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Current evidence on mesenchymal stem cell therapy for traumatic spinal cord injury: systematic review and meta-analysis

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ABSTRACT

Background aims: The authors aim to analyze the evidence in the literature regarding the efficacy and safety of mesenchymal stem cell (MSC) therapy in human subjects with traumatic spinal cord injury (SCI) and identify its potential role in the management of SCI.

Methods: The authors conducted independent and duplicate searches of electronic databases, including PubMed, Embase and the Cochrane Library, until May 2020 for studies analyzing the efficacy and safety of stem cell therapy for SCI. American Spine Injury Association (ASIA) impairment scale (AIS) grade improvement, ASIA sensorimotor score, activities of daily living score, residual urine volume, bladder function improvement, somatosensory evoked potential (SSEP) improvement and adverse reactions were the outcomes analyzed. Analysis was performed in R platform using OpenMeta[Analyst] software.

Results: Nineteen studies involving 670 patients were included for analysis. On analysis, the intervention group showed statistically significant improvement in AIS grade ($P < 0.001$), ASIA sensory score ($P < 0.017$), light touch ($P < 0.001$), pinprick ($P = 0.046$), bladder function ($P = 0.012$), residual urine volume ($P = 0.023$) and SSEP ($P = 0.002$). However, no significant difference was noted in motor score ($P = 0.193$) or activities of daily living score ($P = 0.161$). Although the intervention group had a significant increase in complications ($P < 0.001$), no serious or permanent adverse events were reported. On subgroup analysis, low concentration of MSCs ($<5 \times 10^7$ cells) and initial AIS grade A presentation showed significantly better outcomes than their counterparts.

Conclusions: The authors' analysis establishes the efficacy and safety of MSC transplantation in terms of improvement in AIS grade, ASIA sensory score, bladder function and electrophysiological parameters like SSEP compared with controls, without major adverse events. However, further research is needed to standardize dose, timing, route and source of MSCs used for transplantation.

Introduction

Spinal cord injury (SCI) is a debilitating disease with a high rate of disability involving paralysis, sensorimotor dysfunction, urinary incontinence and gastrointestinal dysfunction [1,2]. Subsequently, SCI patients and their families suffer a low quality of life, with the burden of long-term medical care and disability [3,4]. As a result of SCI, neuronal cells die in the span of the first 12 h to a few weeks, which leads to further substantial neuronal and glial cell loss, demyelination, cavitation and glial scarring, and this in turn results in loss of sensory perception, distal motor paralysis and severe functional limitations [5,6].

Recovery is often difficult because of the limited capability of the central nervous system to regenerate lost cells, restore disrupted myelin and reestablish functional neural connections [7], but recent developments and impulses in molecular and regenerative medicine have paved the way for the induction of biologically active cells such as stem cells, bioactive materials and growth factors toward the healing and tissue regenerative process. In this connotation, mesenchymal stem cells (MSCs) serve as the perfect cell-based tissue regenerative modality for treating disorders in a minimally invasive environment without any significant morbidity, which further induces cellular proliferation, differentiation, characterization, regeneration and rejuvenation of degenerated tissue to attain native homeostasis [8,9]. The efficacy of such cell therapies in animal models has been widely recognized [10].

Several pre-clinical studies and clinical trials have revealed that neuronal progenitor and stem cells can be used to repair SCI because

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of their self-renewal property and capacity for neuronal differentiation into functional neural cells to form new synapses, release various neurotrophic factors and provide an appropriately conducive microenvironment to promote neuronal repair [11–13]. Although the reliability of such treatment methodologies for SCI has been tested in human subjects in a few clinical trials, they provide us with conflicting results and thereby cloud the only ray of hope for SCI patients [14,15]. Hence, with this meta-analysis, the authors aim to analyze the evidence in the literature on the efficacy and safety of MSC therapy in human subjects with traumatic SCI and identify its potential role in the management of SCI.

Methods

This meta-analysis was conducted following the guidelines of the Cochrane Collaboration Back Review Group [16] and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [17].

Search strategy

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, Embase and Cochrane Library databases up to May 2020. No language or date restrictions were applied. Key words used for the search were as follows: "Spinal Cord Injury," "Stem Cells," "Stem Cell Therapy" and "Mesenchymal Stem Cells."

The reference lists of the selected articles were also searched to identify studies not identified in the primary search. As per the inclusion and exclusion criteria, eligible studies were included for meta-analysis. Any discrepancy between the authors was resolved through discussion until a consensus was obtained. A detailed study selection flow diagram is given in Figure 1.

Inclusion criteria

Studies were included for quantitative review if they met the following population, intervention, comparator, outcome and study design criteria:

(i) Population: patients with traumatic SCI.
(ii) Intervention: stem cell therapy.
(iii) Comparator: usual care.
(iv) Outcome: American Spine Injury Association (ASIA) impairment scale (AIS) scores, including motor score, pinprick score, light touch score and improvement in ASIA grades; urodynamic parameters like residual urine volume; functional outcomes for activities of daily living (ADLs), such as the Barthel Index; radiological outcomes with magnetic resonance imaging changes; electrophysiological parameters, such as motor evoked potential, somatosensory evoked potential (SSEP) and adverse events.
(v) Study design: any study design satisfying the above criteria.

Exclusion criteria

Trials were excluded if they had the following characteristics: (i) animal studies involving stem cell therapy for SCI models and (ii) review articles and *in vitro* studies involving stem cell therapy.

Data extraction

Two reviewers retrieved independently relevant data from articles included for analysis. The following data were extracted:

(i) Study characteristics: year of publication, authors, country, number of patients enrolled.
(ii) Baseline characteristics: mean age, sex proportions, level of SCI, time from injury to therapy, source of MSCs, cell count used, passage number, volume of preparation injected, dosage frequency, location and method of transplantation, follow-up duration and assessment parameters utilized.
(iii) Efficacy outcomes: 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; functional outcome measures of ADLs, such as the Barthel Index; radiological outcomes with magnetic resonance imaging changes; electrophysiological improvement with motor evoked potential and SSEP.
(iv) Safety outcomes: adverse events in the included studies. For missing data, the authors tried to contact the original author first. If that failed, the authors calculated the missed values from other available data using formulas in the Cochrane Handbook for Systematic Reviews of Interventions. Any disagreement in data collection was resolved until a consensus was attained by discussion.

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 has seven domains of bias assessment [18].

Statistical analysis

Meta-analysis was conducted in the R platform with OpenMeta [Analyst] [19]. 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. Heterogeneity was assessed using the I^2 test [20]. If I^2 <50% and P> 0.1, the authors used a fixed effects model to evaluate; otherwise, a random effects model was used. P< 0.05 was considered significant. 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.

Results

Search results

Electronic database search resulted in 358 articles, with seven other articles from bibliographic search resulting in seven additional articles from the Chinese literature, which, after initial screening for duplicate removal, gave a total of 321 articles. Title and abstract screening was done in these 321 articles, and 255 of them were excluded. Sixty-six articles qualified for full-text review, of which 47 were excluded. Finally, 19 studies [14,15,21–37] with 670 patients were included for qualitative analysis. Of the 19 articles, 12 qualified for meta-analysis with a comparator group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection is given in Figure 1. Nine of 19 studies under selection were from China, whereas South Korea and Egypt contributed two studies each.

There was a high male predominance noted in the included studies, with 77.9% of the total subjects being male. There was a wide variability noted in the age of the included subjects within individual studies and among included studies. The mean age of subjects in the included studies was 34.8 years, with an overall range between 16 and 45 years. Hence, 15 of 19 studies utilizing autologous bone marrow MSCs made analysis of the efficacy of MSC therapy based on donor cell age impractical. Included studies had follow-up ranging between 3 and 25.2 months. General characteristics of the studies

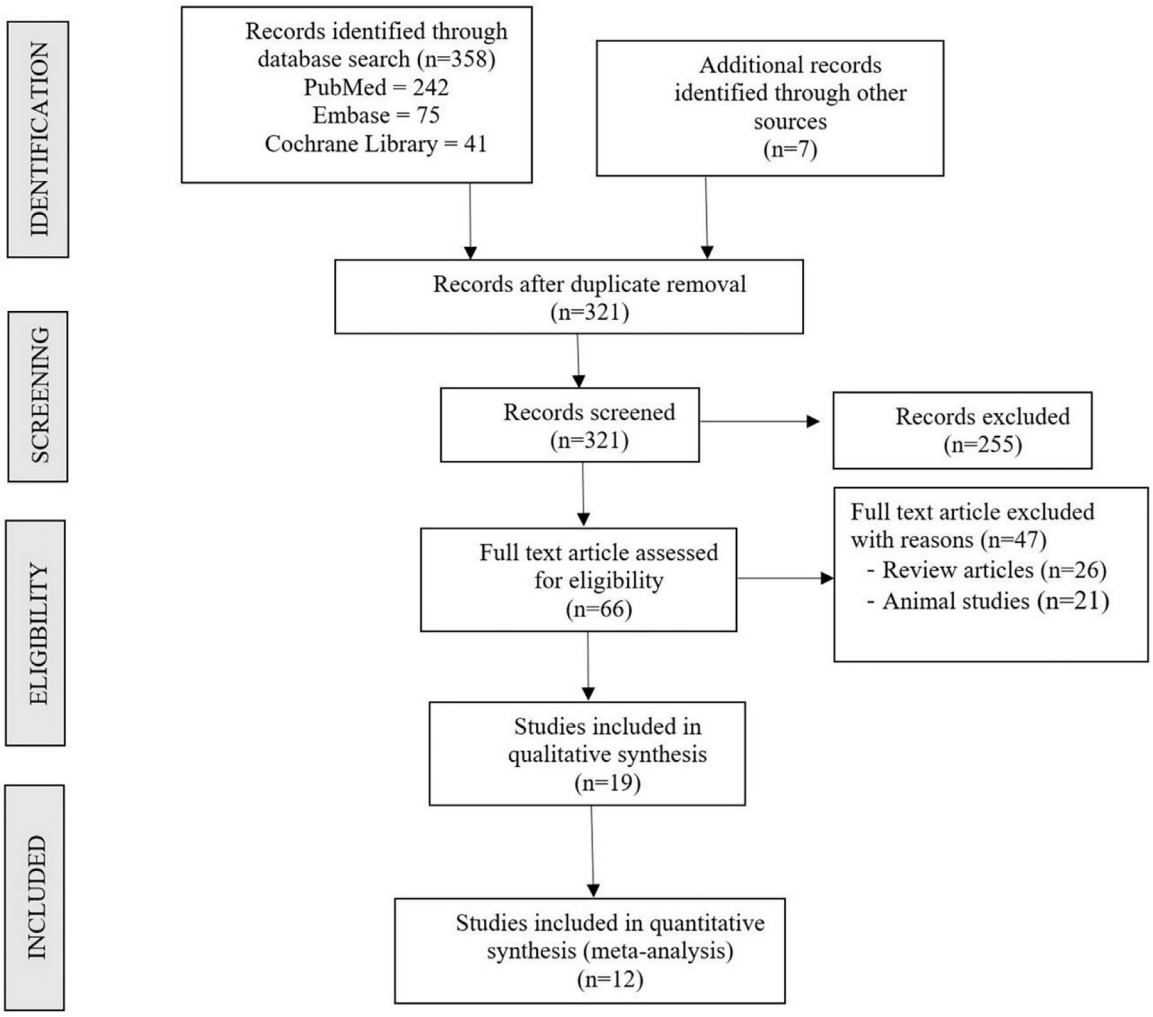

Fig. 1. PRISMA flow diagram of the included studies.

included are given in Table 1. Only six of 19 studies mentioned the number of passages involved in culturing MSCs, which ranged from three to six cycles. Of 19 studies, five injected MSCs at the injury site, whereas nine injected them via lumbar puncture below the L3 level and the rest chose an intravascular route of MSC transplantation. The transplantation protocol of the included studies is given in Table 2.

SCI was located at the cervical level in four of 19 studies, cervicothoracic level in 11 of 19 studies and thoracolumbar level in the remaining studies. The duration between SCI and MSC therapy in the included studies ranged between 0.3 and 62.5 months. Although 15 studies utilized autologous MSCs, four utilized an umbilical source of MSCs. The cell count of the transplanted MSCs ranged from 0.8×10^7 cells to 100×10^7 cells. There was variability in the included subjects on their initial AIS grade from grade A to grade D. To analyze the impact of the aforementioned factors, the authors stratified the results of the included studies by their location and duration of SCI, source and dose of MSCs used and initial AIS grade of the subjects and performed subgroup analysis, as shown in Table 3.

Quality assessment

The methodological quality of the included studies is mentioned in Figure 2. None of the included studies had an overall high risk of bias that would result in exclusion from the analysis.

Efficacy outcomes

AIS grade improvement

Six studies involving 259 patients reported AIS grade improvement in the neurological status of the patients compared with the controls. There was no significant heterogeneity observed between the included studies ($I^2 = 0.0\%$, $P = 0.899$). Hence, a fixed effects model was used for analysis, which showed a significant improvement in total AIS grade and AIS grade A in the experimental group compared with the controls (total AIS grade RR = 1.787, 95% CI, 0.976, 2.598, $P < 0.001$ and AIS grade A RR = 1.751, 95% CI, 0.899, 2.603, $P < 0.001$) (Figure 3A,B). However, no significant difference was found in AIS grade B, C or D (RR = 2.140, 95% CI, −0.215, 4.495, $P = 0.075$) (Figure 3C).

ASIA sensory score

Eleven studies involving 538 patients reported ASIA sensory scores regarding neurological analysis of the patients compared with the controls. There was a significant heterogeneity observed among the included studies ($I^2 = 88.3\%$, $P < 0.001$). Hence, a random effects model was used for analysis, which showed a significant improvement in general ASIA sensory score (WMD = 13.014, 95% CI, 2.308, 23.721, $P = 0.017$) (Figure 3D).

Six studies mentioned ASIA light touch scores without heterogeneity ($I^2 = 0\%$, $P = 0.204$). Hence, a fixed effects model was used for analysis, which showed a significant improvement in ASIA light touch

Table 1
Characteristics of included studies.

Sl. No.	Authors	Year	Country	Sample size	Treatment/control	Male/female	Age, years	SCI location	MSC source	Duration of SCI in months (SD)	Follow-up in months (SD)
1	Cheng *et al.* [21]	2014	China	34	10/24	NR	35.30	Thoracolumbar	UC	21.4 (12.96)	6
2	Dai *et al.* [22]	2013	China	40	20/20	28/12	34.7	Cervical	BM	51.9 (18.3)	6
3	El-Kheir *et al.* [14]	2014	Egypt	70	50/50	61/9	16–45	Cervicothoracic	BM	18.25 (5)	18
4	Guo *et al.* [23]	2014	China	80	40/40	63/17	37.25	Cervicothoracic	BM	NR	NR
5	Guo *et al.* [24]	2012	China	24	12/12	21/3	30	Cervicothoracic	UC	2.3 (1.2)	5
6	Karamouzian *et al.* [25]	2012	Iran	31	11/20	23/8	33.2	Thoracolumbar	BM	27.3 (8.4)	20.3 (7.2)
7	Kishk *et al.* [15]	2010	Egypt	60	40/20	51/9	31.7	Cervicothoracic	BM	43 (30)	12
8	Li *et al.* [26]	2012	China	30	15/15	22/8	37.36	Cervical	UC	1–108	4
9	Xiao *et al.* [27]	2012	China	96	70/26	63/33	41.5	Cervicothoracic	BM	0.3	6
10	Xie *et al.* [28]	2007	China	24	11/13	19/5	18–49	Cervicothoracic	BM	1–10	3
11	Zhang *et al.* [29]	2012	China	60	30/30	50/10	18–45	Cervicothoracic	UC	1–10	3
12	Zhang *et al.* [30]	2015	China	30	15/15	22/8	35.5	Thoracolumbar	UC	21.3 (5.7)	6
13	Geffner *et al.* [31]	2008	USA	8	8/0	7/1	33.75	Thoracolumbar	BM	62.13 (88.55)	24
14	Moviglia *et al.* [32]	2006	Argentina	2	2/0	1/1	20	Cervicothoracic	BM	19 (15.55)	6
15	Oh *et al.* [33]	2015	South Korea	16	16/0	15/1	40.9	Cervical	BM	62.5 (14.4)	6
16	Pal *et al.* [34]	2009	India	30	30/0	27/3	33.2	Cervicothoracic	BM	14.4 (9.2)	22.4 (9.2)
17	Park *et al.* [35]	2005	South Korea	5	5/0	5/0	35.8	Cervicothoracic	BM	0.3 (0.1)	12.16 (4.79)
18	Park *et al.* [36]	2011	South Korea	10	10/0	8/2	46	Cervical	BM	40.2 (40.2)	25.2 (22.1)
19	Sykova *et al.* [37]	2006	Czech Republic	20	20/0	16/4	30.05	Cervicothoracic	BM	5.17 (6.32)	12

NR, not reported; SD, standard deviation.

score in the experimental group compared with the controls (WMD=6.316,95%CI,2.751,9.881,$P<0.001$)(Figure3E).

Six studies mentioned ASIA pinprick scores, with significant heterogeneity (I^2 = 89.1%, $P < 0.001$). Hence, a random effects model was used for analysis, which showed a significant improvement in ASIA pinprick score in the experimental group compared with the controls (WMD = 12.350, 95% CI, 0.244, 24.456, P = 0.046) (Figure 3F).

ASIA motor score

Eleven studies involving 538 patients reported ASIA motor scores with regard to neurological analysis of the patients compared with the controls. There was no significant heterogeneity observed between the included studies (I^2 = 0.0%, P = 0.564). Hence, a fixed effects model was used for analysis, which showed no significant improvement in the ASIA motor score in the experimental group compared with the controls (WMD = 1.294, 95% CI, −0.656, 3.244, P = 0.193) (Figure 3G).

ADL score

Eight studies involving 348 patients reported ADL scores, with significant heterogeneity observed among the included studies (I^2 = 86.5%, $P < 0.001$). Hence, a random effects model was used for analysis, which showed no significant improvement in ADL score in the experimental group compared with the controls (WMD = 4.994, 95% CI, −2.522, 12.510, P = 0.161) (Figure 3H).

Residual urine volume

Three studies with 84 patients reported residual urine volume, with significant heterogeneity observed between the included studies (I^2 = 72.6%, P = 0.026). Hence, a random effects model was used for analysis, which showed a significant reduction in residual urine volume in the experimental group compared with the controls (WMD = −36.55, 95% CI, −68.105, −4.994, P = 0.023) (Figure 4A).

Bladder function improvement

Two studies with 94 patients reported improvement in bladder function, without heterogeneity between the included studies (I^2 = 0.3%, P = 0.567). Hence, a fixed effects model was used for analysis. On analysis, a significant improvement in bladder function was noted in the experimental group compared with the controls (RR = 2.388, 95% CI, 1.212, 4.706, P = 0.012) (Figure 4B).

SSEP improvement

Three studies with 170 patients reported improvement in electrophysiological monitoring, such as SSEP, without any heterogeneity between the included studies (I^2 = 0.0%, P = 0.574). Hence, a fixed effects model was used for analysis. On analysis, a significant return of somatosensory evoked potentials was noted in the experimental group compared with the controls (RR = 2.558, 95% CI, 0.936, 4.181, P = 0.002) (Figure 4C).

Safety

Twelve studies involving 502 patients reported adverse effects, with low heterogeneity among the included studies (I^2 = 0.0%, P = 0.733). Hence, a fixed effects model was used for analysis. Analysis of adverse events in patients receiving stem cell transplantation showed that they experienced more side effects than the control group (RR = 4.342, 95% CI, 2.248, 6.436, $P < 0.001$) (Figure 4D). The commonly reported adverse events of the intervention included fever, headache and neuropathic pain, which resolved spontaneously or with treatment. However, no major serious adverse events with permanent effects, such as death, tumor or immune reaction to the intervention, were noted during follow-up.

Table 2
Stem cell transplantation protocol of included studies.

Study	MSC source	Donor age	Cell count, 10^7 cells	Culture passages	Volume	Dosage	Location of transplant	Method of transplant	Outcome measures
Cheng *et al.* [21]	UC	Full-term, healthy newborn	4	6–8	50 μL	Two doses, 10 days apart	NR	Subarachnoid	ASIA sensation score, ASIA motor score, muscle tension scale, ADLs, urodynamic examination
Dai *et al.* [22]	BM	34.7 years	2	4	25 μL	One dose	Injury site	Subarachnoid	AIS grading, ASIA motor score, ASIA light touch score, ASIA pinprick score, residual urine volume, EMG, SSEP, MRI
El-Kheir *et al.* [14]	BM	16–45 years	0.2 per kg	6	NR	Monthly dose until target dosage level achieved, median 4 (1–8)	Lumbar puncture	Subarachnoid	AIS grading, SSEP, MRI, ADLs
Guo *et al.* [23]	BM	37.25 years	1.5	NR	NR	One dose	NR	NR	AIS grading, ASIA motor score, ASIA light touch score, ASIA pinprick score, ADLs
Guo *et al.* [24]	UC	Full-term, healthy newborn	2–5	NR	NR	One dose	Lumbar puncture	Subarachnoid	ASIA motor score, ASIA sensory score, ADL
Karamouzian *et al.* [25]	BM	33.2 years	0.07–0.12	NR	NR	One dose	Lumbar puncture at L3–L4	Subarachnoid	AIS grading, ASIA motor score, ADLs
Kishk *et al.* [15]	BM	31.7 years	0.5–1 per kg	NR	NR	One dose per 6 months	Lumbar puncture at L3–L4/L4–L5	Subarachnoid	Barthel trunk muscle assessment, MCS, FAC, AIS grading, ASIA sensation score, ASIA motor score, SSEP
Li *et al.* [26]	UC	Full-term, healthy newborn	5	NR	NR	One dose	Lumbar puncture/ intravenous	Subarachnoid/ intravenous	AIS grading, ASIA motor score, ASIA light touch score, ASIA pinprick score, ADL, SSEP, MCS, SCS, EMG
Xiao *et al.* [27]	BM	41.5 years	1.4	NR	NR	One dose	Lumbar puncture/ intravenous	Subarachnoid/ intravenous	ASIA motor score, ASIA sensory score
Xie *et al.* [28]	BM	18–49 years	4–10	NR	NR	One dose	Lumbar puncture/ intravenous	Subarachnoid/ intravenous	ASIA sensation score, ASIA motor score, ADLs, residual urine volume, AIS grading
Zhang *et al.* [29]	UC	Full-term, healthy newborn	1	NR	NR	One dose	Intravenous	Intravenous	AIS grading, ASIA motor score, ASIA light touch score, ASIA pinprick score
Zhang *et al.* [30]	BM	35.5 years	4	NR	NR	One dose	Lumbar puncture below L3	Subarachnoid	ASIA motor score, ASIA sensory score
Geffner *et al.* [31]	BM	33.75 years	9	NR	80 mL	One dose	Injury site/intravenous	Subarachnoid/ intravenous	AIS grading, AIS motor score, ASIA light touch score, ASIA pinprick score ADL, bladder functional scale, MRI
Moviglia *et al.* [32]	BM	20 years	50–100	NR	NR	One dose per 2– 3 months	Femoral artery 3 cm below inguinal ligament	Intra-arterial	ASIA grading, MEP, SSEP
Oh *et al.* [33]	BM	40.9 years	3.2	NR	2 mL	One dose	Injury site	Subarachnoid	ASIA grading, MEP, SSEP, MRI, DTI
Pal *et al.* [34]	BM	33.2 years	0.1 per kg	3	NR	Three doses, 1 week apart	Lumbar puncture below L3	Subarachnoid	ASIA grading, ADLs, SSEP, MEP, MCS, SCS, MRI
Park *et al.* [35]	BM	35.8 years	20	NR	1.8 mL	One dose	Injury site	Subarachnoid	ASIA grading, AIS motor score, ASIA light touch score, ASIA pinprick score
Park *et al.* [36]	BM	46 years	0.8	5	1 mL	Three doses, 4 weeks apart	Injury site	Subarachnoid	AIS grading, MRI, SSEP, MEP
Sykova *et al.* [37]	BM	30.05 years	8.9	3	30 mL	One dose	Femoral artery/cubital vein	Intra-arterial/ intravenous	AIS grading, ASIA light touch score, ASIA pinprick score, MRI, SSEP, MEP

DTI, diffusion tensor imaging; EMG, electromyography; FAC, functional ambulation category; MCS, motor conduction study; MRI, magnetic resonance imaging; NR, not reported; SCS, sensory conduction study.

Table 3
Subgroup analysis of included studies.

Group	Subgroup	Estimated effect [95% CI] (*P* value)									
		AIS grade improvement	ASIA overall sensory score	ASIA light touch score	ASIA pinprick score	ASIA motor score	ADL score	Residual urine volume	Bladder function improvement	SSEP improvement	Complications
Location of SCI	Cervical	RR = 1.407 [0.516, 2.298] (0.002)	WMD = 10.227 [−1.959, 22.413] (0.100)	WMD = 7.545 [1.266, 13.824] (0.019)	WMD = 13.959 [−3.146, 31.064] (0.110)	WMD = 1.065 [−0.914, 3.043] (0.292)	WMD = 5.977 [−1.486, 13.440] (0.116)	WMD = −36.55 [−68.105, −4.994] (0.023)	RR = 2.388 [1.212, 4.706] (0.012)	RR = 2.558 [0.936, 4.181] (0.002)	RR = 2.145 [1.186, 3.103] (0.002)
	Thoracolumbar	RR = 1.182 [0.048, 2.316] (0.041)	WMD = 26.180 [15.554, 37.806] (< 0.001)	WMD = 4.808 [−6.551, 16.168] (0.407)	WMD = 8.531 [−1.367, 18.428] (0.091)	WMD = 9.153 [−2.421, 20.726] (0.121)	–	–	–	–	RR = 2.085 [0.310, 3.861] (< 0.001)
Duration of SCI	Early (<12 months)	–	WMD = 2.718 [−2.788, 8.223] (0.333)	–	–	WMD = 0.519 [−2.687, 3.726] (0.751)	WMD = 1.610 [−4.353, 7.574] (0.597)	–	–	–	RR = 1.900 [0.528, 3.272] (0.007)
	Late (>12 months)	RR = 1.396 [0.593, 2.200] (< 0.001)	WMD = 21.643 [5.383, 37.903] (0.009)	WMD = 7.383 [1.553, 13.213] (0.013)	WMD = 13.856 [−0.755, 28.468] (0.063)	WMD = 3.099 [−0.987, 7.185] (0.137)	WMD = 8.765 [−3.533, 21.063] (0.162)	WMD = −33.497 [−81.101, 14.108] (0.168)	RR = 2.388 [1.212, 4.706] (0.012)	RR = 2.558 [0.936, 4.181] (0.002)	RR = 2.292 [1.181, 3.404] (< 0.001)
Source of MSCs	BM	RR = 1.424 [0.571, 2.277] (0.001)	WMD = 13.271 [−3.006, 29.549] (0.110)	WMD = 7.545 [1.266, 13.824] (0.019)	WMD = 13.959 [−3.146, 31.064] (0.110)	WMD = 1.305 [−0.786, 3.395] (0.221)	WMD = 6.822 [−7.492, 21.137] (0.350)	WMD = −52.624 [−77.699, 27.549] (< 0.001)	–	RR = 2.558 [0.936, 4.181] (0.002)	RR = 2.235 [1.153, 3.317] (< 0.001)
	UC	–	WMD = 12.293 [0.738, 23.848] (0.037)	WMD = 4.808 [−6.551, 16.168] (0.407)	WMD = 8.531 [−1.367, 18.428] (0.091)	WMD = 1.273 [−4.228, 6.775] (0.650)	WMD = 3.033 [−1.150, 7.216] (0.155)	–	–	–	RR = 1.970 [0.622, 3.318] (0.004)
Dose of MSCs	$<5 \times 10^7$ cells	RR = 2.318 [0.294, 4.343] (0.025)	WMD = 6.548 [1.334, 11.762] (0.014)	WMD = 5.076 [0.756, 9.397] (0.021)	WMD = 4.887 [1.266, 8.508] (0.008)	WMD = 0.920 [−1.281, 3.122] (0.413)	WMD = 3.211 [−1.997, 8.420] (0.227)	WMD = −33.497 [−81.101, 14.108] (0.168)	–	–	RR = 1.732 [0.670, 2.794] (0.001)
	$\geq 5 \times 10^7$ cells	RR = 1.186 [0.439, 1.932] (0.002)	WMD = 23.539 [−0.737, 47.816] (0.047)	WMD = 7.975 [−2.616, 18.566] (0.140)	WMD = 17.946 [−7.829, 43.721] (0.172)	WMD = 5.257 [−2.365, 12.879] (0.176)	WMD = 7.859 [−9.392, 25.109] (0.372)	–	–	RR = 2.358 [0.359, 4.358] (0.021)	RR = 2.814 [1.425, 4.203] (< 0.001)
Initial AIS grade	Grade A	RR = 1.751 [0.899,2.603] (< 0.001)	WMD = 8.922 [2.913, 14.930] (0.004)	WMD = 4.683 [0.288, 9.078] (0.037)	WMD = 4.426 [0.717, 8.135] (0.019)	WMD = 0.825 [−1.744, 3.395] (0.529)	WMD = 5.318 [−0.802, 11.438] (0.089)	WMD = −33.497 [−81.101, 14.108] (0.168)	RR = 2.388 [1.212, 4.706] (0.012)	RR = 2.151 [0.139, 4.163] (0.036)	RR = 2.010 [0.483, 3.536] (0.010)
	Grade B/C/D	RR = 2.14 [−0.215,4.495] (0.075)	WMD = 14.630 [−0.696, 29.955] (0.061)	WMD = 8.676 [0.066, 17.286] (0.048)	WMD = 16.641 [−3.020, 36.303] (0.097)	WMD = 2.094 [−1.265, 5.452] (0.222)	WMD = 4.386 [−5.004, 13.776] (0.360)	–	–	–	RR = 2.185 [1.172, 3.197] (< 0.001)

Fig. 2. Methodological quality and risk of bias assessment of all the included studies.

Subgroup analysis

The authors performed subgroup analysis based on the location of SCI, duration of SCI, source of MSCs, concentration of cells used in transplantation and initial AIS grade before transplantation, as shown in Table 3. On analyzing the intervention group based on the location and duration of SCI and source of MSCs, the subgroups did not have enough studies to perform analysis of all outcome measures, and on analysis of available outcomes, no significant difference was noted in the available efficacy and safety outcomes. Although both SCI location subgroups showed significant improvement in AIS grade compared with the controls, the magnitude of the effect was greater in those with cervical injuries ($P = 0.002$) compared with thoracolumbar injuries ($P = 0.041$).

The authors categorized the intervention groups into studies using low ($<5 \times 10^7$ cells) and high ($\geq 5 \times 10^7$ cells) concentrations of MSCs for transplantation procedure. On analysis, it was noted that the low concentration subgroup was not inferior to its comparator in any outcome measure. The analysis also showed a statistically significant improvement in ASIA sensory light touch score compared with the controls was noted in the low concentration group ($P = 0.021$) which is not seen in the high concentration group ($P = 0.140$).

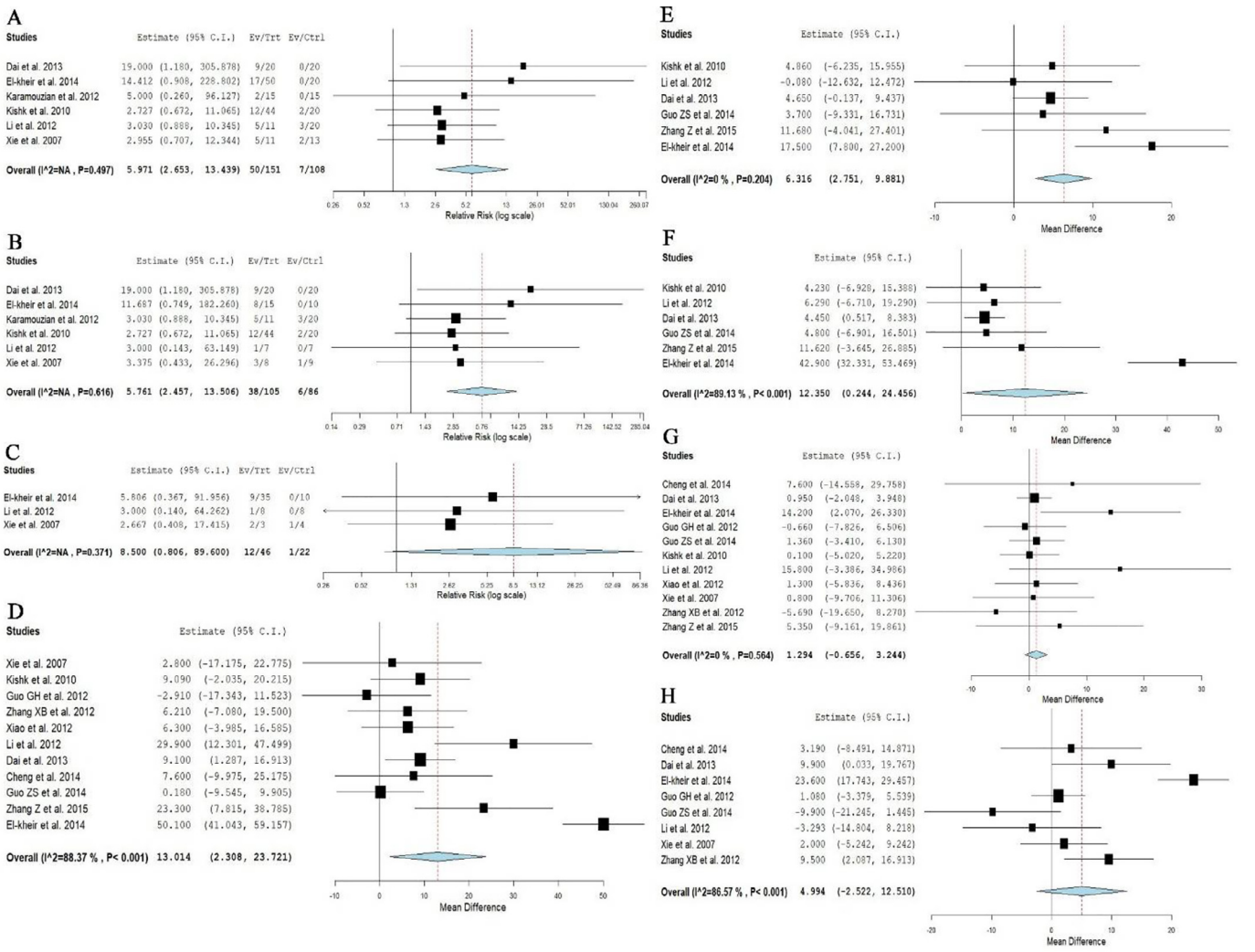

Fig. 3. Forest plot of the included studies comparing stem cell transplantation group with their controls. (A–C) AIS total grade, grade A, grade B/C/D. (D–F) ASIA overall sensory score, light touch score, pinprick score. (G) ASIA motor score. (H) ADL score. ASIA, American Spinal Injury Association; AIS, ASIA Impairment Scale; CI, Confidence Interval; Ev/Ctrl, event/control; Ev/Trt, event/treatment; NA, not applicable.

In addition, the authors made a subgroup analysis based on the initial AIS grade of the patients before transplantation procedure. When the intervention was applied to AIS grade A, a significant improvement was noted in efficacy outcomes like AIS grade ($P < 0.001$), ASIA overall sensory score ($P = 0.004$), ASIA pinprick score ($P = 0.019$), bladder function ($P = 0.012$) and SSEP ($P = 0.036$) compared with grades B, C and D. Both groups did not differ in their safety outcomes.

Sensitivity analysis

A sensitivity analysis was performed in each analysis. Results (AIS grade improvement; ASIA sensory scores, including light touch and pinprick scores; ASIA motor scores; bladder function scores; and electrophysiological parameters like SSEP) were not significantly altered by sequentially omitting each study from the meta-analysis. By contrast, consistency of the results was maintained after reanalysis by changing to the random effects model.

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 5. All studies fell within the 95% CI and were distributed evenly about the axes, implying minimal publication bias.

Discussion

In the field of cellular therapy, various researchers have reported that MSCs are ubiquitous and possess a unique self-renewal capacity, plasticity, multilineage differentiation potential, homing ability, immune-regulatory nature and anti-inflammatory effects [38]. MSCs are readily accessible and expandable *in vitro*and have exceptional genomic stability. The ethical concerns with MSCs are debatable [39,40].

MSCs are multipotent progenitor cells that have the facility to differentiate into mesodermal lineages and induce trophic activities related to neural cells [41]. They improve neurological deficits by generating either neural cells or myelin-producing cells. MSCs promote axonal regeneration by guiding nerve fibers and hence eliminate glial scars in the injured spinal cord [42,43]. The precise mechanism by which transplantation of bone marrow-derived MSCs (BM-MSCs) promotes functional recovery after SCI is still unclear.

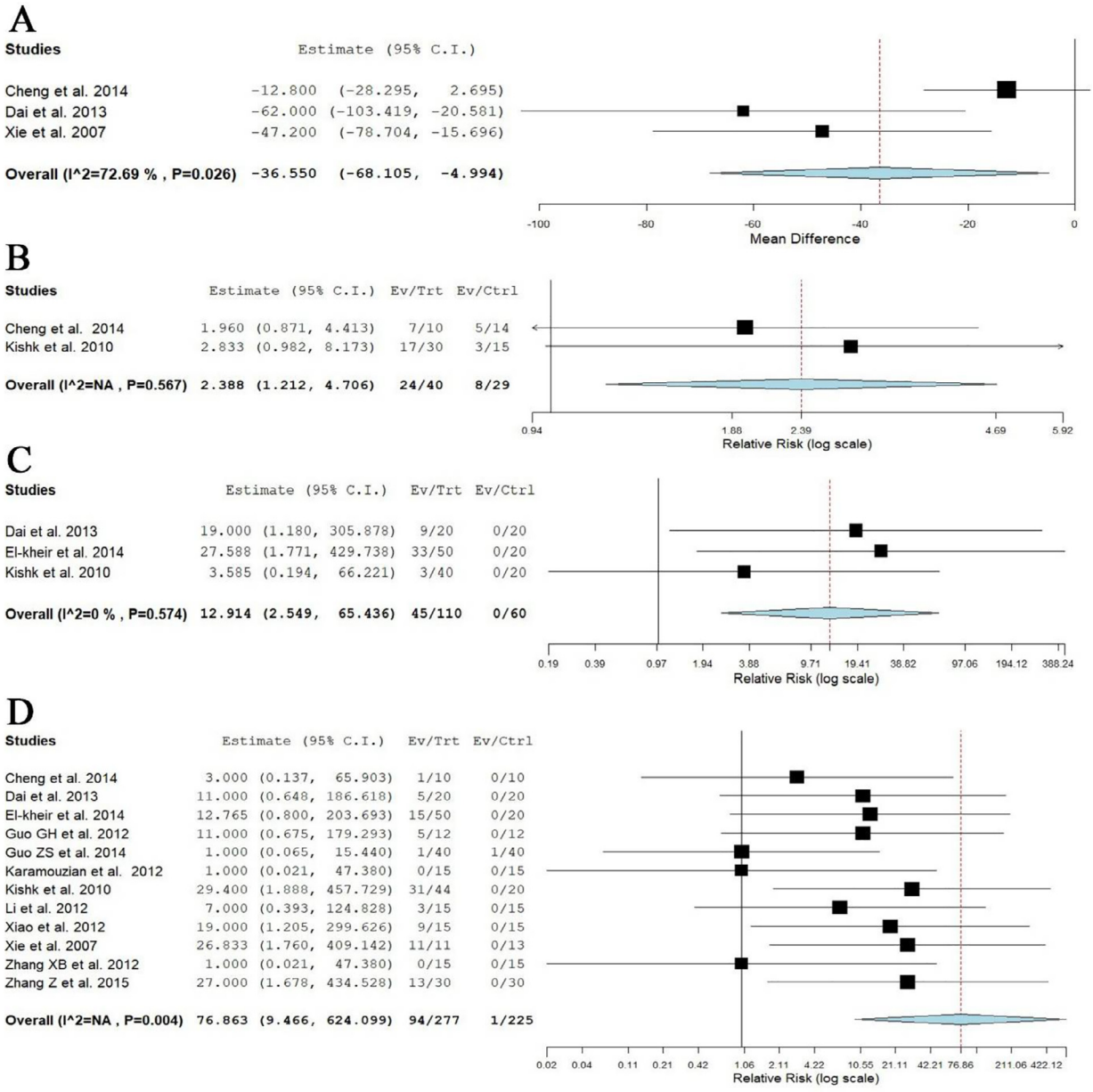

Fig. 4. Forest plot of the included studies comparing stem cell transplantation group with their controls. (A) Residual urine volume. (B) Bladder function improvement. (C) SSEP improvement. (D) Adverse events. SSEP, SomatoSensory Evoked Potential; CI, Confidence INterval; Ev/Ctrl, event/control; Ev/Trt, event/treatment; NA, not applicable.

One plausible explanation is that cytokines (colony-stimulating factor, nerve growth factor, brain-derived neurotrophic factor and vascular endothelial growth factor) secreted from BM-MSCs may be neuroprotective and enhance regeneration by ameliorating functional deficits [44]. MSCs also possess angiogenic properties.

The authors hypothesize that improved blood flow and oxygen supply within the injury area may have contributed to the functional improvements seen in these SCI patients transplanted with autologous MSCs [45]. Alternatively, it is well documented that MSCs promote host endogenous repair [46]. Moreover, significant improvement in neurological outcome despite the varied routes of administration used in the included studies could be explained by the homing properties of MSCs to the site of injury [47]. Granulocyte-macrophage colony-stimulating factor, a hematopoiesis-stimulating factor, can increase neural stem cell proliferation and inhibit neuronal apoptosis, resulting in improvement in neurologic function in animals [48]. MSCs also possess the ability to immunomodulate the inflamed environment, release bioactive factors, restore axon myelin, prevent neuronal apoptosis and contribute to neuroregeneration in individuals with SCI [49].

Although the authors could not investigate the role of age of the donor cells because of the wider variability of the subject population in the included studies, studies have shown that age of the MSC donor does not impair the regenerative potential of MSCs in various scenarios other than SCI [50]. Included studies had limited data for analyzing the role of culture passage in obtaining purified MSC lineages effective in SCI. However, studies have shown that increase in passage from P3 to P7 does not affect the immune-modulatory potential of MSCs [51].

Main findings

The authors comprehensively and systematically reviewed all the available literature on MSC transplantation for SCI and found that

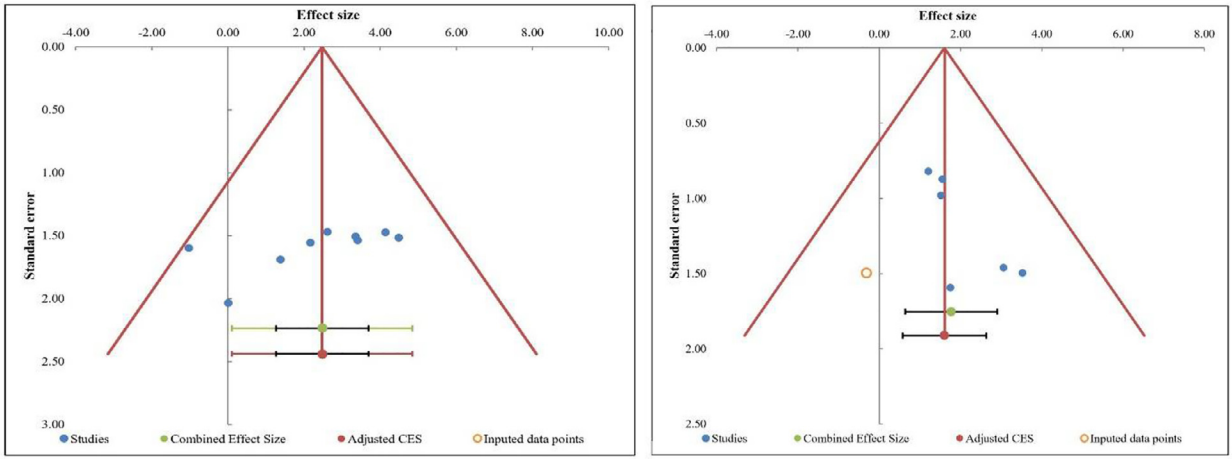

Fig. 5. Publication bias assessment with funnel plot for adverse events and AIS grade improvement in the included studies. CES, Combined Effect Size.

patients receiving MSC transplantation showed a statistically significant improvement in total AIS grade; AIS grade A; ASIA sensory scores, including light touch and pinprick scores; bladder function; and electrophysiological parameters like SSEP compared with rehabilitative therapy for SCI. However, no significant difference was noted in motor scores and ADL scores. In addition, although patients receiving MSC transplantation had mild and transient complications, no serious or permanent adverse events were reported. Moreover, on subgroup analysis, it was noted that the low concentration of cells used for transplant ($<5 \times 10^7$ cells) had outcomes comparable to the high concentration of cells ($\geq 5 \times 10^7$ cells), and patients presenting with AIS grade A showed significantly better improvement compared with AIS grades B, C and D on efficacy outcomes.

Comparison with other studies

The authors' results were concordant with the meta-analysis by Xu and Yang [52], which included 11 studies and 499 patients. The major limitation of their study was the lower number of studies included and the lack of subgroup analysis in terms of duration of SCI and dosage of MSCs transplanted. The authors of the current study not only included more studies in the analysis (n = 19 and 670 patients) but also analyzed the subgroup in terms of location and duration of SCI, source and concentration of MSCs used for transplant and initial AIS grade before transplantation to throw more light on the available evidence and identify the potential lacunae in the literature, which will indirectly widen the scope of future research.

Source of MSCs

The choice of MSCs is debatable. MSCs are found in bone marrow, umbilical cord cells, adipose tissue, molar teeth and amniotic fluid [53]. Autologous BM-MSCs avoid immunogenic reactions once administered [54]. Adipose-derived MSCs are found abundantly in the human body and are easily accessible. The stem cell activity of adipose-derived MSCs is three times higher than that of BM-MSCs [55]. Umbilical cord-derived MSCs (UC-MSCs) are allogeneic in nature. Combating immunological reactions with allogeneic UC-MSCs warrants lyophilization of UC-MSCs, which is a complex procedure [56].

Timing of transplantation

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 [57]. 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 [58,59], human trials on MSCs from the included studies did not show a significant difference in outcome measures.

Dosage and route of MSCs

The dosage and route of MSCs to be delivered to the site of spinal injury are a major concern among regenerative medicine researchers across the globe. There was no uniformity in route and dose standardization among the included studies [14,15,21–37]. Although the authors' analysis shows equivalence in the outcome measures between studies using low ($<5 \times 10^7$ cells) and high ($\geq 5 \times 10^7$ cells) concentrations of MSCs for transplantation, light has to be thrown on this gray area of dosing and route of MSCs to ensure the desired effects in SCI patients.

Direction for future research

Although MSCs play a potential role in the management of SCI, the scope of regenerative and translational medicine in the field of SCI has to be evaluated by large, randomized, controlled interventional trials for the optimization of therapeutic protocols in terms of the type of MSCs, preparation methods and quality and quantity of MSCs to be transplanted. Studies are also needed for the validation of timing and route of administration post-SCI. The scope of induced pluripotent stem cells in the field of SCI has to be evaluated. Ethical issues involved in minimal manipulation of tissue and cellular products and its functional outcome have to be addressed. The potential of MSCs to undergo unwanted differentiation with immunomodulatory and neo-angiogenic properties holds ethical concerns because of the potential of MSCs to promote tumor growth [60]. However, none of the studies which evaluated their use in SCI patients reported the occurence of such major adverse events.

Challenges and logistics involved in channeling stem cell basics into optimal clinical practice need an interdisciplinary approach to make this opportunity a reality for SCI patients. One of the main challenges, despite successful transplantation of the MSCs to the site of injury, is maintaining their survival and ensuring their neuronal-like differentiation. Hence, further research to better understand their mechanism of action and to maintain a conducive environment for their neuronal-like differentiation is needed. Newer avenues of cell-free therapeutics such as MSC-derived exosome therapy needs further investigation to explore their therapeutic potential in SCI patinets [61].

Limitations

The authors' analysis has some limitations. All the included studies were non-randomized trials. With the established efficacy and safety of the intervention based on the current evidence in the literature from the authors' study, there is a staunch need to conduct a large, multicentric, randomized controlled trial to evaluate various aspects of this potential therapeutic option. Heterogeneity was noted in some of the outcome measures from the included studies on analysis, which may be due to the subjective therapeutic efficacy of the autologous MSCs in the SCI patients.

Conclusions

MSC transplantation improves the functional quality of life and neurological outcome in individuals with SCI. The authors' analysis establishes the efficacy and safety of MSC transplantation in terms of improvement in AIS grade, ASIA sensory scores, bladder function and electrophysiological parameters like SSEP compared with the controls, without major adverse events. However, future research must be directed to standardizing the dose, timing, route and source of MSCs used for transplantation. Indeed, this therapy opens the doorway to newer avenues of cell-free therapeutics, such as MSC-derived exosome therapy, for SCI patients, which holds promise for the future.

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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: SM,MJ. Acquisition of data: SM,MJ,AG,AA. Analysis and interpretation of data: SM. Drafting or revising the manuscript: SM,MJ,AG,AA. All authors have approved the final article.

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