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Therapeutic efficacy of autologous bone marrow mesenchymal stem cell transplantation in patients with spinal cord injury: a meta-analysis

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- *Objective:* To investigate the efficacy of autologous bone marrow mesenchymal stem cell (BMSC) transplantation in patients with spinal cord injury (SCI) using meta-analysis, aiming to provide evidence-based guidance for clinical practice.
- *Methods:* Electronic databases such as PubMed, Web of Science, Cochrane Library and Embase were searched. Studies comparing the therapeutic effects of autologous BMSC transplantation and rehabilitation therapy on patients with SCI were included. The pooled effect size of autologous BMSC transplantation on the American Spinal Injury Association (ASIA) scores was calculated using the random- or fixed-effects model.
- *Results:* A total of seven eligible studies involving 288 patients with SCI were included in this study. The meta-analysis results showed that autologous BMSC transplantation significantly improved ASIA sensory scores (mean difference (MD): 8.80; 95% confidence interval (CI): 5.93, 11.67), ASIA motor scores (MD: 7.94; 95% CI: 2.05, 13.83), ASIA grade improvement (odds ratio (OR): 4.88; 95% CI: 2.48, 9.61) and somatosensory evoked potential improvement (OR: 3.34; 95% CI: 1.54, 7.25). This study did not find a statistically significant positive effect of autologous BMSC transplantation on bladder function and adverse events.
- *Conclusion:* The therapeutic efficacy of autologous BMSC transplantation is encouraging, but further multicentre, large-sample, prospective studies are still needed.

Keywords: autologous; bone marrow mesenchymal stem cells; spinal cord injury; meta-analysis

Introduction

Spinal cord injury (SCI) is the most severe complication of spinal trauma, often leading to transient or permanent loss of sensory, motor and autonomic functions below the level of injury (1). Epidemiological data indicate an estimated global incidence of SCI at approximately 10.5 per 100,000 individuals (2). This condition has a profound and devastating impact on the health and socioeconomic well-being of patients, their families and society. Although standard care for SCI management, including fracture reduction, decompression of the spinal canal, spinal stabilisation and rehabilitation, is an integral part of treatment, it can only mitigate the effects of secondary injury and does not directly promote neuronal regeneration (3, 4). Surgical intervention to decompress and release pressure, thereby facilitating the rapid recovery of neurological function, is the ideal treatment.

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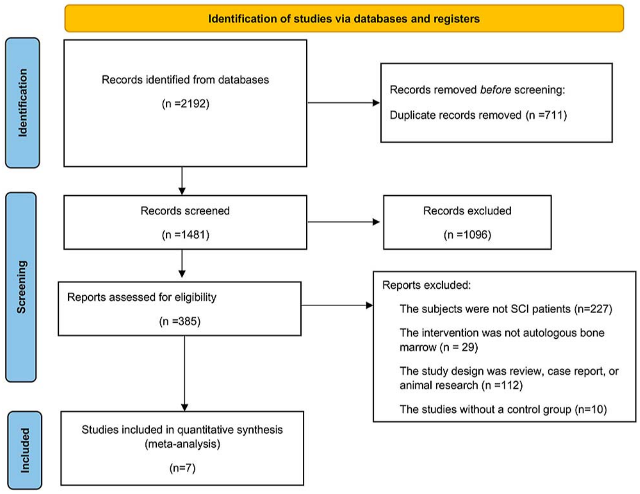

Figure 1

Literature screening flowchart.

However, there is currently no optimal therapeutic strategy for repairing damaged neuronal cells (5).

In recent years, regenerative medicine strategies based on cell therapy have garnered the attention of researchers (6). Bone marrow mesenchymal stem cells (BMSCs) possess the capabilities of differentiation and self-renewal, can release cytokines and exosomes to alleviate inflammation at the site of injury and have been widely applied as potential therapeutic agents for various diseases (7). The use of BMSCs represents a promising approach for SCI cell therapy. Notably, compared with allogeneic BMSCs, autologous BMSCs are easier to obtain and have the advantages of low immunogenicity and weaker immune rejection responses (5). Therefore, autologous BMSCs may be a good choice for stem cell therapy in SCI. The potential of BMSCs for SCI treatment has been confirmed in animal models (8, 9). In recent years, researchers have conducted clinical treatment studies of BMSCs in patients with SCI. However, the safety and efficacy of autologous BMSCs for SCI treatment remain controversial (10, 11). Thus, this study aims to perform a meta-analysis of clinical evidence for the treatment of SCI with autologous BMSCs to assess their safety and efficacy.

Materials and methods

Literature search

In accordance with the PRISMA 2020 statement (12), a systematic search was conducted in PubMed, Web of Science, Cochrane Library and Embase. The search period spanned from the inception of the databases to 10 August 2024. The search strategy encompassed the following keywords: 'SCI' OR 'spinal cord trauma' OR 'stem

Table 1 Basic characteristics of eligible studies.

Study	Location	Study design	Sample size, M/F	SCI type	Injury level	Mean age (years), M/F	Male %	ASIA (A/B/C/D)	TR type	Cells, *n*	FU, months
Chhabra *et al.* (20)	India	RCT	14/7	Acute	NA	NA	66.67	7/7/7/0	IT, IL	2×10^8/1.8 mL	12
Dai *et al.* (19)	China	RCT	20/20	Chronic	CR: 40	34.7/35.1	70/70	40/0/0/0	IL	8×10^5/μL	6
El-Kheir *et al.* (18)	Egypt	RCT	50/20	Chronic	CR: 17; TH: 53	16–45	87.14	25/45/0/0	IT	2×10^6/kg	18
Karamouzian *et al.* (17)	Iran	Non-RCT	11/20	Subacute	TH: 31	33.2/33.5	63.6/85	NA	IT	1.2×10^6	12
Kishk *et al.* (16)	Egypt	CCS	43/20	Chronic	CR: 8; TH: 55	31.7/33.8	83.7/75	NA	IT	5×10^6 to 10×10^6/kg	6
Saini *et al.* (22)	India	RCT	14/13	Acute	NA	28.2/32.6	85.71/76.92	27/0/0/0	IL	2×10^8	6
Song *et al.* (21)	China	RCT	18/18	Acute	CR: 21; TH: 9; LU: 6	41.2/41.7	66.67/55.56	NA	IT	1.0×10^7	12

SCI, spinal cord injury; ASIA, American Spinal Injury Association Score; RCT, randomised controlled trials; CCS, case-control study; CR, cervical; FU, follow-up; LU, lumbar; M/F, male/female; NA, not available; IT, intrathecal injection; IL, intralesional injection; TH, thoracic; TR, transplantation.

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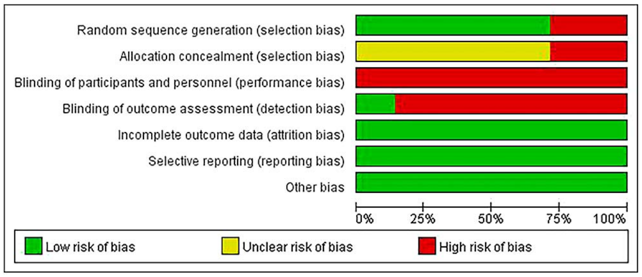

Figure 2

Risk of bias graph of seven eligible studies.

cell therapy' OR 'mesenchymal stem cells' OR 'bone marrow stromal cells'. Furthermore, to broaden the search scope, the reference lists of the included studies were reviewed to identify the additional target literature.

Eligible studies

Studies were included if they met the following criteria: i) they were published in peer-reviewed journals in both Chinese and English; ii) the patients were diagnosed with SCI, with no restrictions on age, gender or ethnicity; iii) the exposure of interest was the administration of autologous BMSC transplantation; iv) the control group underwent rehabilitation therapy without stem cell treatment; v) at least one of the following outcome measures was reported: American Spinal Injury Association (ASIA) sensory scores, motor scores or grade improvement, bladder function improvement, somatosensory evoked potential (SSEP) improvement or the incidence of adverse events; and vi) the study design was a randomised or non-randomised controlled trial, cohort study or case-control study.

Studies were excluded if they met the following criteria: i) non-population-based studies; ii) study types such as conference papers, case reports or systematic reviews; iii) duplicate reporting of the literature studies; iv) studies where the full text was not accessible; or v) studies in which patients received autologous BMSC transplantation combined with other therapies.

Literature screening and data extraction

Two researchers independently conducted the literature screening based on the predefined inclusion and exclusion criteria. Initially, a preliminary selection was made by reviewing the titles and abstracts of the literature. Subsequently, full-text reading was performed for studies that potentially met the inclusion criteria. In cases of disagreement between the two researchers, a third researcher was consulted to reach a consensus through discussion.

After completing the literature screening, two researchers independently extracted data according to a standardised extraction form. The extracted information included publication details, the demographic characteristics of the patients, disease characteristics, intervention measures, study duration and outcome events.

Literature quality

The quality of the literature was assessed using the Cochrane Risk Assessment Tool (13), which evaluated aspects such as the method of random sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting and other potential sources of bias. For observational studies, the Newcastle-Ottawa Scale (NOS) (14) was utilised to assess the quality. This scale evaluated the representativeness of the study population, the comparability of the groups and the adequacy of the assessment of outcomes, with a total of eight items and a full score of nine points. Studies scoring seven or above were considered the high-quality literature, whereas those scoring five or below were considered low-quality articles.

Statistical methods

Data analysis was conducted using RevMan 5.3 and Stata software. Continuous data were represented by the mean difference (MD), and count data were expressed using the odds ratio (OR). In studies including zero events (15), risk difference (RD) or Peto fixed-effect models were used for meta-analysis, with a 95% confidence interval (CI) estimating effect size ranges. Heterogeneity was assessed using the Q test and I^2 statistic. If $I^2 < 50\%$ or $P > 0.05$, a fixed-effect model was applied, indicating good homogeneity. Otherwise, a random-effects model was used. The significance level was set at 0.05 unless specified otherwise.

Results

Basic information

After searching the electronic databases, a total of 2,192 studies were included in the literature review process, as shown in Fig. 1. After excluding 711 duplicate studies and

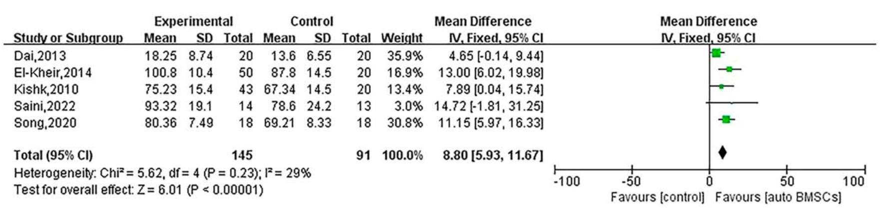

Figure 3

Effects of autologous bone mesenchymal stem cell on ASIA sensory score in SCI patients (16, 18, 19, 21, 22).

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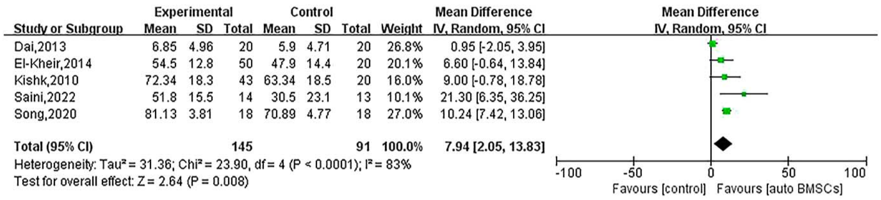

Figure 4

Effects of autologous bone mesenchymal stem cell on ASIA motor score in SCI patients (16, 18, 19, 21, 22).

1,064 irrelevant studies, 385 articles were included in the full-text review process. Based on the inclusion and exclusion criteria, seven comparative studies (16, 17, 18, 19, 20, 21, 22) were ultimately included. The publication dates of the studies ranged from 2010 to 2022, with five randomised controlled trials, one non-randomised controlled trial and one case-control study. These seven studies involved 288 patients with SCI, with three studies focusing on patients with acute or chronic SCI and one study on patients with subacute SCI. The injury sites were mainly in the thoracic and lumbar vertebrae, with two studies not providing information on the injury site. In addition, the study participants were mostly men aged between 16 and 45 years. The follow-up time for these studies ranged from 6 to 18 months. More detailed information about the included studies can be found in Table 1.

Quality of studies

We initially used the Cochrane Collaboration's risk assessment tool to evaluate the studies included in the review. The results indicated a significant risk of bias in the blinding process across the seven studies, with potential risks also present in allocation concealment (see Fig. 2). In addition, the NOS was applied to assess the one case-control study (16), which demonstrated commendable quality with an NOS score of 8. Overall, the quality of the included studies was considered acceptable.

American spinal injury association sensory scores

Five studies reported the ASIA sensory scores of patients with SCI after autologous BMSCs transplantation. The assessment of heterogeneity indicated good homogeneity among the included studies, and the fixed-effect model was used to calculate the combined effect size. Meta-analysis results showed that autologous BMSCs transplantation significantly improved the ASIA sensory scores of patients with SCI compared with the control group (MD: 8.80; 95% CI: 5.93, 11.67) (see Fig. 3).

American spinal injury association motor scores

Five studies reported the outcomes of the ASIA motor scores of patients with SCI following autologous BMSCs transplantation. The heterogeneity assessment indicated variability among the included studies, suggesting the use of a fixed-effects model for statistical analysis. The findings demonstrated a significant improvement in ASIA motor scores by 7.94 points (95% CI: 2.05–13.83) in patients with SCI after undergoing autologous BMSC transplantation, as depicted in Fig. 4.

American spinal injury association grade improvement

Four studies reported an improvement in ASIA grade following autologous BMSCs transplantation in patients with SCI. The heterogeneity assessment indicated no heterogeneity among the included studies. However, one study had zero events. Thus, the Peto fixed-effect model was used to calculate the combined OR. Meta-analysis results demonstrated that the likelihood of improvement in ASIA grade after autologous BMSCs transplantation was 4.88 times greater than that of the control group (95% CI: 2.48, 9.61) (see Fig. 5).

Bladder function

Four studies reported outcomes on bladder function improvement in patients with SCI following autologous BMSCs transplantation. The heterogeneity assessment indicated moderate variability among the included studies, with zero events present in two studies, necessitating the use of a random-effects model to calculate the combined RD. The meta-analysis suggested that autologous BMSCs transplantation might

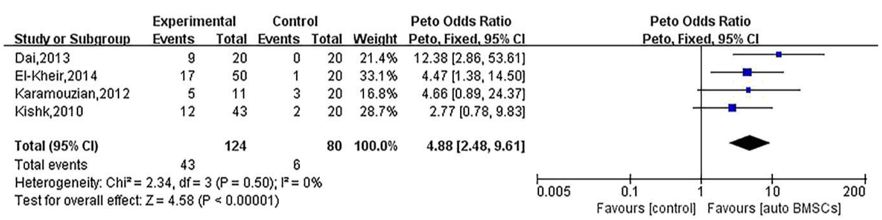

Figure 5

Effects of autologous bone mesenchymal stem cell on ASIA grade improvement in SCI patients (16, 17, 18, 19).

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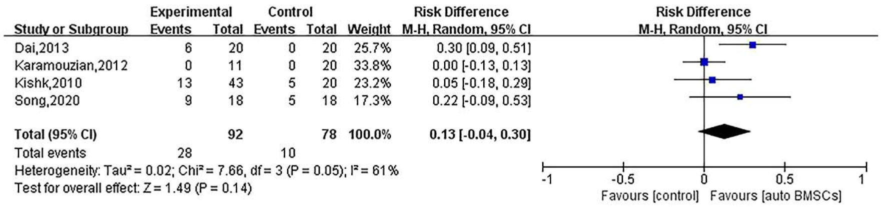

Figure 6

Effects of autologous bone mesenchymal stem cell on bladder function improvement in SCI patients (16, 17, 19, 21).

improve bladder function, although this positive effect was not statistically significant (RD: 0.13; 95% CI: −0.04, 0.30) (see Fig. 6).

Somatosensory evoked potential improvement

Four studies reported the improvement of SSEP in patients with SCI following autologous BMSCs transplantation. The heterogeneity assessment indicated good homogeneity among the included studies, with zero events present in one arm, necessitating the use of the Peto fixed-effect model to calculate the combined OR. The meta-analysis results demonstrated a significant positive effect of autologous BMSCs transplantation on SSEP improvement (OR: 3.34; 95% CI: 1.54, 7.25) (see Fig. 7).

Adverse events

Seven studies reported the occurrence of total adverse events after autologous BMSCs transplantation in patients with SCI. The meta-analysis, based on the random-effects model, showed that the impact of autologous BMSCs transplantation on adverse events in patients with SCI was not statistically significant compared with no stem cell therapy (RD: 0.03; 95% CI: −0.08, 0.14) (see Fig. 8).

Discussion

Comparative studies on the efficacy of autologous BMSCs transplantation in patients with SCI were included in this study. We used meta-analysis to evaluate the impact of autologous BMSCs transplantation on ASIA sensory and motor scores, grade improvement, bladder function improvement, SSEP improvement and safety. Six prospective clinical studies and one case-control study met the inclusion criteria, involving 288 patients with SCI. The meta-analysis confirmed a significant positive effect of autologous BMSCs transplantation on ASIA scores, grade improvement and SSEP improvement. However, no significant effect on bladder function improvement or adverse reactions was found.

Currently, clinical research on stem cells primarily focuses on Phase I clinical studies and retrospective studies, with a lack of high-quality randomised controlled trials, and even simple controlled trials are rare. Therefore, conducting meta-analysis for head-to-head comparisons to evaluate the efficacy and safety of stem cell transplantation is challenging. Previous studies have mainly summarised the impact of stem cell transplantation on SCI through systematic reviews, but quantitative analysis on the efficacy of autologous BMSCs transplantation is still lacking. Shang *et al.* (23) found that 48.9% of patients benefited from stem cell therapy, with at least one-grade improvement in ASIA scores. Our study also found improvements in ASIA sensation, motor function and grade in patients with SCI after autologous BMSCs transplantation. Chen *et al.* (24) also found a positive effect of mesenchymal stem cell transplantation, particularly BMSCs. However, these results represent only a slight improvement in sensory and motor functions, far from meeting the expected requirements for walking or daily activities. It is worth noting that the assessment of sensory and motor function based on ASIA scoring depends on the subjective evaluation of both assessors and patients, which somewhat reduces the reliability of the results (25). In addition, more patients now consider bladder function recovery as important as, or more important than, motor function. Although our study shows a trend of improvement in bladder function in patients with SCI after autologous BMSCs transplantation, it still falls short of patient expectations (26).

In preclinical studies, mesenchymal stem cell transplantation has shown multiple advantages in the treatment of SCI, which may explain why patients with SCI benefit from mesenchymal stem cell transplantation. The exosomes of mesenchymal stem cells have immune-regulating, anti-inflammatory, neurotrophic, neuroprotective and angiogenesis-promoting effects in

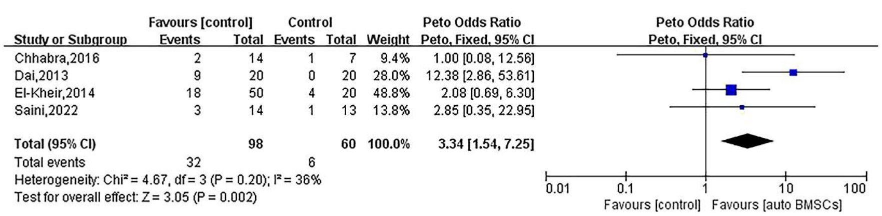

Figure 7

Effects of autologous bone mesenchymal stem cell on SSEP improvement in SCI patients (18, 19, 20, 22).

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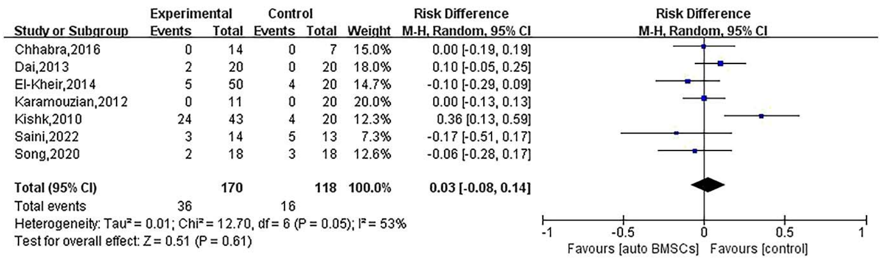

Figure 8

Effects of autologous bone mesenchymal stem cell on total adverse events in SCI patients (16, 17, 18, 19, 20, 21, 22).

the host microenvironment (27). Mesenchymal stem cells play an immunomodulatory role by inhibiting the activation, proliferation and differentiation of T cells (28), while also exerting an anti-inflammatory effect by secreting various soluble factors, such as TNF-β1, IL-10, IL-27 and NT-3 (29). In addition, as part of neuroprotection, mesenchymal stem cells secrete various neurotrophic factors, including BDNF, GDNF, NGF, NT-1 and NT-3 (8, 30).

This study has the following limitations. First, all included studies had small sample sizes, with each group having between 11 and 50 participants, which may lead to insufficient positive event numbers and potentially impact the study results. Due to limited reports on bladder function improvement in the included studies and inconsistent statistical methods, the consistency of the data could not be extracted, so the binary variable method was used to evaluate its effectiveness. In addition, due to limited data from the original studies, this study could not analyse the treatment effects of different autologous BMSCs transplantations in terms of size, transplantation time, SCI grading and disease course.

Conclusion

Autologous BMSCs transplantation can yield better results than rehabilitation therapy in patients with SCI, including improvements in motor function and sensation. However, due to the limitations of this study, the results should be interpreted with caution. Furthermore, more large-sample, multi-centre prospective clinical studies are needed to confirm the efficacy and safety of autologous BMSCs transplantation.

ICMJE Statement of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author Contribution Statement

Z Li and Y Liu conceived and designed the study. G Liu and W Xu screened the studies and extracted the data. L Ma and Z Li evaluated the quality of the studies. Y Liu and W Xu analysed and interpreted the data and wrote the manuscript. Z Li revised the entire manuscript. All authors read and approved the final manuscript.

Patient Consent

The manuscript is not submitted for publication or consideration elsewhere.

Data availability

All data generated or analysed during this study are included in this published article.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of China-Japan Union Hospital of Jilin University (YS-2023083002).

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