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Review Paper

Effectiveness of Platelet-rich Plasma in Treating Spinal Cord Injuries: A Systematic Review & Meta-analysis

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ABSTRACT

Introduction: The present systematic review and meta-analysis was designed to investigate platelet-rich plasma (PRP) as an effective treatment for spinal cord injury in animal models.

Methods: An extensive literature search was conducted using electronic databases. The included studies were summarized based on the investigated outcomes, including functional recovery and cavity size. Data were recorded as Mean±SD. The relationships between variables and the outcomes were investigated based on the "meta" command in the STATA 17.0 statistical program.

Results: In total, 9 articles were included in the present meta-analysis. Pooled data analysis showed that administrating PRP significantly improved the motor function of animals (standardized mean differences [SMD]=1.5; 95% CI, 0.9%, 2.1%; P<0.0001). In subgroup analysis based on the severity of the injury, PRP administration significantly improved the motor function of animals in both moderate (SMD=2.59; 95% CI, 1.59%, 3.59%; P<0.0001; I^2=30.22%) and severe injuries (SMD=1.22; 95% CI, 0.64%, 1.79%; P<0.0001; I^2=56.35%). However, the recovery of function was significantly more in animals with moderate spinal cord injury (meta-regression coefficient=-1.36; 95% CI, -2.68%, -0.09%; P=0.035). In assessing cavity size, pooled data analysis showed that PRP administration significantly reduces cavity size (SMD=-2.2; 95% CI, -3.44%, -0.95%; P<0.0001).

Conclusion: This meta-analysis shows that PRP can significantly improve motor function and reduce the cavity size in animals with moderate to severe spinal cord injuries.

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Highlights

- The administration of platelet-rich plasma (PRP) improves the motor function of rodents with spinal cord injury.
- The administration of PRP reduces the cavity size in spinal cord injury.
- Treatment with PRP is more effective in moderate spinal cord injuries.

Plain Language Summary

Spinal cord injury mostly affects the younger population and older people. Since injuries to the spinal cord can cause debilitating, long-lasting complications, new strategies must be tried to minimize the effect of this disease on society. Several treatment strategies for spinal cord injuries are available, most of which focus on conservative and symptomatic treatments. However, researchers have turned to novel strategies, including stem cell and molecular therapies, whose efficacy has been shown to improve chronic conditions. Human blood is a rich source of proteins that enhance tissue regeneration, and platelets are known to be one of the cells responsible for their production. Thus, separating these cells and molecules and administering them to the spinal cord injury could have beneficial effects. We need to gather all data provided before us, try to reach a conclusion with what we have and find the gaps in knowledge to guide other researchers to redirect their focus. We summarized previous studies on the outcome of spinal cord injuries after PRP administration. In conclusion, we showed that this treatment strategy has beneficial effects on the movement of rodents and reduces the size of the injured tissue in the spinal cord. However, considering the low number of studies conducted on this matter, more comprehensive studies are needed to confirm our findings.

1. Introduction

Spinal cord injuries (SCIs) primarily affect young adults and thus have devastating physical, psychological, and social impacts. This condition substantially burdens healthcare systems (Badhiwala et al, 2019; James et al., 2019). SCI leads to sensory and or motor deficits, which often present as gait disturbances, loss of coordination, severe neuropathic pain, and incontinence. Despite advances in healthcare, patients with spinal cord injuries often have a decreased quality of life (QoL) and suffer more from morbidities due to subsequent chronic symptoms (Sezer et al., 2015).

The current management strategies for SCI involve surgery, symptomatic treatment, and physical rehabilitation (Walters et al., 2013). In the acute phase of the disease, methylprednisolone is recommended during the first 8 hours. However, there is insufficient evidence to support the use of high-dose steroids 8 hours after an acute SCI (Bracken, 2012). Although physical rehabilitation and other treatment strategies can relatively improve the complications caused by spinal cord injuries, patients often face lifelong severe disabilities and chronic morbidities. Research in this field is still in progress and various therapeutic strategies from the molecular, gene, or cellular therapy or even the use of high-tech equipment such as virtual reality have been recommended to ameliorate symptoms (Janzadeh et al., 2017; Mammana et al., 2019; Miguel-Rubio et al., 2020; Nakhjavan-Shahraki et al., 2018; Sarveazad et al., 2017; Sarveazad et al., 2019; Silvestro et al., 2020). However, proposing these treatment options for Food and Drug Administration (FDA) approvals needs sufficient preclinical and clinical studies.

Platelet-rich plasma (PRP) has recently received much attention as a potential candidate for treating SCI. PRP contains several growth factors responsible for tissue regeneration and repair. The presence of growth factors and protective cytokines such as platelet-derived growth factor, transforming growth factor beta, fibroblast growth factor, insulin-like growth factor-1, insulin-like growth factor-2, vascular endothelial growth factor, epidermal growth factor, interleukin 8, keratinocyte growth factor, and connective tissue growth factor makes PRP a suitable agent for the treatment of neurodegenerative and inflammatory diseases (Marx, 2004). Regarding the pathophysiology of SCI, we observe the simultaneous occurrence of inflammation and neurodegeneration. In the acute phase of the injury, severe inflammation causes a cascade of pathophysiological events, ultimately initiating neurodegeneration and permanent lesions in the spinal cord (Alizadeh et al., 2019).

Recent research shows that PRP administration in the acute, subacute, and chronic phases of SCI improves locomotor function and reduces long-term side effects such as neuropathic pain (Salarinia et al., 2020; Salarinia et al., 2017). The administration of PRP improves angiogenesis and promotes axonal regeneration but does not significantly affect the immune system's reaction (Chen et al., 2018). Therefore, if PRP administration can prevent the occurrence of permanent damage in spinal cord injuries, it could be used as an easy and accessible treatment in the future. Moreover, the isolation and preparation of autologous PRP are simple and fast, and these beneficial effects have created a promising window for treating spinal cord injuries. Developments in the administration of PRP for spinal cord injuries are still in the preclinical phase, and there is no conclusion on this matter. It is still not yet clear which treatment protocol of PRP has the best effectiveness, and the best time and method of administration are yet unknown. Therefore, to start clinical trials, it is necessary to provide valid preclinical evidence of PRP being a potential candidate for the treatment of SCI. The present systematic review and meta-analysis intend to collect preclinical evidence on the efficacy of different PRP administration protocols in spinal cord injuries, emphasizing functional recovery and cavity size. As a supplementary analysis, we assessed the effect of different PRP protocol treatments and the severity of spinal cord injury on the effectiveness of PRP treatment following spinal cord injury.

2. Materials and Methods

Study design

The present systematic review and meta-analysis collected preclinical evidence on the effectiveness of PRP administration in spinal cord injuries, emphasizing functional recovery and cavity size. For this purpose, an extensive literature search was conducted using the electronic databases of Medline, Embase, Scopus, and Web of Science until October 23, 2022. The search strategy was based on keywords related to PRP and SCI—the search strategy in the Medline database (Appendix 1).

Inclusion criteria

The PICO (population, intervention, comparison, outcome) components are as follows. The population includes animals (rats or mice) with SCI caused by compression, contusion, transection, or hemi-section. Intervention is the administration of PRP. A comparison was performed with a similar group that did not receive PRP, and the outcome was functional recovery and cavity size. Based on these criteria, studies conducted on animals with SCI for which PRP was administered have been included. The exclusion criteria were studies without a control group, review articles, and retracted studies.

Data gathering

Two independent researchers collected the data. After the search, articles were obtained from the mentioned databases and gray literature (Google and Google Scholar and the thesis section of the ProQuest database) in the eighth version of Endnote. These two researchers independently performed the initial screening process. The title and abstract of each article were reviewed, and if the article was relevant or likely to be relevant, the full text of the study was collected and studied. Then, the data of these studies were summarized in a checklist designed based on PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines. The extracted data included information about the study design, the characteristics of the sample and control groups (age, gender, etc.), the sample size, the type of SCI, the time interval from the occurrence of injury, and the administration of PRP, the dose of PRP, the location of SCI, the method of PRP administration, and the follow-up period.

Quality control

The quality assessment of the articles was done by two researchers independently with the SYRCLE risk of bias tool (Hooijmans et al., 2014). In case of disagreement between the researchers, the disagreement was resolved through discussion with each other or a third researcher.

Statistical analyses

The analyses were performed using the statistical program STATA 17.0. Data are recorded as Mean±SD. The presence of heterogeneity has been investigated using the I^2 test. The relationships between the location of SCI, the severity of the injury, PRP dosage, PRP administration method, follow-up period, functional recovery, and cavity size were assessed using the "meta" command. Egger's test and the funnel plot were also used to investigate publication bias.

3. Results

The search resulted in 168 articles. After removing duplicates, 105 articles were advanced for screening. After reviewing the full text of 26 articles, the data from 9 original articles were included in the present meta-analysis: Behroozi et al. (2021); Behroozi et al. (2022); Chen

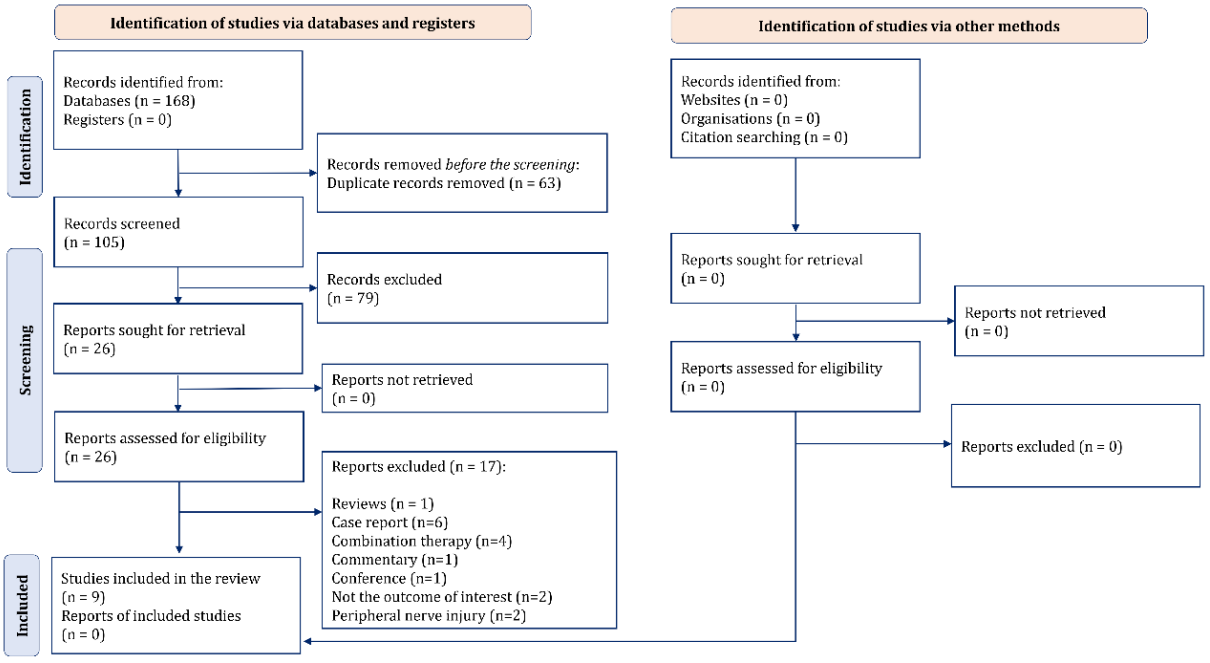

Figure 1. PRISMA flowchart of the article selection process

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PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

et al. (2018); EL-Seddawy et al., 2020; Hu et al. (2022); Lam et al. (2016); Salarinia et al., (2020); Salarinia et al. (2017); and Zhao et al., (2013) (Figure 1).

Of these 9 articles, 8 were performed on rats and 1 on mice. All studies used the SCI model in the thoracic region of the spinal cord. The injury model was compression in 3 studies, contusion in 4 studies, transection in 1 study, and hemi-section in 1 study. The severity of the injury was moderate in 3 studies and severe in 6 studies.

PRP was taken from human umbilical cord blood (xenograft) in 3 studies and peripheral blood (allograft/autograft) in 6 studies. In 5 studies, PRP administration was performed 24 hours after the injury, and in 3 studies, during the first 24 hours. In one study, the intervention was done in two separate groups, less than 24 hours and after 24 hours from the time of injury. The follow-up period was more than 4 weeks in 6 studies and 4 weeks or less in 3 studies. The outcome was the functional recovery in 7 studies and cavity size in one study. One article investigated the PRP administration effect on functional recovery and cavity size. All included studies examining functional recovery reported this outcome using the Basso Beattie and Bresnahan (BBB) scale. Table 1 presents the characteristics of the included articles.

The effect of PRP administration on function recovery

A total of 8 articles examined functional recovery. Using the Galbraith plot to find the outlier data, it was found that the study of EL-Seddawy et al. (2020) is an outlier. Therefore, it was excluded from the analysis. Eventually, 7 studies with 10 separate analyses were included in the current meta-analysis. The results of the pooled-data analysis showed that PRP administration has significantly improved the motor function of animals with SCI (standardized mean differences [SMD]=1.5; 95% CI, 0.9%, 2.1%; P<0.0001). Due to the moderate heterogeneity (I^2=67.01%), the subgroup analyses were performed (Figure 2).

In the subgroup analysis based on the severity of SCI, treatment with PRP in both moderate injuries (SMD=2.59; 95% CI, 1.59%, 3.59%; P<0.0001; I^2=30.22%) and severe ones (SMD=1.22; 95% CI, 0.64%, 1.79%; P<0.0001; I^2=56.35%) has been associated with a significant improvement in the motor function of animals. However, the extent of this recovery in moderate injuries was significantly greater than in the severe injury group (meta-regression coefficient=-1.36; 95% CI, -2.68%, -0.09%; P<0.035). PRP from peripheral blood (SMD=1.3; 95% CI, 0.62, 1.97%; P<0.0001; I^2=58.99%) and human umbilical cord blood (SMD=1.97; 95% CI, 0.63%, 3.3%; P<0.0001; I^2=80.74%) were both effec-

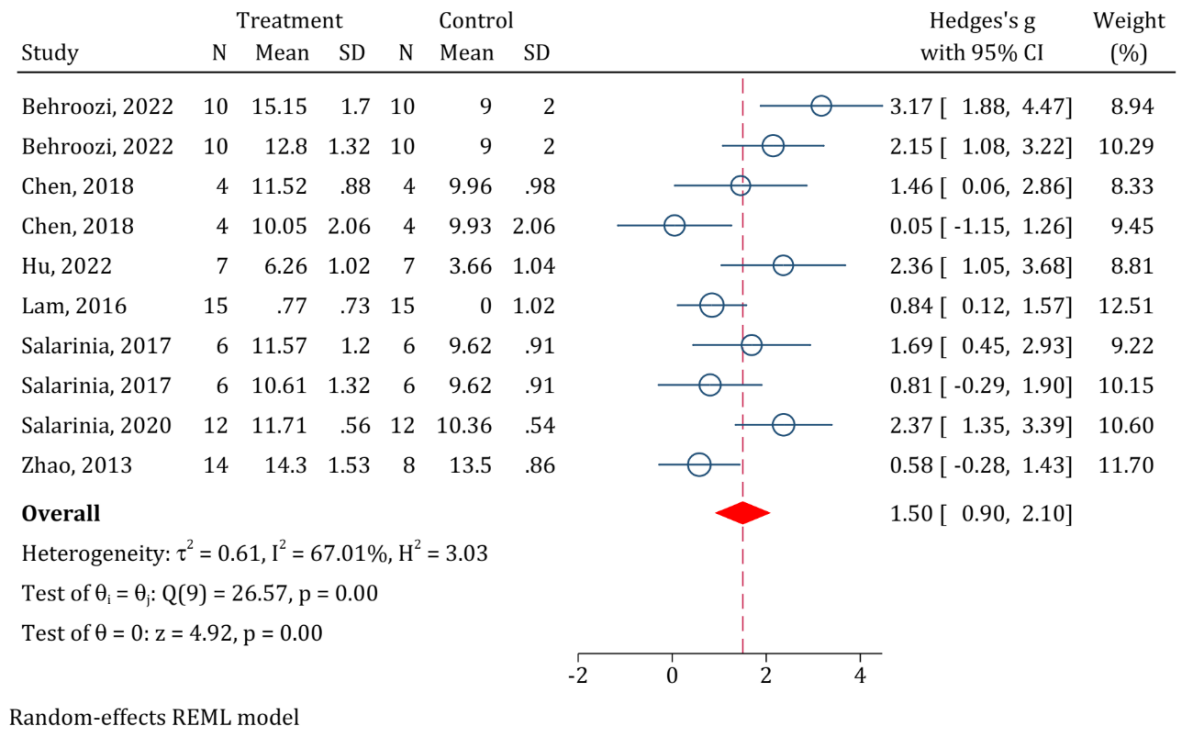

Figure 2. Pooled-data analysis for assessing functional recovery following spinal cord injury

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tive in improving the motor function of animals. However, no significant difference was observed between the two groups (meta-regression coefficient=0.62; 95% CI, -0.69%, -1.94%; P=0.35). PRP administration in the first 24 hours after SCI (SMD=0.86; 95% CI, 0.17%, 1.56%; P=0.015; I^2=32.36%) and after 24 hours (SMD=1.87; 95% CI, 1.11%, 2.64%; P<0.0001; I^2=67.93%) both were effective in improving the motor function of ani-

Table 1. Characteristics of the included studies

Study	Injury Level	Injury Model	Severity	Antibiotics	Species	Strain	Sex	Origin of PRP	Days to Injection	Site of Injection	Total Volume (µL)	Platelet Number (×10⁶)	Follow-Up (wk)
Behroozi et al., 2021	T12-T13	Compression	Moderate	Tetracycline	Rat	Wistar	M	hUCB	2, 14	Intra-spinal	6	1000	6
Behroozi et al., 2022	T12-T13	Compression	Moderate	Tetracycline	Rat	Wistar	M	hUCB	2, 14	Intra-spinal	6	1000	6
Chen et al., 2018	T10	Contusion	Severe	Cephalosporine	Rat	Wistar	F	Peripheral blood	0	Intrathecal	10	4800, 9600	4
Hu et al., 2022	T10	Contusion	Severe	Penicillin	Rat	SD	M	Peripheral blood	3	Intra-spinal	10	NR	4
Lam et al., 2016	T8-T10	Transection	Severe	Penicillin	Mice	NR	NR	hUCB	7	Intra-spinal	20	NR	5
Salarinia et al., 2017	T10	Contusion	Severe	Cefazolin	Rat	Wistar	M	Peripheral blood	1, 7	Intra-spinal	5	NR	5
Salarinia et al., 2020	T10	Contusion	Severe	Cefazolin	Rat	Wistar	M	Peripheral blood	7	Intra-spinal	1	NR	5
EL-Seddawy et al. 2020	T9	Compression	Moderate	Gentamicin	Rat	SD	F	Peripheral blood	0	Intra-spinal	100	4800	4
Zhao et al., 2013	T10	Hemi-section	Severe	Penicillin	Rat	SD	F	Peripheral blood	0	Intra-spinal	15	3000	8

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Abbreviations: T: Thoracic vertebrae; PRP: Platelet-rich plasma; SD: Sprague-Dawley; hUCB: Human umbilical cord blood.

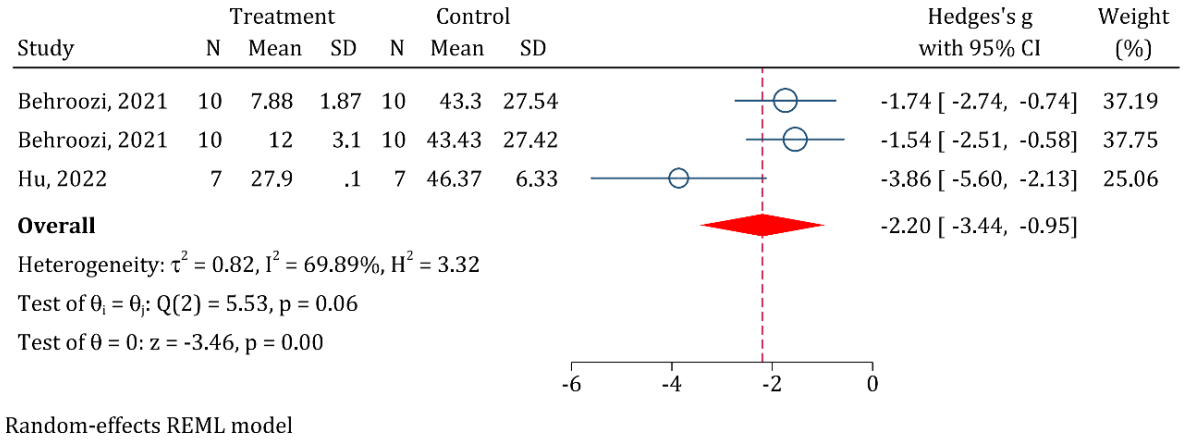

Figure 3. Pooled-data analysis for assessing cavity size following spinal cord injury

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mals. Meta-regression showed no significant difference between the administration of PRP in the first 24 hours and after 24 hours from injury (meta-regression coefficient=0.96; 95% CI, -0.16%, 2.09%; P=0.09). Finally, there was no significant difference regarding the follow-up period (meta-regression coefficient=0.33; 95% CI, -1.07%, 1.74%; P=0.64) (Table 2).

The effect of PRP administration on cavity size

In this section, 2 articles and 3 analyses were included. Pooled-data analysis showed that PRP administration significantly reduces the cavity size in animals with SCI (SMD=-2.2; 95% CI, -3.44%,-0.95%; P<0.0001) (Figure 3).

Quality control

None of the articles in the quality control assessment section reported housing randomization or random outcome assessment. Therefore, the risk of bias was considered unclear in these items. The risk of bias was low in other items in the included articles. Generally, the quality of data was considered fair (Table 3).

Publication bias

Egger's test showed no publication bias in the reports of functional recovery (P=0.64) (Figure 4). Since the assessment of cavity size was reported in 3 analyses, publication bias assessment was not feasible in terms of methodology.

Table 2. Subgroup analysis to investigate the relationship between different variables in functional recovery

Variables	Subgroups	No. of Analyses	SMD [95% CI]	P	Heterogeneity	Meta-regression Coefficient	P
Severity	Severe	8	1.22 [0.64 to 1.79]	<0.0001	56.35%	-1.39 [-2.68 to -0.098]	0.035
	Moderate	2	2.59 [1.59 to 3.59]	<0.0001	30.22%		
Origin of PRP	Peripheral blood	7	1.30 [0.62 to 1.97]	<0.0001	58.99%	0.62 [-0.69 to 1.94]	0.354
	Human umbilical-cord blood	3	1.97 [0.63 to 3.30]	0.004	80.74%		
Type of graft	Allograft/Autograft	7	1.30 [0.62 to 1.97]	<0.0001	58.99%	0.62 [-0.69 to 1.94]	0.354
	Xenograft	3	1.97 [0.63 to 3.30]	0.004	80.74%		
Injury to intervention	≤24 hours	4	0.86 [0.17 to 1.56]	0.015	32.36%	0.96 [-0.16 to 2.09]	0.093
	>24 hours	6	1.87 [1.11 to 2.64]	<0.0001	67.93%		
Follow-up duration	≤4 weeks	3	1.26 [-0.08 to 2.61]	0.066	68.92%	0.33 [-1.07 to 1.74]	0.64
	> 4 weeks	7	1.59 [0.88 to 2.29]	<0.0001	70.30%		

PRP: Platelet-rich plasma; SMD: Standardized mean difference.

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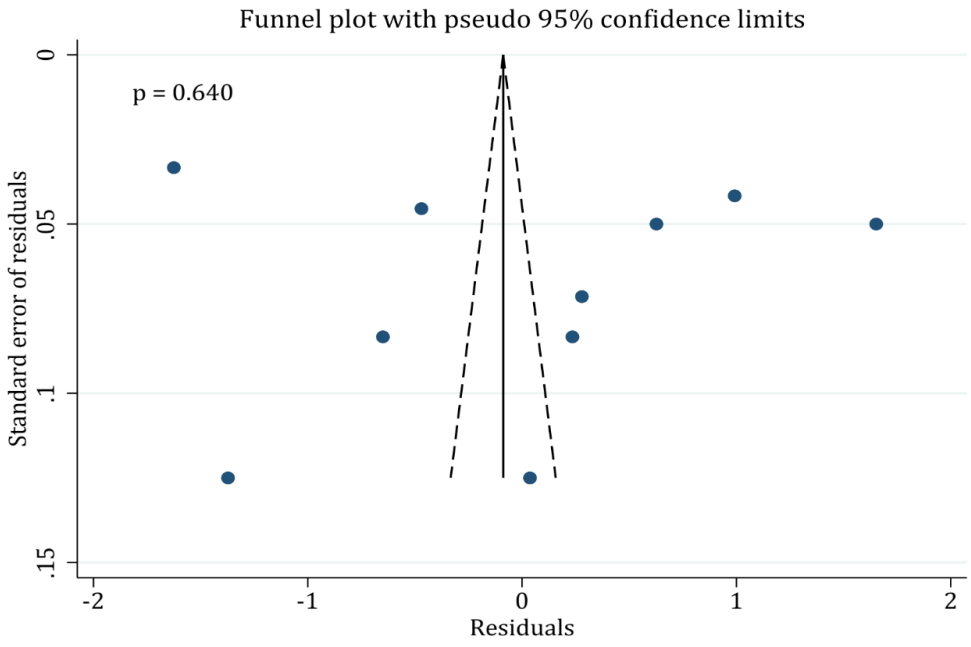

Figure 4. Funnel plot with pseudo 95% confidence interval in the assessment of publication bias

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4. Discussion

The purpose of this meta-analysis was to investigate the effectiveness of PRP administration in the treatment of spinal cord injuries. By analyzing the data of current original studies, we showed that PRP administration can significantly improve motor functions and cavity size after SCI. However, there was considerable heterogeneity in the findings of the articles. To find the cause of this heterogeneity, a subgroup analysis was performed on the severity of the SCI, the origin of PRP, the time elapsed from the injury to the administration of PRP, and the length of follow-up. According to these analyses, the severity of injury was the reason for heterogeneity in the articles.

The studies conducted on moderate spinal injuries had significantly less heterogeneity than those conducted on severe injuries. Although motor function improvements were significant in both moderate and severe injuries, the improvement of motor function in animals with moderate SCI was significantly higher than in animals with severe SCI. In addition to the fact that even in the absence of therapeutic intervention, moderate SCI has a better outcome than severe injury, it should be noted that the low number of analyses performed on moderate spinal cord injuries can be one of the reasons that we observed a significant difference.

Our review shows that the studies that used the peripheral blood of animals to prepare PRP had a lower heterogeneity than those that used human umbilical cord blood. Although the difference between the two groups was not significant, the extent of improvement in the motor function of animals using human umbilical cord blood was higher than the other group. The results of the grouping of articles based on the allograft/autograft and xenograft transplantation were completely the same as the grouping based on the origin of PRP.

Cell damage and the activation of inflammatory cascades in the spinal cord are responsible for the formation of scar tissue and preventing an effective regeneration of nervous tissue by inactivating growth factors, and stem cells in the injury site, reducing the activity of glial cells and increasing the activity of macrophages (Pang et al., 2021). Current treatment strategies, both in medical treatments and surgical interventions, emphasize the greater effect of treatment in faster interventions. For example, current findings emphasize the high effectiveness of spinal decompression surgeries in the first 24 hours after SCI (Li et al., 2014; Yousefifard et al., 2017). Moreover, even more recent review studies consider surgical intervention in the first 12 hours after SCI more effective (Yousefifard et al., 2022). Nonetheless, the evidence of greater effectiveness of PRP administration after 24 hours of SCI is notable in the present study.

Table 3. Quality control of the included articles

No.	Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Overall
1	Behroozi et al., 2021	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
2	Behroozi et al., 2022	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
3	Chen et al., 2018	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
4	Hu et al., 2022	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
5	Lam et al., 2016	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
6	Salarinia et al., 2017	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
7	Salarinia et al., 2020	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
8	EL-Seddawy et al, 2020	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
9	Zhao et al., 2013	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair

Low: Low risk of bias.

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Notes: Item 1. Was the allocation sequence adequately generated and applied?

Item 2. Were the groups similar at baseline, or were they adjusted for confounders in the analysis?

Item 3. Was the allocation adequately concealed?

Item 4. Were the animals randomly housed during the experiment?

Item 5. Were the caregivers and/or investigators blinded from knowledge, and which intervention did each animal receive during the experiment?

Item 6. Were animals selected at random for outcome assessment?

Item 7. Was the outcome assessor blinded?

Item 8. Were incomplete outcome data adequately addressed?

Item 9. Are reports of the study free of selective outcome reporting?

Item 10. Was the study apparently free of other problems that could result in a high risk of bias?

To illustrate this more, it can be pointed out that the SCI environment is unsuitable for the survival of growth factors in the acute phase of injury due to severe inflammation (Garcia et al., 2016). Since the effect of PRP administration on the immune response is a matter of debate (Chen et al., 2018), the possibility of intensification of the immune response due to inflammation could reduce the survival and effectiveness of PRP growth factors in the acute phase. As a result, it seems that the administration of PRP after 24 hours of injury is a potentially suitable treatment for improving motor function following SCI.

In review studies, the researcher does not control the intervention and control groups, so it is impossible to match the confounding variables between the studied groups. In the included studies, antibiotic treatment type and duration have been variable. Also, one of the included studies was conducted on mice, and the other studies were conducted on rats. The site of PRP administration in all studies was intra-spinal, while it was intra-thecal in one study. The number of platelets in the administered PRP was not mentioned in 4 studies. In all the cases mentioned, grouping the findings was impossible due to the low number of analyses.

5. Conclusion

The findings of the present meta-analysis show that PRP administration significantly improves the motor function of animals and the cavity size following SCI. Also, the present study shows the necessity of designing and implementing more comprehensive prospective studies to investigate the effectiveness of PRP treatment in spinal cord injuries. In addition, it is necessary to investigate the effectiveness of this treatment on other outcomes, such as pain and inflammation following SCI.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Iran University of Medical Sciences (Code: IR.IUMS.FMD.REC.1400.526).

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Authors' contributions

Data analysis: Mahmoud Yousefifard; Study design, writing and final approval: All authors.

Conflict of interest

All authors declared no conflict of interest.

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Appendix 1. Search strategy in the Medline database

1- Spinal cord injuries[mh] OR spinal cord compression[mh] OR central cord syndrome[mh] OR spinal cord injuries[tiab] OR spinal cord compression[tiab] OR central cord syndrome[tiab] OR spinal cord trauma[tiab] OR cord trauma, spinal[tiab] OR cord traumas, spinal[tiab] OR spinal cord traumas[tiab] OR trauma, spinal cord[tiab] OR traumas, spinal cord[tiab] OR myelopathy, traumatic[tiab] OR myelopathies, traumatic[tiab] OR traumatic myelopathies[tiab] OR traumatic myelopathy[tiab] OR injuries, spinal cord[tiab] OR cord injuries, spinal[tiab] OR cord injury, spinal[tiab] OR injury, spinal cord[tiab] OR spinal cord injury[tiab] OR spinal cord transection[tiab] OR cord transection, spinal[tiab] OR cord transections, spinal[tiab] OR spinal cord transections[tiab] OR transection, spinal cord[tiab] OR transections, spinal cord[tiab] OR spinal cord laceration[tiab] OR cord laceration, spinal[tiab] OR cord lacerations, spinal[tiab] OR laceration, spinal cord[tiab] OR lacerations, spinal cord[tiab] OR spinal cord lacerations[tiab] OR post-traumatic myelopathy[tiab] OR myelopathies, post-traumatic[tiab] OR myelopathy, post-traumatic[tiab] OR post traumatic myelopathy[tiab] OR post-traumatic myelopathies[tiab] OR spinal cord contusion[tiab] OR contusion, spinal cord[tiab] OR contusions, spinal cord[tiab] OR cord contusion, spinal[tiab] OR cord contusions, spinal[tiab] OR spinal cord contusions[tiab] OR compression, spinal cord[tiab] OR compressions, spinal cord[tiab] OR spinal cord compressions[tiab] OR myelopathy, compressive[tiab] OR compressive myelopathy[tiab] OR spinal cord compression, extramedullary[tiab] OR extramedullary spinal cord compression[tiab] OR conus medullaris syndrome[tiab] OR conus medullaris syndromes[tiab] OR syndrome, conus medullaris[tiab] OR syndromes, conus medullaris[tiab] OR central spinal cord syndrome[tiab] OR central cord injury syndrome[tiab]

2- Platelet-rich plasma[mh] OR platelet-rich plasma[tiab] OR plasma, platelet-rich[tiab] OR platelet rich plasma[tiab]

3- #1 AND #2

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