin D in improvement of outcomes in patients with traumatic brain injury: a randomized clinical trial with placebo group. Ahv Biomed Res 2012; 4: 1-5.
[26] Lu LQ, Sheng LP, Li JL, Chen RH and Zhu W. Effect of progesterone on serum TNF-α, IL-1β and prognosis in patients with severe traumatic brain injury. J Trauma Surg 2012; 14: 157-160.
[27] Soltani Z, Shahrokhi N, Karamouzian S, Khaksari M, Mofid B, Nakhaee N and Reihani H. Does progesterone improve outcome in diffuse axonal injury? Brain Inj 2017; 31: 16-23.
[28] Shakeri M, Boustani MR, Pak N, Panahi F, Salehpour F, Lotfinia I, Meshkini A, Daghighi S, vahedi P, Khani M and Taghiloo D. Effect of progesterone administration on prognosis of patients with diffuse axonal injury due to severe head trauma. Clin Neurol Neurosurg 2013; 115: 2019-2022.
[29] Mofid B, Soltani Z, Khaksari M, Shahrokhi N, Nakhaee N, Karamouzian S, Ahmadinejad M, Maiel M and Khazaeli P. What are the progesterone-induced changes of the outcome and the serum markers of injury, oxidant activity and inflammation in diffuse axonal injury patients? Int Inunophcrmacol 2016; 32: 103-110.
[30] Xiao GM, Wei J, Wu ZH, Wang WM, Jiang QZ, Cheng J, Lu F, Wu JY, Xu HS and Fang R. Clinical study on the therapeutic effects and mechanism of progesterone in the treatment for acute severe head injury. Zhonghua Wai Ke Za Zhi 2007; 45: 106-108.
[31] Cheng XW, Cheng J, Huang XC, Wang HH, Zha ZZ and Qian Y. Effect of progesterone therapy on endogenous opioid peptides in serum of patients with acute craniocerebral injury. Chin J Neurosurg Dis Res 2017; 16: 354-355.
[32] He J, Evans CO, Hoffman SW, Oyesiku NM and Stein DG. Progesterone and allopregnanolone reduce inflammatory cytokines after traumatic brain injury. Exp Neurol 2004; 189: 404-412.
[33] Candolfi M, Jaita G, Zaldivar V, Zárate S, Ferrari L, Pisera D, Castro MG and Seilicovich A. Progesterone antagonizes the permissive action of estradiol on tumor necrosis factor-alpha-induced apoptosis of anterior pituitary cells. Endocrinology 2005; 146: 736-743.
[34] Pan ZY, Zhao YH, Huang WH, Xiao ZZ and Li ZQ. Effect of progesterone administration on the prognosis of patients with severe traumatic brain injury: a meta-analysis of randomized clinical trials. Drug Des Dev Ther 2019; 13: 265-273.
[35] Lu XY, Sun H, Li QY and Lu PS. Progesterone for traumatic brain injury: a meta-narrative review of randomized controlled trials. World Neuro Surg 2016; 90: 199-210.
[36] Bitran D, Shiekh M and McLeod M. Anxiolytic effect of progesterone is mediated by the neurosteroid allopregnanolone at brain GABAA receptors. J Neuroendocrinol 1995; 7: 171-177.
[37] Bayir H, Marion DW, Puccio AM, Wisniewski SR, Janesko KL, Clark RS and Kochanek PM. Marked gender effect on lipid peroxidation after severe traumatic brain injury in adult patients. J Neuritrauma 2004; 21: 1-8.
[38] González SL, Labombarda F, González Deniselle MC, Guennoun R, Schumacher M and De Nicola AF. Progsterone up-regulates neuronal brain-derived neurotrophic factor expression in the injured spinal cord. Neuroscience 2004; 125: 605-614.
[39] Guo Q, Sayeed I, Baronne LM, Hoffman SW, Guennoun R and Stein DG. Progesterone administration modulates AQP4 expression and edema after traumatic brain injury in male rats. Exp Neurol 2006; 198: 469-478.
[40] Pettus EH, Wright DW, Stein DG and Hoffman SW. Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury. Brain Res 2005; 1049: 112-119.
[41] Roof R and Hall E. Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. J Neurotraum 2000; 5: 367-400.
[42] Yao XL, Liu J, Lee E, Ling GS and McCabe JT. Progesterone differentially regulates pro- and anti-apoptotic gene expression in cere bral cortex following traumatic brain injury in rats. J Neurotrauma 2005; 22: 656-668.
[43] Zhang M, Wu JY, Ding HJ, Wu W and Xiao G. Progesterone provides the pleiotropic neuroprotective effect on traumatic brain injury through the Nrf2/ARE signaling pathway. Neurocrit Care 2016; 26: 292-300.
[44] Qi L, Jacob A, Wang P and Wu R. Peroxisome proliferator activated receptor-γ and traumatic brain injury. Int J Clin Exp Med 2010; 3: 283-292.
[45] Zhang B and Zhao J. Red blood cell distribution width as a prognostic biomarker for mortality in traumatic brain injury. Int J Clin Exp Med 2015; 10: 19172-19175.
[46] Gao J and Zheng Z. Development of prognostic models for patients with traumatic brain injury: a systematic review. Int J Clin Exp Med 2015; 8: 19881-19885.