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The Efficacy and Safety of Mesenchymal Stem Cell Transplantation for Spinal Cord Injury Patients: A Meta-Analysis and Systematic Review

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Abstract

Spinal cord injury (SCI) is a devastating disease, with a high rate of disability. In this meta-analysis, we aimed to comprehensively assess the efficacy and safety of mesenchymal stem cells (MSCs) in treating clinical SCI patients. We systematically searched the PUBMED, EMBASE, Chinese Biomedical (CBM), Web of Science and Cochrane databases using the strategy of combination of free-text words and MeSH terms. The indicators of the American Spinal Injury Association (ASIA) impairment scale (AIS)-grading improvement rate and adverse effects were displayed with an overall relative risk (RR). For the continuous variables of the ASIA motor score, light-touch score, pinprick score, activities of daily living (ADL) score, and residual urine volume, we used odds ratio (OR) to analyze the data. Eleven studies comprising 499 patients meeting all inclusion and exclusion criteria were included. No serious heterogeneity or publication bias was observed across each study. The results showed that significant improvements of total AIS grade (RR: 3.70; $P < 0.001$), AIS grade A (RR: 3.57; $P < 0.001$), ASIA sensory score (OR: 8.63; $P < 0.001$) and reduction of residual urine volume (OR: -36.37; $P = 0.03$) were observed in experimental group compared with control group. However, no significant differences of motor score (OR: 1.37, $P = 0.19$) and ADL score (OR: 2.61, $P = 0.27$) were observed between experimental and control groups. In addition, there were no serious and permanent adverse effects after cell transplantation. Cell transplantation with MSCs is effective and safe in improving the sensory and bladder functions of SCI patients.

Keywords

spinal cord injury, mesenchymal stem cell, cell transplantation, meta-analysis

Introduction

Spinal cord injury (SCI) is a devastating disease, with a high rate of disability. Patients with SCI always suffer from paralysis, locomotor and sensory dysfunction, urinary incontinence or gastrointestinal dysfunction[1,2]. The incidence of SCI is 27–83 per million in the US and 10–30 per million in Europe[3,4], which poses a great burden on society. Therefore, there is an urgency to develop an effective therapy for cure of these patients.

The underlying mechanisms of SCI include direct mechanical damages and secondary injuries. Direct mechanical damages involve compression and contusion from the fractured and dislocated bone fragments and discs around the spinal cord[5]. Secondary injuries include neural apoptosis, spinal cord swelling, inflammatory response, oxidative stress and electrolyte disturbance[6–8]. Both primary and secondary injuries can cause devastating tissue damage, axonotmesis, demyelination, Wallerian degeneration, syringomyelia, and glial scar formation[9–11]. Many methods have been explored to treat SCI, including surgery, drugs, and rehabilitation, however, no treatment with good efficacy has been reported.

Recently, stem cell transplantation has attracted attention and is reported to be an effective treatment in treating SCI in

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animal models[12,13]. A variety of stem cell types have shown their potential for transplantation, such as neural stem cells[14], mesenchymal stem cells (MSCs)[4] , Schwann cells[15], embryonic stem cells[16], and induced pluripotent stem cells[17,18]. Among these, MSCs have played a pivotal role in repairing the damaged spinal cord. MSCs can not only differentiate and replace the damaged cells, but also secrete neuroprotective cytokines, including vascular endothelial growth factor (VEGF), glial-cell-line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), which all increase neural regeneration, strengthen axon growth, and revive damaged neurons[19,20]. Currently, the efficacy and safety of cell transplantation with MSCs have been verified in the animal SCI models. However, it is unclear whether MSCs have the same efficacy in treating SCI in humans as in animals. No meta-analysis has extensively evaluated the efficacy and safety of MSCs in treating patients with SCI.

Therefore, we conducted this meta-analysis to comprehensively assess the efficacy and safety of MSCs in treating clinical patients by evaluating outcomes including the American Spinal Injury Association (ASIA) motor score, ASIA sensory score (including light-touch and pinprick scores), ASIA Impairment Scale (AIS)-grading improvement rate, activities of daily living (ADL) score, residual urine volume, and adverse events.

Materials and Methods

Protocol

We conducted this meta-analysis based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)[21] (Supplemental Table 1).

Search Strategy

The databases of PUBMED, EMBASE, Chinese Biomedical (CBM), Web of Science and Cochrane were systematically searched for eligible studies (up to 25 July 2018). The search strategy consisted of free-words and MeSH terms as follows: (a) "mesenchymal stromal cells" or "MSCs," and (b) "spinal cord injury" or "SCI," (c) patient. In addition, other potential eligible studies were identified manually from references of included studies or other reviews pertaining to this topic.

This selection process of eligible articles was conducted by two authors independently (P Xu and X Yang).

Selection Criteria

The inclusion criteria are listed as: (a) Randomized controlled trials or other comparative studies; (b) patients diagnosed with SCI based on ASIA international standards for neurological classification; (c) patients only receiving transplantation of MSCs, or MSCs combined with rehabilitation; (d) the data regarding one or more of the following outcomes could be extracted: AIS grading, ASIA sensory score (including light-touch score and pinprick score), locomotor function, residual urine volume, ADL score or adverse effects; and (e) no overlapping data among different studies.

The exclusion criteria are listed as: (a) The study did not meet the inclusion criteria; (b) reviews, editorials, clinical conference, abstracts, case reports, comments, congresses; (c) non-human studies; (d) single-arm studies.

Data Extraction and Quality Assessment

We extracted the following data from included studies. (a) Identity: authors, years. (b) Patients included in each study: age, duration of injury, size of each group. (c) Treatments: treatment strategy, transplantation methods, cell sources, cell number, follow-up period. (d) Outcomes: AIS grading, ASIA motor score, ASIA sensory score (including light-touch and pinprick scores), ADL, residual urine volume, incidence of adverse effects.

The data of interest from included articles were extracted and processed by two authors, independently (Xu PF and Yang XL). Any disagreement was settled by discussion.

The risks of bias within the included studies were evaluated with the domain-based Cochrane Collaboration tool[22]. Detailed content of this assessment tool included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Any dispute was resolved by discussion.

Types of Outcome Measures

The following indicators were applied to assess the efficacy and safety of treatment with MSCs for SCI patients: AIS grading improvement rate, ASIA motor score, ASIA sensory score (including light-touch and pinprick scores), ADL score, residual urine volume, and adverse effects.

Statistical Analysis

This meta-analysis was completed with Stata 14 and Review Manager version 5.0 software (Cochrane Collaboration, software update, Oxford, UK), which was provided by the Cochrane Collaboration. The indicators of AIS grading improvement rate and adverse effects were displayed with an overall relative risk (RR), with corresponding 95% confidential interval (CI). For the continuous variables of ASIA motor score, light-touch score, pinprick score, ADL score, and residual urine volume, we used odds ratio (OR), with corresponding 95% CI to analyze the data.

We used the chi-squared value test and inconsistency index (I^2) to assess the heterogeneity across each study. A value of $P < 0.1$ or $I^2 > 50\%$ was deemed to have significant heterogeneity, a random-effect model was then used to analyze the data. Otherwise, the fixed-effect model was used. Subgroup analysis was used to find potential source of heterogeneity[23,24]. We adopted the Egger funnel plot and Egger's test to test publication bias with Stata14.0

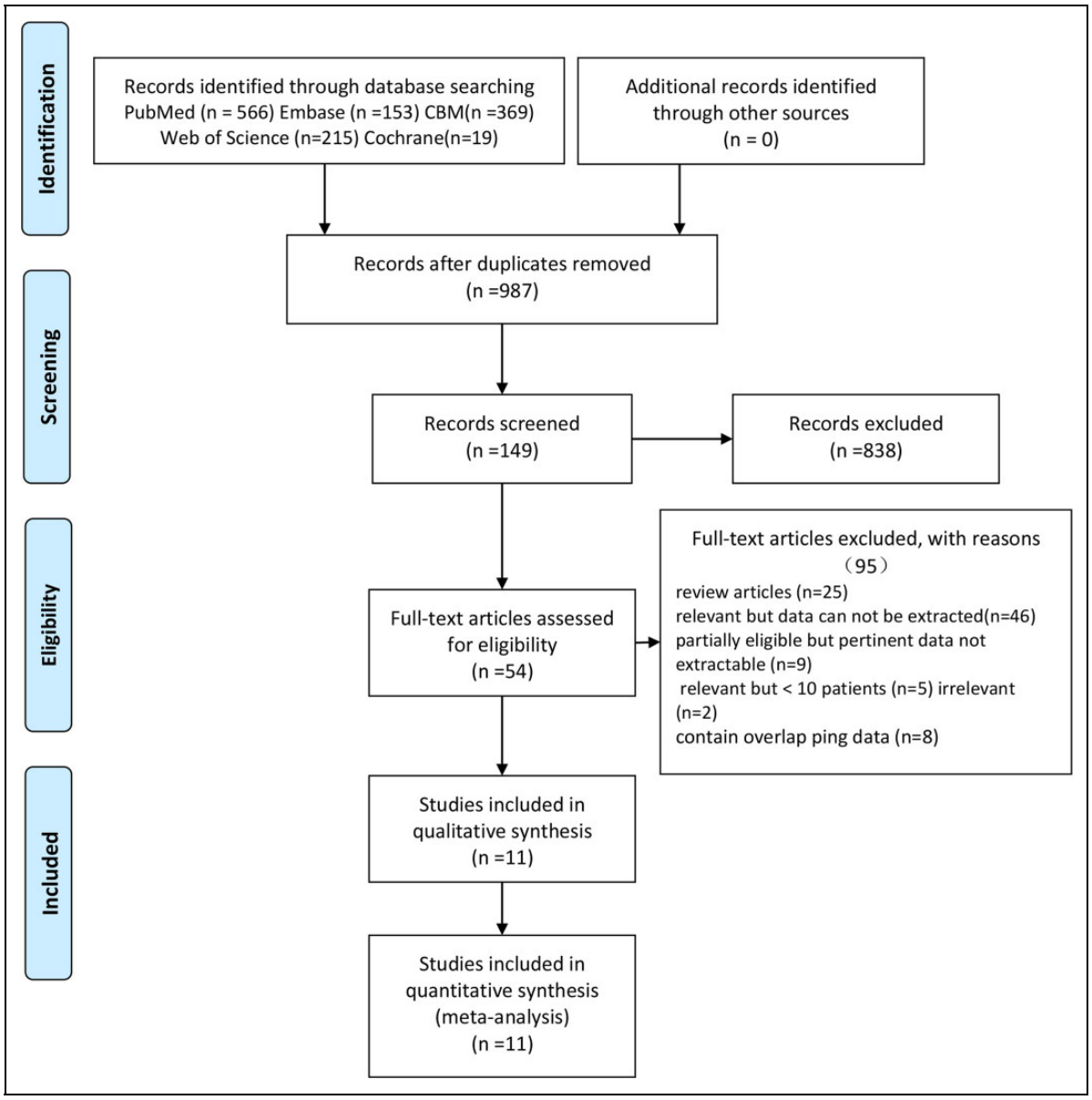

Fig 1. Flow Diagram of the Study Selection Process.

(StataCorp LP, College Station, TX, US)[25,26], with $P < 0.05$ indicating significant asymmetry[27].

Results

Study Screen

Searches of the PUBMED, EMBASE, Chinese Biomedical (CBM), Web of Science and Cochrane databases identified 566, 153, 369, 215 and 19 studies, respectively. After removing duplicated studies, 987 studies remained for screening by title and abstract. Subsequently, 59 records with full text were assessed. Finally, 11 studies[28–37] containing a total number of 499 cases were included in this meta-analysis (Fig 1).

Study Characteristics

The basic characteristics of all 11 studies are summarized in Table 1. The sample sizes ranged from 20 to 96. Nine studies were conducted in China[28,29,31–38], one study was conducted in Iran[30], and another was performed in Egypt[31]. Four studies were reported in English[28–31], and the other seven were in Chinese[32–38]. All studies chose rehabilitation therapy as the control. The MSCs originated from umbilical cord in five studies[29,32,34,37,38] and bone marrow in six studies[28,30,31,33,35,36]. Six studies adopted subarachnoid injection as the process used for cell transplantation[28–33,38]; two studies[35,37] used intravenous injection and the other two studies reported both methods[34,36]. The course of SCI ranged from 1 week to 9 years and the follow-up period ranged from

Table 1. Characteristics of Included Studies.

Author(s)	Year	Size	Treatment/ control	M/F	Age (years)	Treatments	Cell source	Method of transplantation	Cell number	Duration	Assessment	Follow up	Adverse events
Xie et al.	2007	24	11	9/2	18-49	R + SCT	BMMSCs	Intravenous/ subarachnoid	(4.08–10.20) $\times 10^7$	1–10 months	ASIA sensation score; ASIA motor score; ADL (BI); residual urine volume; AIS grading	3 months	Fever (7); headache (2); abdominal distention (1); numbness (1)
			13	10/3	21–53	R							None
Guo et al.	2012	24	12	11/1	29	R + SCT	UCMSCs	Subarachnoid	(2–5) $\times 10^7$	2.3 months	ASIA sensation score; ASIA motor score;	5 months	None
			12	10/2	31	R				2.5 months	ADL		None
Li	2012	30	15	12/3	37.36	R + SCT	UCMSCs	Intravenous/ subarachnoid	5×10^7	1 months–9 years	AIS grading; ASIA motor score; ASIA light-touch score; ASIA pinprick score; ADL; SEP; MCS; SCV; EMG	4 months	Fever (2); headache (4); backache (3)
			15	10/5	37.67	R							None
Dai et al.	2013	40	20	14/6	34.7	R + SCT	BMMSCs	Subarachnoid	2×10^7	51.9 months	AIS grading; ASIA motor score; ASIA light-touch score; ASIA pinprick score; residual urine volume; EMG; PSSEP; MRI	6 months	Fever (2); headache (1); pain and numbness (2)
			20	14/6	35.1	R				43.2 months			None
Guo et al.	2014	80	40	30/10	37.25	R + SCT	BMMSCs	Unknown	1.5×10^4	None	AIS grading; ASIA motor score; ASIA light-touch score; ASIA pinprick score; ADL	None	Fever (1)
			40	33/7	36.37	R							None
Cheng et al.	2014	20	10	Uknown	32.25	R + SCT	UCMSCs	Subarachnoid	4×10^7	21.4 months	ASIA sensation score; ASIA motor score; muscle tension scale; ADL; urodynamic examination	6 months	Radiating neuralgia (1)
			10			R				18.57 months			None
Zhang et al.	2015	30	15	11/4	35.5	R + SCT	UCMSCs	Subarachnoid	4×10^7	21.3 $\pm$ 5.7 months	AIS grading; ASIA motor score; ASIA light-touch score; ASIA pinprick score	6 months	Fever (7); headache (2); numbness (4)
			15	11/4	35.7	R				21.3 $\pm$ 5.7 months			None
Zhang et al.	2012	60	30	50/10	18–45	R + SCT	UCMSCs	Intravenous	1×10^7	1–10 months	ASIA sensation score; ASIA motor score	3 months	Fever (1); headache (2)
			30			R							None
Kishk et al.	2010	64	44	36/8	31.7	R + SCT	BMMSCs	Subarachnoid	3.75×10^8 to 7.5×10^8	3.6 years	Barthel trunk muscle assessment; MCS; FAC; ASI grading; ASIA sensation score; ASIA motor score; SSEP	6 months	Neuropathic pain (24); post-infectious myelitis (1)
			20	15/5	33.8	R				3.7 years			None
Karamouzian et al.	2012	31	11	7/4	33.2	R + SCT	BMMSCs	Subarachnoid	7×10^5 to 1.2×10^6	23.7 $\pm$ 8.4 days	AIS grading; ASIA motor score	20.3 months	None
			20	17/3	33.5	R						23.4 months	
Xiao et al.	2012	96	38	25/13	42.3	R + SCT	BMMSCs	Subarachnoid	1.4×10^7	1 week	ASIA sensation score; ASIA motor score	6 months	Fever (5)
			32	21/11	41.5	R + SCT	BMMSCs	Intravenous					
			26	17/9	41.2	R							None

M: male; F: female; R: rehabilitation; SCT: stem cell transplantation; BMMSCs: bone marrow mesenchymal stem cells; UCMSCs: umbilical cord mesenchymal stem cells; ASIA: American Spinal Injury Association; AIS: ASIA impairment scale; ADL: activities of daily living; MCS: motor nerve conduction studies; SEP: sensory-evoked potential; SCV: sensory nerve conduction studies; EMG: electromyography; FAC: functional ambulation categories ; SSEP: somatosensory evoked potential; BI: barthel index; PSSEP: paraspinal somatosensory evoked potential.

3 to 23.4 months. For reporting the outcomes, five studies reported AIS grading improvement rate[28,30,31,34,36], ten studies reported ASIA motor score[28,29,31–38], five studies reported ASIA light-touch and pinprick scores[28,31,33,34,38], seven studies reported ADL score[28,29,32-34,36,37], three studies reported residual urine volume[28,29,36], and 11 studies reported some mild adverse effects[28–38].

Methodological Quality of Included Studies

We used the standard Cochrane Collaboration tool to evaluate the risks of bias within included studies, and the results of methodological quality of each study are shown in Fig 2. Ten studies reported random sequence generation and one study did not mention it. Additionally, three studies had the details of blinding of outcome assessment, one study lacked blinding of outcome assessment and the others did not state the blinding of outcome assessment. Overall, the methodological quality of included studies was acceptable.

Efficacy of Treatment

American Spinal Injury Association Impairment Scale Grading Improvement Rate. Five studies containing 189 cases reported AIS grading improvement rate, low heterogeneity was observed across each trial ($P = 0.25$, $I^2 = 26\%$, Fig 3A). A fixed-effects model was applied to evaluate the AIS improvement rate. The results indicated significant improvements of total AIS grade and AIS grade A in the experiment group compared with control group (total AIS grade: RR: 3.70; 95% CI 2.63–6.25; $P < 0.001$; AIS grade A: RR: 3.57; 95% CI 2.5–6.67; $P < 0.001$, respectively; Fig 3A and 3B), however, no significant difference was found in AIS grading B/C/D (RR: 4.46; 95% CI 0.42–47.34; $P = 0.22$; Fig 3C).

American Spinal Injury Association Sensory Score. Ten studies containing 468 cases reported ASIA sensory score (including ASIA light-touch and pinprick scores); low heterogeneity was observed among included studies ($P = 0.16$, $I^2 = 31\%$). A fixed-effects model was applied to evaluate the ASIA sensory score. The results indicated significant improvements of general ASIA sensory score, ASIA light-touch score and ASIA pinprick score in the experiment group, compared with the control group (general ASIA sensory score: OR: 8.63; 95% CI 4.84–12.41, $P < 0.001$; ASIA light-touch score: OR: 4.57; 95% CI 0.74–8.4, $P = 0.02$; ASIA pinprick score: OR: 4.92; 95% CI 1.59–8.25, $P = 0.004$; Fig 3D, 3E and 3F).

American Spinal Injury Association Motor Score. Ten studies containing 468 cases reported ASIA motor score; low heterogeneity was observed across each trial ($P = 0.43$, $I^2 = 1\%$). A fixed-effects model was applied to evaluate the ASIA motor score. The results showed that no significant improvements of ASIA motor score were observed in the experiment group compared with the control group (OR: 1.37; 95% CI 0.70–3.44; $P = 0.19$; Fig 3G).

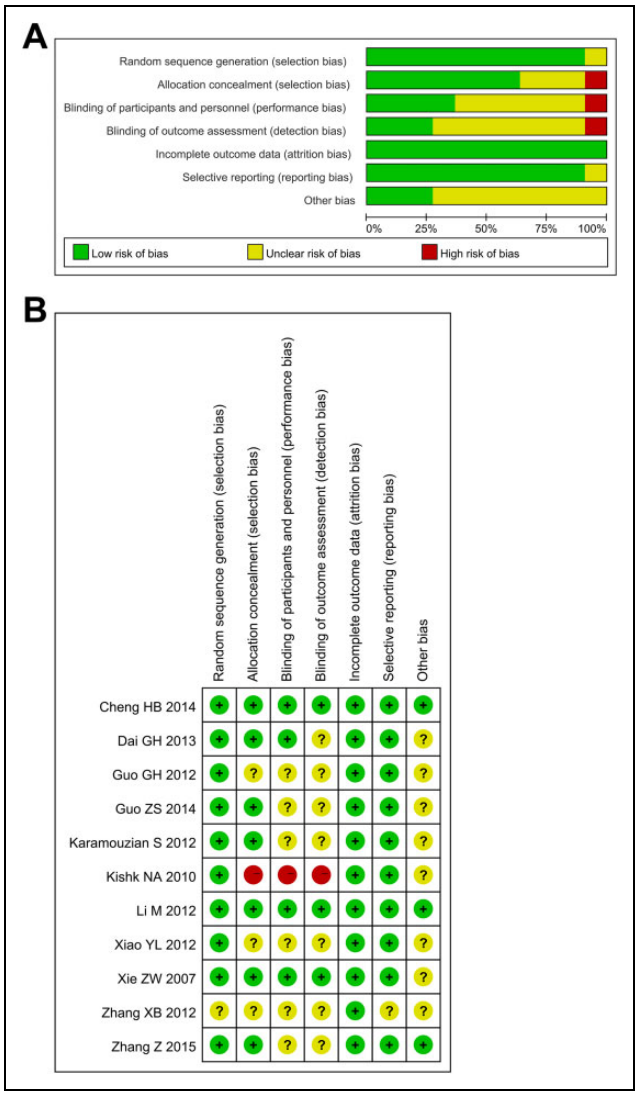

Fig 2. Risk of Bias Percentile Chart. (2A) Risk of bias graph: A plot of the distribution of review authors' judgements across studies for each risk of bias item; (2B) Risk of bias summary: A summary table of review authors' judgements for each risk of bias item for each study.

Activities-of-Daily-Living Score. Seven studies containing 278 cases reported ADL score; moderate heterogeneity was observed ($P = 0.02$, $I^2 = 59\%$). Therefore, the random-effects model was applied to evaluate the ADL score. The results showed that no significant improvements of ADL score were observed in the experiment group compared with the control group (OR: 2.61; 95% CI 2.04–7.26; $P = 0.27$; Fig 3H).

Residual Urine Volume. Three studies containing 84 cases reported residual urine volume; moderate heterogeneity was observed among included trials ($P = 0.02$, $I^2 = 73\%$).

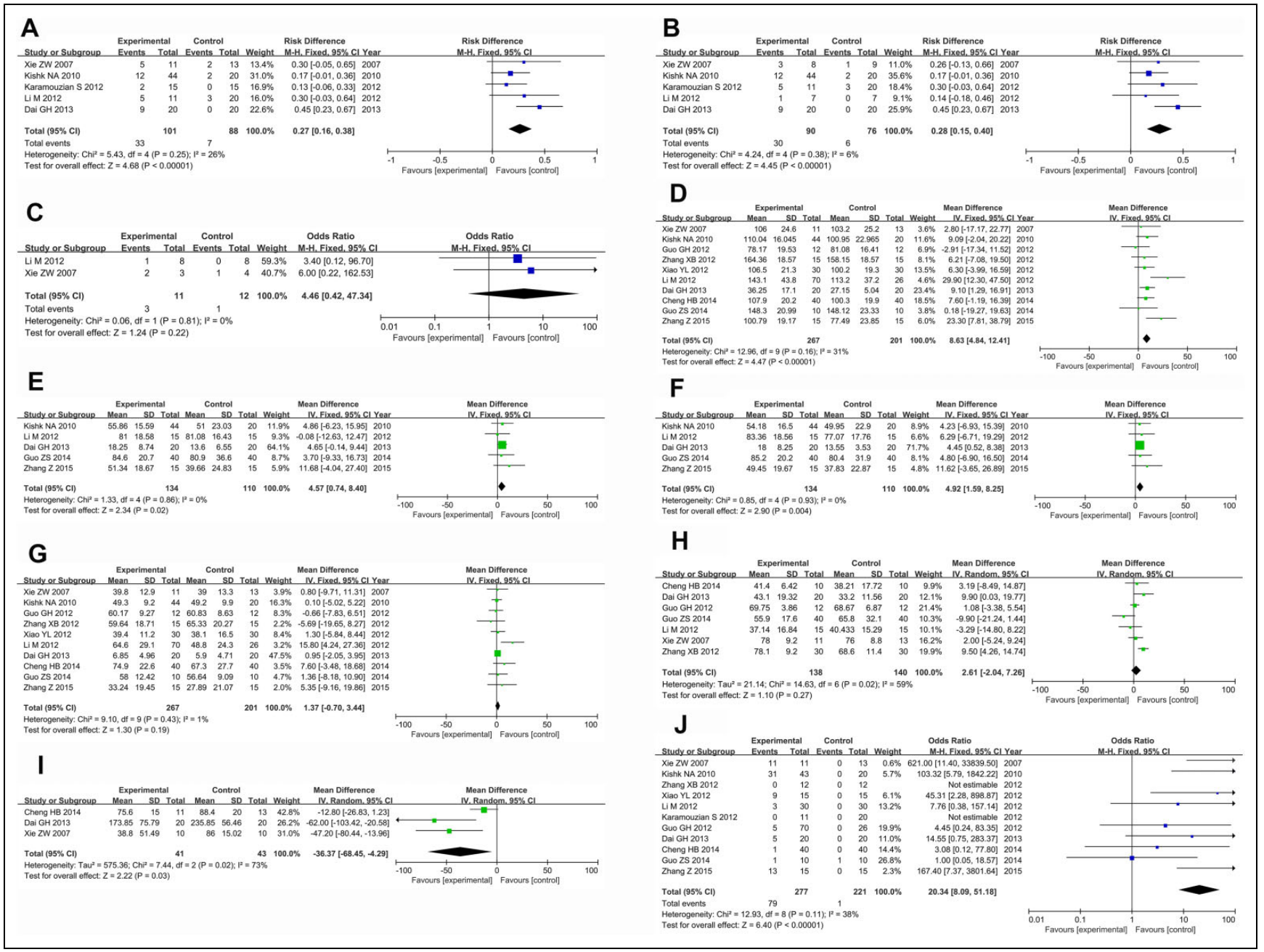

Fig 3. Forest Plot of Comparison: Cell Transplantation Group Versus Control Group.
(A–C) AIS total grade, grade A and grade B/C/E; (D–F) general ASIA sensory score, ASIA light-touch score and ASIA pinprick score; (G) ASIA motor score; (H) ADL score; (I) residual urine volume; (J) adverse effects.
ADL: activities of daily living; ASIA: American Spinal Injury Association; AIS: ASIA Impairment Scale; CI: confidence interval; SD: standard deviation; IV: inverse variance; M-H: Mantel-Haenszel.

A random-effects model was applied to evaluate the residual urine volume. The results showed that significant reduction of residual urine volume was observed in the experiment group compared with the control group (OR: 36.37; 95% CI 68.45–4.29; $P = 0.03$; Fig 3I).

Safety

Eleven studies containing 499 cases reported adverse effects; low heterogeneity was observed across each trial ($P = 0.11$, $I^2 = 38\%$). The fixed-effects model was then employed in the RR pooled analyses. The results showed that patients receiving cell transplantation of MSCs experience more toxicity than that of the control group (RR: 20.34; 95% CI 8.09–51.18, $P < 0.001$; Fig 3J). Common adverse effects include fever, headache, backache, numbness, and abdominal distension, which were alleviated spontaneously or following treatment intervention. However, no serious or permanent adverse effects, such as death, tumor, or immune reaction, were observed during follow up.

Subgroup Analysis

We performed subgroup analysis based on cell sources and follow-up period. For analyzing the effects of cell transplantation on motor function and self-care ability, no significant differences were observed between experiment and control groups with different cell sources and follow-up periods ($P > 0.05$; Fig 4A–4G). However, regarding the adverse effects of cell transplantation, the experiment group showed a higher rate of adverse effects than that in the control group, no matter which different cell sources or follow-up periods ($P < 0.05$; Fig 4H–4K).

Publication Bias

The Egger's funnel plot and rank correlation test showed no significant publication bias across each study regarding sensory score, motor function, and adverse effects ($P = 0.387$, $P = 0.091$ and $P = 0.07$, respectively; Fig 5A–5C). For other indicators, the assessment of publication bias cannot be conducted due to insufficient number of studies ($n < 10$).

Discussion

This meta-analysis included 11 studies and comprehensively evaluated the safety and efficacy of MSC transplantation for treating patients with SCI. Although the efficacy of this method for treating SCI patients remains unclear, this study showed that when compared with rehabilitation therapy, MSC transplantation significantly improved the neurological functions, including ASIA light touch, pinprick, ADL, and bladder function. However, this meta-analysis found that no significant difference was observed for the improvement of motor score, and the patients who received MSC transplantation displayed some mild and temporary side effects.

MSCs could be extracted from autologous bone marrow, umbilical cord or adipose tissue[39,40]. In the animal studies, MSCs have displayed many advantages in the treatment of SCI. Some studies showed that MSCs could survive in the site of injury and differentiate into different types of cells (neurons, oligodendrocytes, vascular endothelial and astrocytes)[41]. In addition, MSCs can also secrete neuroprotective cytokines, including VEGF, GDNF, and BDNF, which support neural regeneration, promote axon growth, and activate damaged neurons[19,20]. Furthermore, MSCs are reported to inhibit glial scar formation, alleviate scar obstructions, and activate endogenous neural stem cells[42,43].

Although some studies demonstrated no advantages with stem cell transplantation in the treatment of SCI[30], most of the studies included in this meta-analysis indicated that MSC transplantations could significantly improve the sensory functions, including light touch and pinprick. Their results showed that sensory functions were improved in two respects. On the one hand, the improvement was reflected on the downward level of damaged spinal cord with loss of sensation. On the other hand, the sensory functions were improved from insensitivity or weak sensation to strong sensation. In addition, regarding AIS grading, cell transplantation could significantly improve AIS grading in all patients and in patients with AIS grade A before cell transplantation. However, for the patients with AIS grade B or lower before cell transplantation, no advantage was gained from cell transplantation. Furthermore, some studies reported that cell transplantation could significantly improve motor functions[32,33], but the results of the present study demonstrated that no significant difference was observed between patients receiving cell transplantation and those in the rehabilitation group. Seven studies reported self-care ability. The results of this study showed that no significant improvement of self-care ability was observed in both short-term and long-term follow up after cell transplantation. Regarding bladder function, urine residual volume was significantly reduced after cell transplantation. Cheng et al. also performed urodynamic examination. Their results showed that maximum bladder capacity increases, residual urine volume decreases, maximum detrusor pressure decreases, and maximum urinary flow rate increases[29].

Although the results showed some adverse effects in the present study, all were only displayed as temporary and light side effects, including fever, headache, backache, numbness, and abdominal distension, primarily caused by spinal puncture. No devastating and long-term adverse effects, such as wound infection, cerebrospinal fluid leakage from incision, or intracranial infection were observed in patients receiving stem cell transplantation, indicating the safety of cell transplantation.

Limitations

Some limitations cannot be ignored in this study. First, only 11 studies were included in this study. Some important

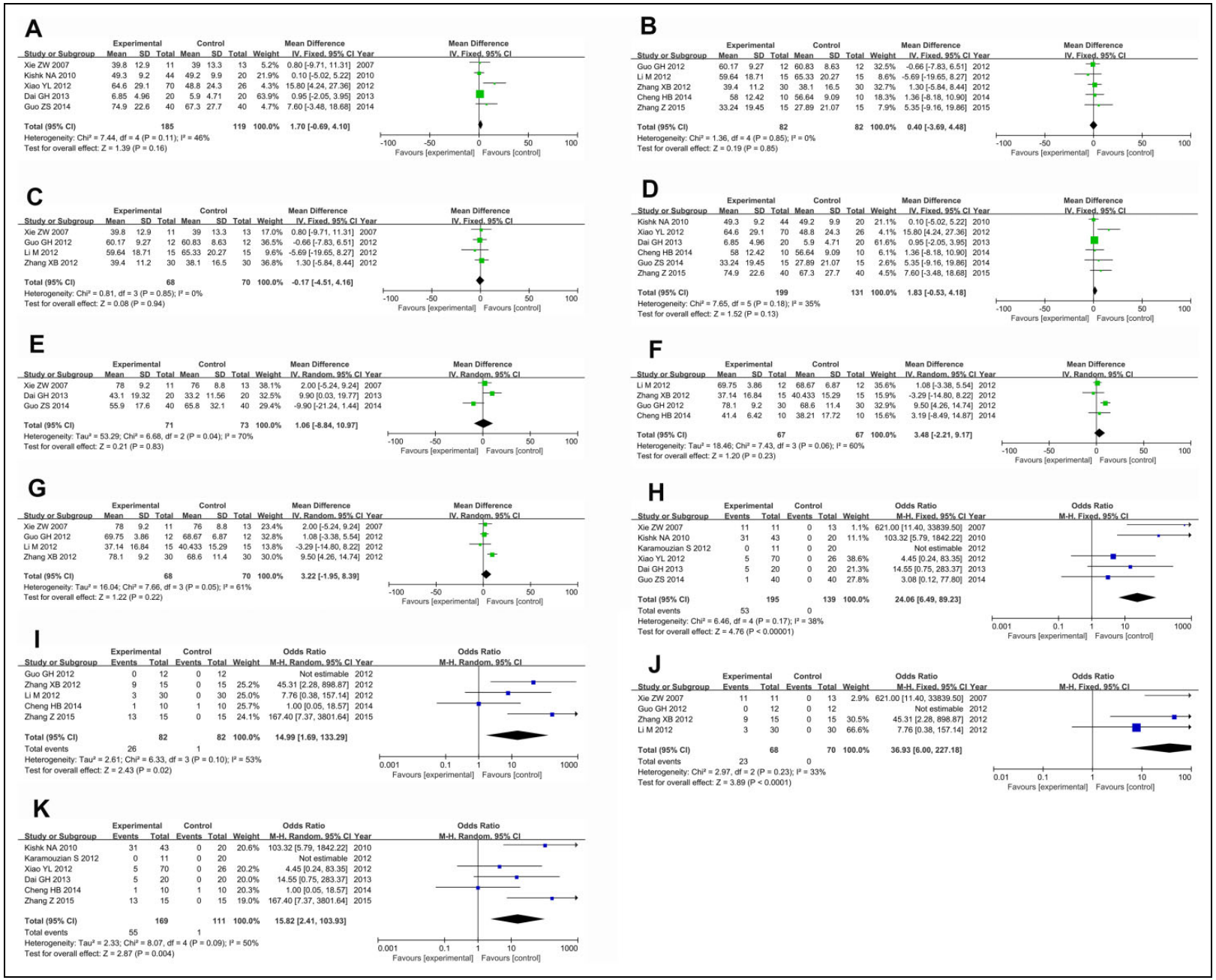

Fig 4. Forest Plot of Subgroup Analysis Based on Cell Source and Follow-Up Periods.
(A, B) Motor functions of patients receiving mesenchymal stem cells derived from bone marrow and umbilical cord, respectively; (C, D) motor functions of patients being followed up for less than 6 months and more than 6 months, respectively; (E, F) ADL score of patients receiving mesenchymal stem cells derived from bone marrow and umbilical cord, respectively; (G) ADL score of patients being followed up for less than 6 months; (H, I) adverse effects for patients receiving mesenchymal stem cells derived from bone marrow and umbilical cord, respectively; (J, K) adverse effects for patients being followed up for less than 6 months and more than 6 months, respectively.
ADL: activities of daily living; CI: confidence interval; SD: standard deviation; IV: inverse variance; M-H: Mantel-Haenszel.

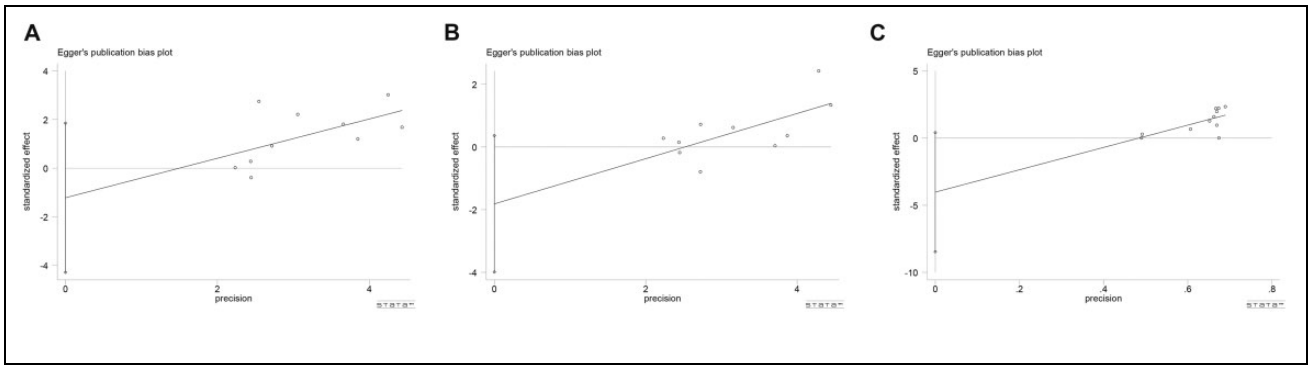

Fig 5. Funnel Plot of Publication Bias.
(A) Motor functions; (B) sensory score; (C) adverse effects.

subgroup analyses, such as different courses of disease and number of cells given to the patients, could not be performed. Second, we only included the papers published in English and Chinese in this meta-analysis, which may leave out other eligible studies that were reported in other languages. In addition, most of these studies included were conducted in China. There may be some differences of the effects and safety in other populations. Therefore, the results should be interpreted cautiously due to the limited data, although the results of this meta-analysis are robust. Third, no significant publication bias in the overall analysis was observed in this study, but many factors, including stem cell preparation and identification, social economic level, or nursing care could have impacts on the outcomes of stem cell transplantation for SCI. Therefore, multi-centric and large-sample randomized controlled studies with reasonable random sequence generation, adequate allocation concealment, and low risk of reporting bias are required to provide more medical evidence base.

Conclusions

Cell transplantation with MSCs is effective and safe in improving the sensory and bladder functions in SCI patients; however, its effect on motor function is unclear.

Ethical Approval

Ethical Approval is not applicable to this study.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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