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Role of stem cells transplantation for patients with spinal cord injury: systematic meta-analysis

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ABSTRACT

Background: Spinal cord injury is a devastating condition that leads to physical, social, and vocational impairment due to the irreversible loss of neural function below the injury site. The objective of this study is to investigate the efficacy and safety of bone marrow mononuclear cells (BM-MNCs) transplant in patients with spinal cord Injury in systematic meta-analysis.

Methods: This systematic review and meta-analysis study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The authors searched the PubMed, Web of Science, Cochrane, and Embase databases, OVID, China Biomedical Database (CBM), SinoMed databases and Library databases up to March 15, 2022. Inclusion criteria included for quantitative review, two well-trained author's retrieved independently relevant data from articles included for analysis and cross-checked it. In case of disagreements, a third party was consulted to reach a consensus. The methodological quality of the included studies was assessed independently by two reviewers using the Cochrane Collaboration's ROBINS-I tool for non-randomized studies.

Results: Preliminary search database resulted in 549 articles, finally, after excluded all articles did not meet the study criteria 26 studies were included in study and 569 Spinal cord injury patients were included for qualitative analysis in this meta-analysis. Male 77.9% with male/female ration 485/84 variability in the age among included studies. Resulted data showed minor adverse events after bone marrow mononuclear cells (BM-MNCs) transplant; low heterogeneity was observed across each trial ($P = 0.11$, $I2 = 38\%$). The average risk ratio of these studies was 10.12 (95%CI: 4.24–29.12, $p < 0.00003$) without heterogeneity ($p = 0.81$, $I2 = 0\%$) between studies. The methodological quality of the included studies used the standard Cochrane Collaboration tool to analysis is the risk of bias.

Conclusions: Bone marrow mononuclear cells (BM-MNCs) significantly improve neurological function in patients with spinal cord injury. Furthermore, this type of procedures has no systemic nor serious complications after autologous transplantation.

Keywords: *PRISMA, Spinal cord injury, BM-MSCs, Heterogeneity*

INTRODUCTION

Spinal cord injury (SCI) is a devastating condition that leads to physical, social, and vocational impairment due to the irreversible loss of neural function below the injury site [1]. Subsequently, SCI patients and their families suffer a low quality of life, with the burden of long-term medical care and disability [2]. Spinal Cord Injury is a common neurological disorder with a worldwide incidence ranging from 52 to 56 cases per 1,000,000 people per year and estimated hospitalization costs ranging from $1.6 billion to $1.7 billion per year [3]. Therefore, functional improvement after SCI remains an important issue in recent decades. Regarding the lack of capacity for central nervous system regeneration, there is no definitive cure for these disorders. Advanced therapies like cell transplantation could be a promising option for treating SCI patients [4]. Stem Cell Therapy (SCT) brings new hope for achieving potential neurological improvement of disabled patients after SCI [5]. It represents an emerging treatment modality using the differentiation, paracrine, and self-renewal capabilities of stem cells to regenerate or replace damaged cells and tissues [6]. Mesenchymal Stem Cells or Mesenchymal Stromal Cells (MSCs) are multipotent progenitor cells, which exhibit the greatest potential for treating spinal cord injury among all stem cell types [7]. Several types of stem cells have been tested or being tested clinically for the treatment of SCI, including MSCs, ESC-derived oligodendrocytes precursor cells, fetal-derived neural stem cells, and central nervous system stem cells [8]. Most of the trials used MSCs isolated from bone marrow (BMSCs), umbilical cord (UC-MSCs) and adipose tissue (ADSCs) to treat SCI [9]. MSCs were used to treat SCI as the cells can suppress the inflammation to limit the secondary injury, secrete paracrine factors that protect the remaining axons and promote axonal regeneration, and differentiate into nerve cells to replace the damaged cells [10-11]. A recent clinical study evaluating bone marrow mononuclear cells (BM-MNCs) intrathecally administered for sub-acute and chronic SCI patients demonstrated symptomatic improvement in motor, sensory, and bladder functions without serious complications [12-13]. The advantages of using BM-MNSCs; minimize all problems associated with the immunological rejection which are frequently caused in allogeneic cell transplantation, autologous cell infusion is considered safe by not being associated with carcinogenesis [14]. The objective of this study is to investigate the efficacy and safety of bone marrow mononuclear cells (BM-MNCs) transplant in patients with spinal cord Injury in systematic meta-analysis.

METHODS

This systematic review and meta-analysis study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. Two reviewers performed an independent electronic literature search for studies evaluating the safety and efficacy of stem cell therapy for SCI. The authors searched the PubMed, Web of Science, Cochrane, and Embase databases, OVID, China Biomedical Database (CBM), SinoMed databases and Library databases up to March 15, 2022. The literature search strategy consisted of keywords, spinal cord injury, Spinal cord trauma, spinal cord contusion, paraplegia, hematopoietic stem cell, neural stem cells, human embryonic stem cells, and mesenchymal stem cells. A detailed study selection flow diagram is given in figure 1.

Inclusion and exclusion criteria Studies

Inclusion criteria

Were included for quantitative review if they met the following study design criteria: (1) randomized controlled trials of patients with SCI, (2) patients diagnosed with SCI based on American Spinal Injury Association (ASIA) international standards for neurological classification, (3) patients with SCI that received only stem cell transplantation or stem cell transplantation combined with rehabilitation.

Exclusion criteria

This study were excluded if they had the following characteristics: (1) small sample size, (2) repeatedly published research, (3) review articles and in vitro studies involving stem cell

therapy, (4) only abstract published, (5) Studies that were not controlled studies, such as case reviews, reports, meetings, conference, (6) patients with complications such as diabetes mellites, severe anemia, organic failure, infections, (7) single-arm studies, and (8) animal studies involving stem cell therapy for SCI models.

Data extraction

Two well-trained authors retrieved independently relevant data from articles included for analysis and cross-checked it. In case of Disagreements, a third party was consulted to reach a consensus. The following data were extracted;

(1) Characteristics of studies such as authors, year of publication, country, and number of patients enrolled, and type of study,

(2) patients included in each study, mean age, sex, level of SCI, time from injury to therapy, source of MSCs, method of transplantation, follow-up duration and assessment parameters utilized, and treatment strategy,

(3) assessment outcomes including, neurological assessment with AIS grade improvement, ASIA sensory scores, including pinprick score and light touch score, and ASIA motor score; urodynamic parameters like residual urine volume, radiological outcomes with magnetic resonance imaging changes, electrophysiological improvement with motor evoked potential and SSEP, incidence of adverse reactions, and relevant elements of the bias risk assessment.

Risk of bias and quality assessment

The methodological quality of the included studies was assessed independently by two reviewers using the Cochrane Collaboration's ROBINS-I tool for non-randomized studies, which included seven domains of assessments: allocation concealment, random sequence generation, incomplete outcome data, selective outcome reporting, blinding of participants, and personnel, blinding of outcome assessment, and other biases. Any discussion, report or disagreement regarding data during extraction and analysis was discussed and resolved by the third author.

Outcome indicators

In the present meta-analysis, outcome indicators of American Spine Injury Association (ASIA) motor score including, (1) light touch score, (2) motor score, (3) pinprick score, (4) ASIA grading improvement rate including; (a) urodynamic parameters like residual urine volume; (b) functional outcomes for Activities of Daily Living (ADLs).

Statistical analysis

All network meta-analyses and standard meta-analyses were performed using the STATA 16.0 (Stata Corp, College Station, TX). The ASIA motor and sensory scores, ASIA grade improvement, BI, and adverse reactions were used as outcome indicators. For dichotomous variable outcomes, risk ratio (RR) with 95% confidence interval (CI) was used, and for continuous variable outcomes, weighted mean difference (WMD) with 95% CI was used. We used the chi-squared value test and inconsistency index (I2) to assess the heterogeneity across each study. A value of $P < 0.1$ or $I2 > 50\%$ was deemed to have significant heterogeneity, a random-effect model was then used to analyze the data. Sensitivity analyses were performed to explore the source of heterogeneity when it existed. Publication bias was analyzed with a funnel plot for the outcomes in the included studies. $P< 0.05$ was considered significant.

RESULTS

Study search

Preliminary search database resulted in 549 articles, after initial screening for duplicate removal, gave a total of 534 unique articles. Eighty studies were retained pending title and abstract screening. While, ninety-six articles qualified for full-text review, of which sixty were excluded. Seventy-seven articles were further excluded due to the reported in other language rather than in English, non-compliance of research type, non-compliance of intervention, lack of access to data. Finally, 26 studies were

included in study and 569 SCI patients were included for qualitative analysis in this meta-analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection is given in Figure 1.

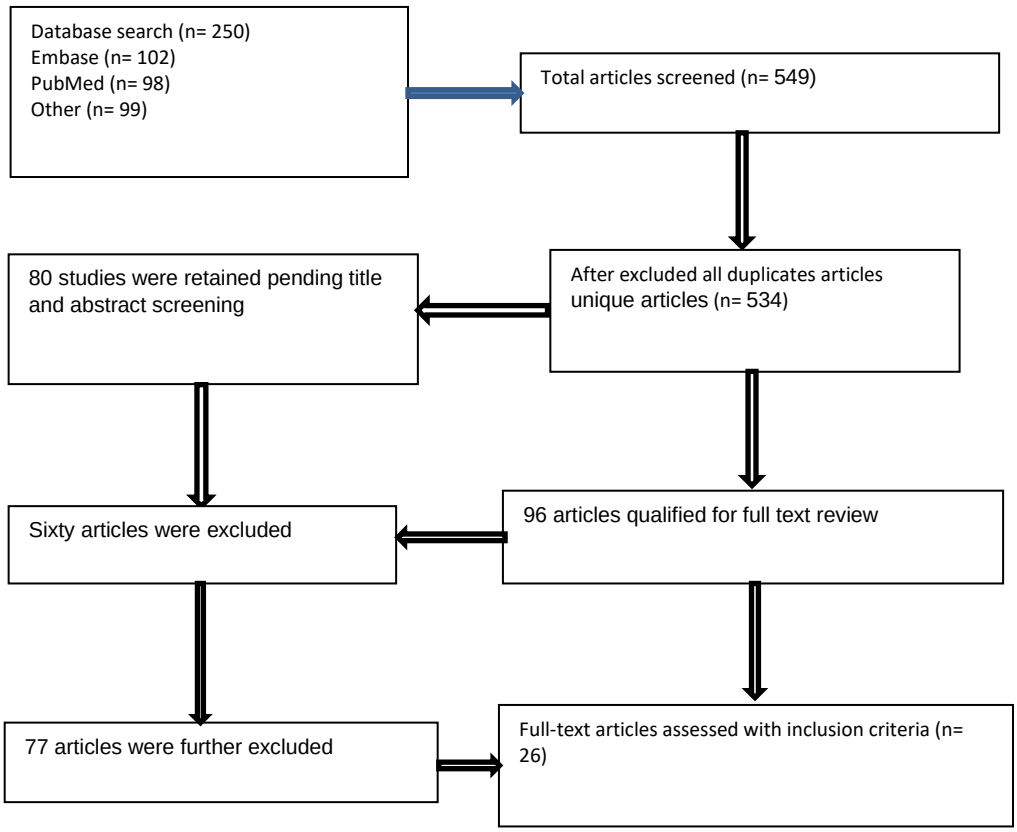

FIGURE 1: PRISMA flow diagram of the included studies.

Study characteristics

The total subjects being male 77.9% with male/female ration 485/84 variability in the age among included studies. The mean age of subjects in the included studies was 38.4 years, with an overall range between 18- and 47-years Table 1.

TABLE 1: Study characteristics

	Author(s) and year of publication	Sample size	M/F	Injury level (C/T/L)	Transplant route	Cell source	Follow up (months)	Out come
1	Song et al. 2020 [16]	36	30/6	C/T/L	IT	BMMS	12	A B C
2	Cheng et al. 2014 [18]	34	27/7	C/T/L	IT	BMMS	10	A B
3	Albu, et al. 2021 [20]	10	7/3	C	IT	BMMS	12	A B C E
4	Bhanot, et al. 2011 [22]	13	10/3	C/T/L)	IT	BMMS	6	B C
5	Yoon, et al. 2007 [23]	35	29/6	C/T	IT	BMMS	12	A C
6	Xiao, et al. 2016 [24]	5	4/1	C/T/L	IT	BMMS	10	A B C E
7	El-Kheir, et al. 2014 [25]	50	40/10	C/T	IT	BMMS	60	A B

8	Guanghui Dai, et al. 2013 [26]	40	36/4	C/T	IT	BMMS	13	A B C
9	Kishk NA, et al. 2010 [27]	62	58/4	C/T	IT	BMMS	12	A C E
10	Suzuki, et al. 2014 [28]	10	10/0	C/T	IT	BMMS	10	A C
11	Sharma A, et al. 2020 [29]	24	20/4	C/T	IT	BMMS	13	A B C
12	Srivastava, et al. 2019 [30]	70	63/7	C/T	IT	BMMS	12	A B C
13	Park, et al. 2012 [31]	6	6/0	C	IT	BMMS	18	A D E
14	Oraee, et al. 2016 [32]	10	8/2	C/T/L	IT	BMMS	12	A B
15	Oh SK, et al. 2016 [33]	16	14/2	C	IT	BMMS	16	C E
16	Larocca, et al. 2017 [34]	5	5/0	C	IT	BMMS	10	A E
17	Jeon, et al. 2010 [35]	10	8/2	C	IT	BMMS	15	A B C E
18	Goni, et al. 2014 [36]	9	8/1	C	IT	BMMS	12	A D
19	Chhabra, et al. 2016 [37]	7	6/1	C	IT	BMMS	14	A B
20	Abdelaziz, et al. 2010 [38]	20	19/1	C	IT	BMMS	12	A B C E
21	Saito F, et al. 2012 [39]	5	5/0	C	IT	BMMS	40	A E
22	Vaquero, et al. 2016 [40]	11	8/3	C/T/L	IT	BMMS	10	A B C
23	Thakkar, et al. 2016 [41]	10	8/2	C/T	IT	BMMS	34	C E
24	Adel N, et al. 2009 [42]	43	36/7	C/T	IT	BMMS	6	B C E
25	Al-Zoubi, et al. 2014 [43]	19	16/3	C	IT	BMMS	60	A B
26	Deda, et al. 2008 [44]	9	4/5	C/T/L	IT	BMMS	24	A B C
	Total	569		485/84			Average 17.38	

C/T/L: cervical/thoracic/lumbar spinal cord; C/T: cervical/thoracic; C: cervical; M/F: male/female; BMA: Bone marrow aspiration stem cells derived; IT: intrathecal injection; A: American Spinal Injury Association Motor Score, B: American Spinal Injury Association Sensory Score, C: Barthel index, D: adverse reactions, E: ASIA grade improvement

Safety and Adverse effects

Common adverse effects caused by transplantation included increase in spasticity, numbness, or tingling sensation, and neuropathic pain which were alleviated spontaneously, fever, headache, backache, numbness, and abdominal distension. Resulted data showed five studies was carried out to assess the relative risk (RR) of any adverse effects during treatment. Adverse effects; low heterogeneity was observed across each trial (P = 0.11, I2 = 38%). The average risk ratio of these studies was 10.12 (95%CI: 4.24–29.12, P < 0.00003) without heterogeneity (P = 0.81, I2 = 0%) between studies. However, serious adverse effects, such as sever anaphylactic shock, death, were not observed during follow-up period.

Quality assessment of methodology

The methodological quality of the included studies used the standard Cochrane Collaboration tool to analysis is the risk of bias. Overall, the methodological quality of included studies was acceptable and none of studies had an overall high risk of bias Table 2.

TABLE 2: Quality assessment of methodology

Study	Allocation concealment Random sequence generation	Random sequence generation	Blinding participant	Incomplete outcome data	Personal performance	Selective reporting
Song et al. 2020 [16]	+	+	+	+	?	+
Cheng et al. 2014 [18]	+	+	+	+	+	+
Albu, et al. 2021 [20]	+	+	?	+	+	?
Bhanot, et al. 2011 [22]	+	+	+	+	+	+
Yoon, et al. 2007 [23]	+	+	+	+	+	?
Xiao, et al. 2016 [24]	?	?	+	+	?	+
El-Kheir, et al. 2014 [25]	?	?	+	+	^	+
Guanghui Dai, et al. 2013 [26]	+	+	+	+	?	+
Kishk NA, et al. 2010 [27]	^	+	+	+	+	+
Suzuki, et al. 2014 [28]	+	+	?	+	+	?
Sharma A, et al. 2020 [29]	+	?	+	+	?	+
Srivastava, et al. 2019 [30]	+	+	+	+	+	+
Park, et al. 2012 [31]	+	+	+	+	+	+
Oraee, et al. 2016 [32]	+	+	+	+	?	+
Oh SK, et al. 2016 [33]	^	+	^	+	+	+
Larocca, et al. 2017 [34]	+	+	?	+	+	?
Jeon, et al. 2010 [35]	?	?	+	+	+	+
Goni, et al. 2014 [36]	^	+	^	+	?	+
Chhabra, et al. 2016 [37]	+	+	+	+	+	+
Abdelaziz, et al. 2010 [38]	+	+	+	+	+	+
Saito F, et al. 2012 [39]	+	+	?	+	+	+
Vaquero, et al. 2016 [40]	?	+	+	+	?	+
Thakkar, et al. 2016 [41]	+	?	+	+	+	+
Adel N, et al. 2009 [42]	+	+	+	+	+	+
Al-Zoubi, et al. 2014 [43]	^	+	+	+	^	?
Deda, et al. 2008 [44]	+	+	+	+	?	+

Low risk: +, Moderate risk: Serious risk: ^

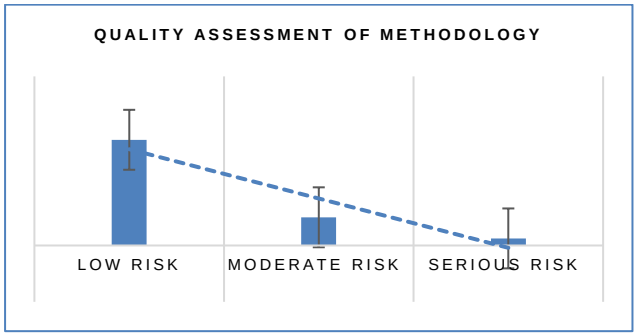

FIGURE 2: Quality assessment of methodology

Efficacy outcomes

American Spinal Injury Association (ASIA) sensory score

Thirteen studies involving 289 patients reported ASIA sensory scores regarding neurological analysis of the patients with spinal cord injury. There was a significant heterogeneity observed among the included studies in Forest plot (I2 = 81.3%, p < 0.002). The random effects model showed a significant improvement in general ASIA sensory score (WMD = 14.021, 95% CI, 2.207, 24.611, p= 0.002) (Figure 3).

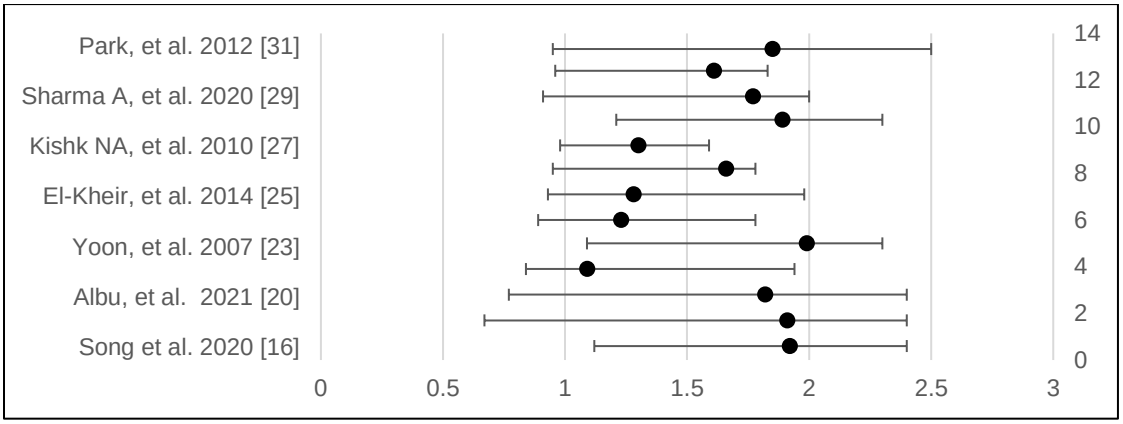

FIGURE 3: American Spinal Injury Association (ASIA) sensory score, Forest plot.

Publications bias

Publication bias was analyzed utilizing a funnel plot and Egger regression test. With regard to the meta-analysis of the efficacy and safety of stem cell therapy versus routine rehabilitative care for SCI, there was no evidence of publication bias by Egger regression test (p = 0.418) and funnel plot, as shown in Figure 4. All studies fell within the 95% CI and were distributed evenly about the axes, implying minimal publication bias.

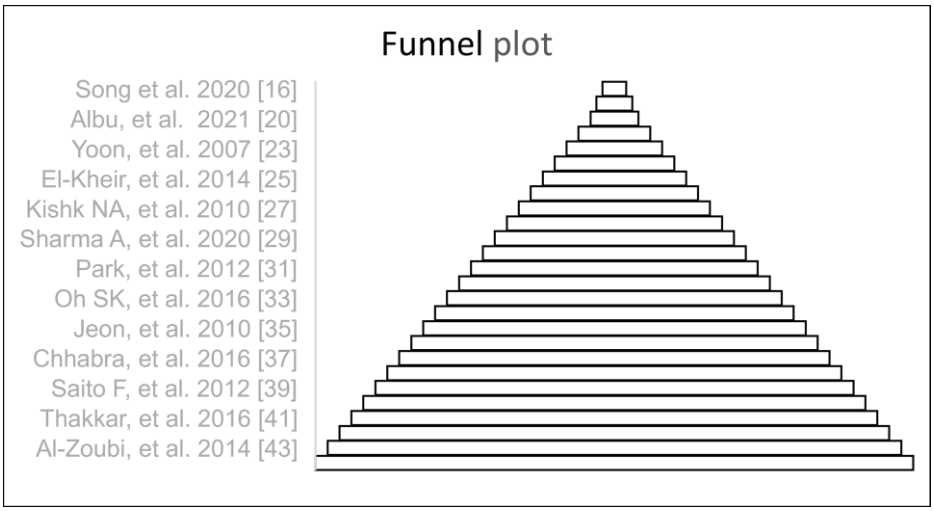

FIGURE 4: Publications bias, funnel plot.

Activities of Daily Living (ADLs) score

Ten studies involving 199 patients reported ADL scores, with significant heterogeneity observed among the included studies (I2 = 74.2%, p < 0.002). Random effects model showed no significant improvement in ADL score p = 0.194).

Residual urine volume

Five studies with 52 patients reported residual urine volume, with significant heterogeneity observed between the included studies (I2 = 51.3%, p = 0.011). Random effects showed a significant reduction in residual urine volume p = 0.019.

DISCUSSION

Describing changes of patients with spinal cord injury includes many aspects consist of neurological, functional, and quality of life changes, multiple changes occur in damaged tissues that require various treatment strategies like neuroprotection, axonal regeneration promotion, and rehabilitation [16, 17, 18]. The distinction of these improvements could be presented by AIS and SCIM III scores which indicated neurological and functional changes, respectively [19]. After the primary injury, the inflammatory process gets activated and leads to secondary injury phase [20]. The main hindrance in the process of neuronal regeneration is growth inhibitors present at the site of injury [21]. Earlier studies were mostly focused on preventing and reducing the extent of secondary injury which may further damage the spinal cord [22]. An initial surgery is usually performed to provide support to damaged tissues and reduce the compression impact. Surgery helps in spinal stabilization, preventing spinal deformity, and facilitating patient mobility but not in neurological recovery [23]. This study investigated the efficacy and safety of BM-MSCs transplantation in SCI treatment. Our study confirms that BM-MSCs transplantation significantly improves neurological function, including the ASIA motor, sensory, ASIA grade improvement [24]. BM-MSCs are multipotent progenitor cells that have the facility to differentiate into mesodermal lineages and induce trophic activities related to neural cells [25]. They improve neurological deficits by generating either neural cells or myelin-producing cells [26]. BM-MSCs promote axonal regeneration by guiding nerve fibers and hence eliminate glial scars in the injured spinal cord [27-29]. The precise mechanism by which transplantation of bone marrow-derived MSCs (BM-MSCs) promotes functional recovery after SCI is still unclear [30-31]. Cell transplantation is a targeted new promising therapeutic strategy for spinal cord regeneration based on a series of animal and clinical studies, and it has been previously reported that stem cells have a potential effect on the SCI treatment [32-33, 24, 35]. The safety and clinical application of SCs and MSCs separately have been reported in the treatment of SCI patients [36-38]. MSCs are an appropriate source for cell therapy due to their ability of high growth rate, low immunogenicity, and favorable ethical profile [39]. Also, MSCs could enhance and support neurite outgrowth, axonal survival, and remyelination [40]. The most important factor in cell transplantation in SCI patients is the time at which the MSCs are transplanted to the site of injury to exert their targeted actions [41]. There is no clear consensus on the timing of transplantation, and the studies included for analysis presented their results based on varied SCI time points. Although animal models show better outcomes with earlier transplantation [42, 43], human trials on MSCs from the included studies did not show a significant difference in outcome measures. The efficacy and safety of BM-MSCs in SCI treatment, the previous meta-analysis results were similar to those in this study [44-46]. Finally, our study used ASIA motor and sensory scores as continuous variables to exclude the grouping errors. Furthermore, this resulted data defined the source of cells and the method of transplantation.

CONCLUSION

Autologous MSC derived from bone marrow significantly improve neurological function in patients with spinal cord injury. Furthermore, this type of procedures has no systemic nor serious complications after autologous transplantation.

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Declaration of Competing Interest

The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the study: NGY, FGA. Analysis and interpretation of data: HA, AUN. Drafting or revising the manuscript: NGY, HA, FGA, AUN. All authors have approved the final article.

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