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Reviews

The Effect of Bone Marrow–Derived Mesenchymal Stem Cell Transplantation on Allodynia and Hyperalgesia in Neuropathic Animals: A Systematic Review with Meta-Analysis

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A B S T R A C T

Stem cell transplantation has been considered a possible therapeutic method for neuropathic pain. However, no quantitative data synthesis of stem cell therapy for neuropathic pain exists. Therefore, the present systematic review and meta-analysis assessed the efficacy of bone marrow mesenchymal stem cell (BMMSC) transplantation on alleviating pain symptoms in animal models of neuropathic pain. In the present meta-analysis, controlled animal studies assessing the effect of administrating BMMSC on neuropathic pain were included through an extensive literature search of online databases. After collecting data, effect sizes were computed and the standardized mean difference (SMD) with 95% confidence interval (CI) was entered in all analyses. Random-effects models were used for data analysis. Sensitivity and subgroup analyses were performed to investigate expected or measured heterogeneity. Finally, 14 study were included. The analyses showed that BMMSC transplantation lead to significant improvement on allodynia (SMD = 2.06; 95% CI, 1.09 to 3.03; $I^2 = 99.7\%$; $P < .001$). The type of neuropathy ($P = .036$), time between injury and intervention ($P = .02$), and the number of transplanted cells ($P = .023$) influence the improvement of allodynia after BMMSC transplantation. BMMSC transplantation has no effect on hyperalgesia (SMD = .3; 95% CI, −1.09 to 1.68; $I^2 = 100\%$; $P < .001$) unless it occurs during the first 4 days after injury ($P = .02$). The present systematic review with meta-analysis suggests that BMMSC transplantation improves allodynia but does not have any significant effect on hyperalgesia unless it is given during the first 4 days after injury.

INTRODUCTION

Neuropathic pain is defined as chronic pain resulting from a lesion or disease affecting the somatosensory system [1]. It can be triggered by central or peripheral nerve injury. The predominant symptoms are acute or sharp pain, impulsive pain, hyperalgesia, and allodynia. These symptoms may have continuous or episodic (paroxysmal) components [2].

Epidemiological evidence shows that the prevalence of neuropathic pain in general population is 3% to 17% [3]. Neuropathic pain leads to decreased quality of life, reduced personal functions, and undermined mental health and social relations. It is 1 of the most complicated pain conditions to diagnosis and treat, and outcome is often poor [4,5]. Current treatment strategies only decrease 30% to 40% of the pain in less than 50% of the patients. Medications are aligned with some problems, such as side effects. New studies suggest that regenerative approaches based on cell therapy may be helpful in alleviating neuropathic pain symptoms [6-10].

In the last 2 decades, stem cell transplantation has been considered a possible therapeutic method for the spinal cord injury and neuropathic pain conditions [6,9-13]. Mesenchymal stem cells are the main source of cell therapy because of their ability of differentiating into multiple cell types, including blood, adipose tissue, connective tissues, osteocytes, chondrocytes, hepatocytes, myocytes, neurons, and cardiomyocytes [14-16]. Bone marrow mesenchymal stem cells (BMMSCs) can easily grow in vitro and exhibit intriguing immunomodulatory properties, nonteratogenicity, and multipotentiality with high genetic stability. They can also improve synaptic transmission and

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promote neuronal networks [17-21]. These properties make BMMSCs prime candidates for various therapeutic applications, especially for nervous system repair. In the context of neuropathic pain, transplantation of BMMSCs into the injured spinal cord reduced the progress of neuropathic pain [6,22-24].

Few clinical studies have been published regarding the use of BMMSCs for spinal cord injury. The findings of these studies have substantial diversity, ranging from improvement in symptoms to no significant improvement [25-32]. These studies have lacked a proper randomized control group and have been underpowered. However, a substantial number of controlled preclinical studies have investigated the effect of BMMSCs on neuropathic pain [6,22-24,33-41]. These studies revealed various degrees of improvement of neuropathic pain and symptoms, such as allodynia and hyperalgesia. Yet there is not a general conclusion about the effectiveness of stem cells in neuropathic pain. For this purpose, a meta-analysis of controlled studies could help estimate the effect of the intervention and, therefore, yield more powerful decision making. However, to our knowledge, no quantitative data synthesis of stem cell therapy for neuropathic pain exists. Therefore, the present systematic review and meta-analysis assessed the efficacy of BMMSCs transplantation on alleviating pain, allodynia, and hyperalgesia in animal models of peripheral or central neuropathic pain.

METHODS

Search Strategy

The study was conducted according to Meta-analysis of Data from Animal Studies Guidelines [42,43], providing a detailed guideline of preferred reporting for systematic reviews and meta-analyses. Relevant articles were identified through a literature search of online databases (PubMed, SCOPUS, Embase, Cochrane, and CINAHL) without publication date and language limitations. The initial search was broad and included the following words: (1) PubMed term: ("mesenchymal stem cells" OR "mesenchymal stromal cells" OR "mesenchymal stem cell" OR "mesenchymal stromal cell" OR "marrow stromal cell" OR "bone marrow stem cell" OR "bone marrow-derived stromal cell" OR "mesenchymal precursor cell" OR "MSCs" OR "MSC" OR "BMSCs" OR "BMSC") AND ("spinal cord injuries" OR "spinal" "spinal cord injury" OR "spinal cord contusion" OR "spinal cord transection" OR "injured spinal cord" OR "pain" OR "pain" OR "neuropathic pain" OR "allodynia" OR "hyperalgesia" OR "hypersensitivity"); and (2) In EMBASE: (mesenchymal stem cells.mp. OR mesenchymal stem cell/OR mesenchymal stromal cells.mp. or mesenchymal stroma cell/OR bone marrow stromal cells.mp.) AND (spinal cord injury.mp. or spinal cord injury/OR pain.mp. or pain.mp. or neuropathic pain.mp. OR allodynia.mp. OR hyperalgesia.mp. OR hypersensitivity.mp.). In addition, we ran a hand search in the reference lists of all relevant articles and previous review articles to find additional studies. We also attempted to contact the authors of all the studies that met the inclusion criteria and we requested unpublished data and abstracts.

Study Selection and Definitions

In the present meta-analysis, the controlled studies assessing the administration of BMMSCs to rat or mouse models of neuropathic pain were included. Peripheral and central models of neuropathic pain induced by contusion, compression, transection, and ligation were studied. Original research studies about the influence of BMMSC transplantation, regardless of donor species or tissue origin, were included. Outcomes measured were the evaluation of allodynia [44] and hyperalgesia [45]. Control interventions consisted of placebo (saline, culture medium, or similar vehicle) or no treatment. Any manipulation of BMMSCs into neuron-like cells, coculture concomitant injection with other cell types, or use of adjuvant products (eg, matrices, scaffolding), and diabetic neuropathy lead to exclusion. In addition, review articles, commentaries, editorials, and letters were excluded.

Two authors (M.Y, H.A) independently appraised all potentially included studies. Any disagreement was resolved using the viewpoint of a third author (F.N). We included all the experimental studies regarding animals in any age, gender, or strain exposed to neuropathic pain induced by contusion, compression, transection, and ligation. Those that had poor quality were excluded.

Table 1
Characteristics of Studies Using Bone Marrow Stem Cells in Treatment of Neuropathic Pain

Author and Year	Sample Size	Method			Observation Time
		Species/Weight	Model/Intervention	Dose/Graft Type	
Neuhuber 2005	28 BMMSC/7 vehicle	Female Sprague-Dawley rats/225-250 g	Hemi-section/spinal cord delivery 2 wk after SCI in injury site	2×10^5 cell/xenogeneic	8 wk
Vaquero 2006	20 BMMSC/10 vehicle	Female adult Wistar rats/250-300 g	Contusion/spinal cord delivery 3 mo after SCI in T6-T8 level	3×10^6 cell/allogeneic	26 wk
Urdzikova 2006	15 BMMSC/15 vehicle	Male Wistar rats/300-330 g	Compression/intravenously 1 wk after injury	2×10^6 cell/allogeneic	4 wk
Lee 2007	8 BMMSC/8 vehicle	Male Sprague-Dawley rats/300-350 g	Contusion/spinal cord delivery 1 wk after SCI in T9 level	1×10^5 cell/xenogeneic	8 wk
Klass 2007	12 BMMSC/11 vehicle	Male Sprague-Dawley rats/250-300 g	CCI/intravenously immediately after injury	1×10^7 cell/allogeneic	10 days
Musolino 2007	8 BMMSC/8 vehicle	Male Sprague-Dawley rats/200-300 g	SLN/dorsal root ganglia immediately after injury	2×10^5 cell/allogeneic	8 wk
Amemori 2010	23 BMMSC/23 SCI	Male Wistar rat/270-300 g	Compression/spinal cord delivery 1 wk after SCI in T8 level	3×10^5 cell/allogeneic	8 wk
Guo 2011	16 BMMSC/11 vehicle	Male Sprague-Dawley rats/225-250 g	CCI-ION/injury site delivery 3 d after CCI	1.5×10^6 cell/allogeneic	22 wk
Siniscalco 2011	18 BMMSC/18 vehicle	Male CD-1 mice/35-40 g	SNL/tail vein delivery 4 d after injury	2×10^6 cell/xenogeneic	13 wk
Kumagai 2013	12 BMMSC/12 vehicle	female Fischer rats/180-200 g	Contusion/spinal cord delivery 1 wk after SCI in T8 level	4×10^5 cell/allogeneic	6 wk
Schäfer 2014	11 BMMSC/9 vehicle	Female Sprague-Dawley rats/225-250 g	partial SLN/spinal cord delivery 2 d after injury in injury site	3×10^6 cell/allogeneic	3 wk
Torres-Espin 2014	15 BMMSC/15 SCI	Female Sprague-Dawley rats/250-300 g	Contusion/spinal cord delivery 1 wk ($n = 7$) after SCI in T8 level	4.5×10^5 cell/allogeneic	6 wk
Zhang 2014	10 BMMSC/10 vehicle	Male Sprague-Dawley rats/180-200 g	SNL/intrathecal delivery 1 wk after SNL in L5-L6 level	1×10^5 cell/allogeneic	17 d
Yousefifard 2014	10 BMMSC/10 vehicle	Male Wistar rats/140-160 g	Compression/spinal cord delivery 1wk after SCI in T6-T8 level	1×10^6 cell/allogeneic	8 wk

SCI indicates spinal cord injury; CCI, chronic constriction injury; SLN, single ligature nerve constriction; ION, infraorbital nerve; SNL, spinal nerve ligation.

Quality Assessment

Two reviewers (M.Y, H.A) independently evaluated each study and allocated them a quality rating of "good," "fair," or "poor." Quality assessment was conducted to evaluate the impact of methodological quality on the reported outcomes, accounting for study design and presence of bias, including performance, recording, and reporting bias. In this regard, adequacy of randomization and concealment of allocation, blinding of study personnel and outcome assessors, and registered sample size estimations or power calculations were assessed (inter-rater reliability was 91%). Disagreements were discussed with a third reviewer (F.N).

Data Synthesis

The following data were collected and recorded: recipient animal (species, strain, sex, weight), type of neuropathy (contusion, compression, transection, and ligation), type of graft (autologous, syngeneic, allogeneic, or xenogeneic), intervention regimen (time from inducing the neuropathic pain to cell transplantation, delivery route, number of injections, and total number of transplanted cells), immunosuppressive usage, methodological quality, observation (follow-up) time, and main findings.

Statistical Analysis

Statistical analysis was performed using Stata software, version 12.0 (Stata Corp, College Station, TX). Effect sizes were computed and the standardized mean difference (SMD) with 95% confidence interval (CI) was entered in all analyses using Hedges' g. By calculating the effect size, pooling the findings and modifying the bias caused by small sample size were possible [43,46]. The authors were contacted if mean values and standard deviations (SD) were not reported. In case of no response, an estimation method was used for the calculation of mean values and SD [47,48]. If the information was reported as graphs, data were extracted from the graphs using the method recommended by Sistrom and Mergo [48]. If the therapeutic effect of different numbers of cells in therapy was reported, the highest number was included in the analysis. In addition, the mean and SD of the latest time of follow-up period of included studies were used.

Based on the experimental diversity between the studies, random-effects models or fixed-effects models were used for data analysis. Random-effects models were used in the presence of heterogeneity, and in the absence of heterogeneity, fixed-effects models were used. Statistical heterogeneity was measured using the I^2 and chi-square tests. In this regard, $P < .10$ was the representative of significant statistical heterogeneity [49]. Sensitivity and subgroup analyses were performed to investigate expected or measured heterogeneity and applied based on a multivariate meta-regression model. All possible causes of heterogeneity including the animal gender (male/female), type of neuropathy (central or peripheral nervous system), delivery route (spinal, intravenous, and dorsal root ganglia), graft type (xenogeneic, allogeneic), time between injury and intervention (equal and fewer than 4 days/more than 4 days), number of transplanted cells (less than 3×10^6 cell dose/kg and more than or equal to 3×10^6 cell dose/kg), and follow-up period (fewer than 8 weeks and equal to or more than 8 weeks) were included as covariates in the meta-regression model. Publication bias was assessed using funnel plots and formal Egger's and Begg's tests [50]. A 2-sided P value $< .05$ was considered statistically significant.

RESULTS

We found 2158 nonduplicate articles using the search strategies described earlier. Of these, 136 potentially relevant papers were screened. Finally, 13 full-text articles were included for the meta-analysis and were studied in detail [6,22-24,33-41] (Table 1). In addition, 1 eligible unpublished set of data, which were obtained from an experiment in our lab, were included in the analysis (unpublished data, F. Nasirinezhad, July 2015). In this study Mean (standard deviation) of heat hyperalgesia in BMMSCs treated and control groups were 20.2 (6.8) seconds and 9.7 (3.1) seconds, receptively (10 rats per each groups). In addition, these

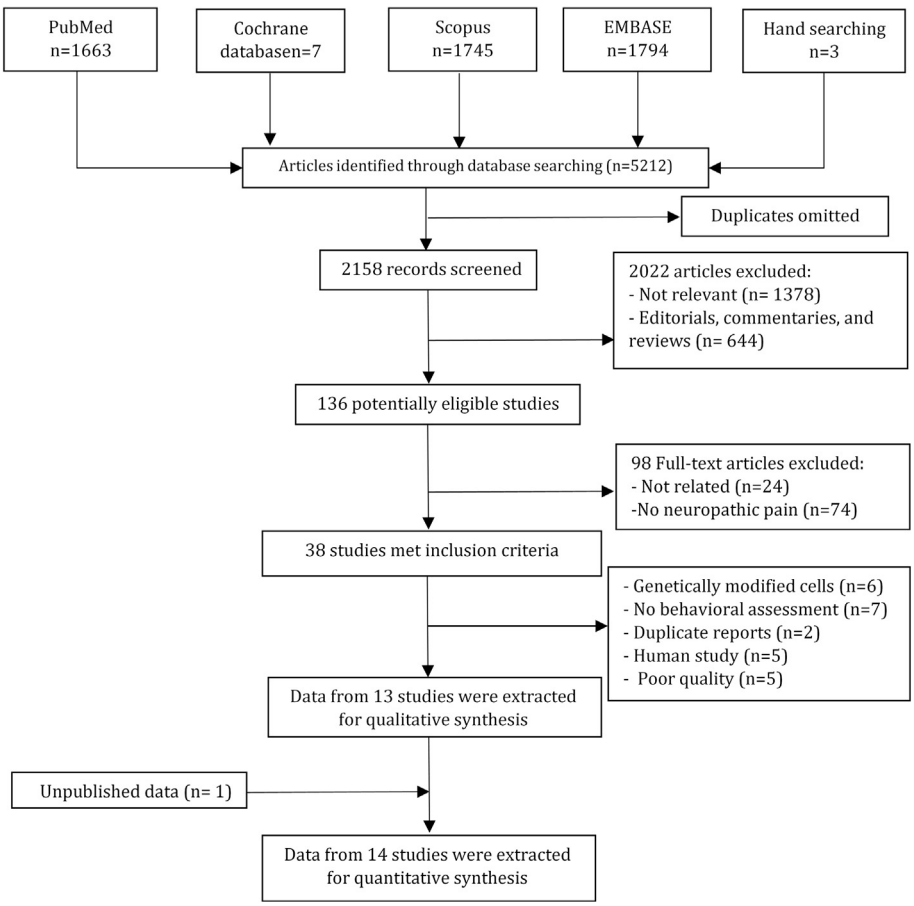

Figure 1. Flow chart of the study.

values for mechanical allodynia were 13.2 (2.27) grams and 7.1 (2.7) grams, respectively. The flow of information from identification to inclusion of studies is summarized in Figure 1. These citations contained a total of 373 rats/mice including 206 BMMSC-treated animals and 167 controls. Of the 14 articles, 4 reported only the impact of BMMSCs transplantation on hyperalgesia [22,35,39,40] and 4 assessed its effect on allodynia [23,33,34,41]. Six articles evaluated the effect on both [6,24,36-38].

Heterogeneity and Publication Bias

According to the result of subgroup analysis of the therapeutic effect of BMMSCs, a significant statistical heterogeneity was found on neuropathic pain, except regarding delivery route ($I^2 = .0\%$; $P = .74$). Therefore, in this case a fixed-effects model was used, whereas other analyses were performed using a random-effects model. No publication bias was observed among the included studies (Tables 2 and 3). In addition, we were not able to calculate the pooled-effect size in xenogeneic graft of BMMSCs because eligible related studies were few (2 studies).

Meta-Analysis

The main outcome measure was the assessment of hyperalgesia and allodynia. According to our analysis, using the random-effects model, BMMSC transplantation leads to a statistically significant improvement on allodynia (SMD = 2.06; 95% CI, 1.09 to 3.03; $I^2 = 99.7\%$; $P < .001$) but does not have a significant effect on hyperalgesia (SMD = .3; 95% CI, −1.09 to 1.68; $I^2 = 100\%$; $P < .001$) (Figures 2 and 3).

Subgroup Analyses

Subgroup analyses were performed based on animal gender, type of neuropathy, randomization, blinding of observer, stem cell delivery route, xenogeneic or allogeneic transplantation, use of immunosuppressive agents, time between injury and intervention, number of transplanted cells, and follow-up periods.

Allodynia

Table 2 presents the subgroup analysis of allodynia. Multivariate meta-regression showed that the type of neuropathy ($P = .036$), time between injury and intervention

Table 2
Subgroup Analyses of the Effect of BMMSC on Mechanical Allodynia

Characteristic	*P* for Bias*	Model	*P* (I^2)†	Effect Size‡ (95% CI)	*P*
Gender					
Male	.34	REM	<.001 (99.3%)	2.45 (1.69-3.2)	<.001
Female	.19	REM	<.001 (99.6%)	1.16 (−.58-2.90)	.19
Overall significance test among subgroups					.49
Type of neuropathy					
Central	.45	REM	<.001 (96.1%)	1.0 (.28-1.71)	.006
Peripheral	.73	REM	<.001 (99.7%)	2.06 (1.09-3.03)	<.001
Overall significance test among subgroups					.036
Randomization					
No	.33	REM	<.001 (99.8%)	2.05 (.74-3.35)	.002
Yes	.76	REM	<.001 (89.7%)	2.36 (1.44-3.17)	<.001
Overall significance test among subgroups					.17
Blinding the outcome assessment					
No	.49	REM	<.001 (99.8%)	1.82 (−.10-3.73)	.06
Yes	.64	REM	<.001 (99.4%)	2.26 (1.33-3.19)	<.001
Overall significance test among subgroups					.37
Delivery route					
Spinal	.14	REM	<.001 (99.0%)	1.32 (.35-2.28)	.007
Intravenous	.23	REM	<.001 (99.4%)	3.53 (2.59-4.47)	<.001
DRG	.65	FEM	.74 (.0%)	3.02 (2.92-3.12)	<.001
Overall significance test among subgroups					.255
Graft type					
Xenogeneic	.32	REM	<.001 (99.9%)	2.33 (−.98-5.63)	.17
Allogeneic	.61	REM	<.001 (99.7%)	1.99 (.96-3.02)	<.001
Overall significance test among subgroups					.99
Use of immunosuppressive agents					
No	NA	NA	NA	NA	NA
Yes	.73	REM	<.001 (99.7%)	2.23 (1.22-3.25)	<.001
Overall significance test among subgroups					NA
Time between injury and intervention§					
Less than 4 d	.28	REM	<.001 (98.9%)	3.1 (2.53-3.68)	<.001
More than 4 d	.13	REM	<.001 (95.6%)	1.08 (.44-1.72)	.001
Overall significance test among subgroups					.02
Number of transplanted cells					
Less than 3×10^6 cell dose/kg	.33	REM	<.001 (86.9%)	.81 (.35-1.26)	<.001
More than or equal to 3×10^6 cell dose/kg	.52	REM	<.001 (98.9%)	2.98 (2.43-3.54)	<.001
Overall significance test among subgroups					.023
Follow-up period					
Less than 8 wk	.19	REM	<.001 (99.7%)	1.6 (.14-3.06)	<.001
More than or equal to 8 wk	.73	REM	<.001 (99.5%)	2.54 (1.41-3.66)	<.001
Overall significance test among subgroups					.72

REM indicates random-effect model; FEM, fixed-effect model; DRG, dorsal root ganglia; NA, not applicable.
* Publication bias based on Begg's and Egger's test.
† Heterogeneity among studies.
‡ Standardized mean difference.
§ Categorization was done based on median of time between injury and intervention in included studies.

Table 3
Subgroup Analyses of the Effect BMMSC on Heat Hyperalgesia

Characteristic	*P* for Bias*	Model	*P* (I^2)†	Effect Size‡ (95% CI)	*P*
Gender					
Male	.37	REM	<.001 (99.8%)	1.24 (−.74-3.22)	.22
Female	.78	REM	<.001 (99.9%)	.64 (−2.87-1.60)	.58
Overall significance test among subgroups					.90
Randomization					
No	.29	REM	<.001 (10.0%)	−.005 (−2.12-1.10)	.99
Yes	.70	REM	<.001 (97.9%)	.78 (−1.27-2.82)	.45
Overall significance test among subgroups					.86
Blinding the outcome assessment					
No	.53	REM	<.001 (100.0%)	−.61 (−3.62-2.41)	.69
Yes	.80	REM	<.001 (99.9%)	1.22 (−1.05-3.49)	.29
Overall significance test among subgroups					.37
Type of neuropathy					
Central	.44	REM	<.001 (99.8%)	−.72 (−2.78-1.35)	.50
Peripheral	.49	REM	<.001 (99.7%)	2.65 (.68-4.61)	.008
Overall significance test among subgroups					.722
Delivery route					
Spinal	.20	REM	<.001 (99.9%)	−.4 (−2.23-1.42)	.66
Intravenous	.49	REM	<.001 (99.8%)	1.96 (.04-3.95)	.054
Overall significance test among subgroups					.765
Graft type§					
Xenogeneic	NA	NA	NA	NA	NA
Allogeneic	.79	REM	<.001 (99.9%)	−.22 (−1.63-1.20)	.77
Overall significance test among subgroups					NA
Use of immunosuppressive agents					
No	.69	REM	.01 (83.0%)	−.78 (−2.1-.56)	.25
Yes	.88	REM	<.001 (99.9%)	.57 (−.98-2.10)	.47
Overall significance test among subgroups					.79
Time between injury and intervention[d]					
Less than 4 d	.11	REM	<.001 (99.9%)	2.65 (.68-4.61)	.008
More than 4 d	.13	REM	<.001 (99.8%)	−.72 (−2.78-1.35)	.50
Overall significance test among subgroups					.022
Number of transplanted cells					
Less than 3×10^6 cell dose/kg	.12	REM	<.001 (98.2%)	−.31 (−1.54-.91)	.62
More than or equal to 3×10^6 cell dose/kg	.80	REM	<.001 (100.0%)	.69 (−1.28-2.66)	.49
Overall significance test among subgroups					.99
Follow-up period					
Less than 8 wk	.11	REM	<.001 (98.2%)	.16 (−4.56-4.88)	.30
More than or equal to 8 wk	.59	REM	<.001 (99.8%)	.50 (−.44-1.44)	.95
Overall significance test among subgroups					.99

* Publication bias based on Begg's and Egger's test.
† Heterogeneity among studies.
‡ Standardized mean difference.
§ Categorization was done based on median of time between injury and intervention in included studies.

($P = .02$), and the number of transplanted cells ($P = .023$) influence the improvement of allodynia after BMMSC transplantation. The effect sizes of BMMSC transplantation on central and peripheral neuropathy were 1.0 (95% CI, .28 to 1.71) and 1.16 (95% CI, 1.09 to 3.03), respectively. The analysis showed that the effect of BMMSC transplantation on allodynia was greater in the peripheral model ($P = .036$). Time between injury and intervention were categorized based on 4 days. Subgroup analysis showed that stem cell therapy during first 4 days (effect size = 3.1; 95% CI, 2.53 to 3.68) is more effective than after 4 days (effect size = 1.08; 95% CI, .44 to 1.72) ($P = .02$). In addition, multivariate meta-regression depicts stem cell therapy with a dose of more than or equal to 3×10^6 cell dose/kg (effect size = 2.98; 95% CI, 2.43 to 3.54) is more effective than cell therapy with dose of less than 3×10^6 cell dose/kg (effect size = 2.98; 95% CI, 2.43 to 3.54) ($P = .023$).

Hyperalgesia

Multivariate meta-regression showed that cell therapy correlated with more improvement in hyperalgesia if it occurred during first 4 days after injury ($P = .02$). Stem cell therapy during first 4 days (effect size = 2.65; 95% CI, .68 to 4.61) is more effective than after 4 days (effect size = −.72; 95% CI, 2.78 to 1.35) ($P = .02$). Table 3 presents the subgroup analysis of the effect of stem cell therapy on hyperalgesia.

DISCUSSION

Meta-analyses of animal studies provide practical evidence for researchers regarding advantages and side effects of an intervention to help them decide to proceed with clinical trials or not. Based on our knowledge, the present study is the first quantitative meta-analytic approach to review all of the available evidence regarding the efficacy of BMMSCs in improving neuropathic pain. The analyses showed that BMMSC transplantation leads to a statistically significant improvement on allodynia but does not have a significant effect on hyperalgesia. We found significant diversity between the studies. Therefore, subgroup analysis was performed to assess possible sources of the heterogeneity. Based on this analysis, type of neuropathy (central or peripheral), time from injury to intervention, and the number of transplanted cells were the most important causes of the heterogeneity. In addition, among 14 included articles, 1 paper assessed the stem cell therapy in a mouse model [37]. Subgroup analysis was not performed based on animal species because of the small number of included studies. However, in the mentioned study, there was the strongest effect

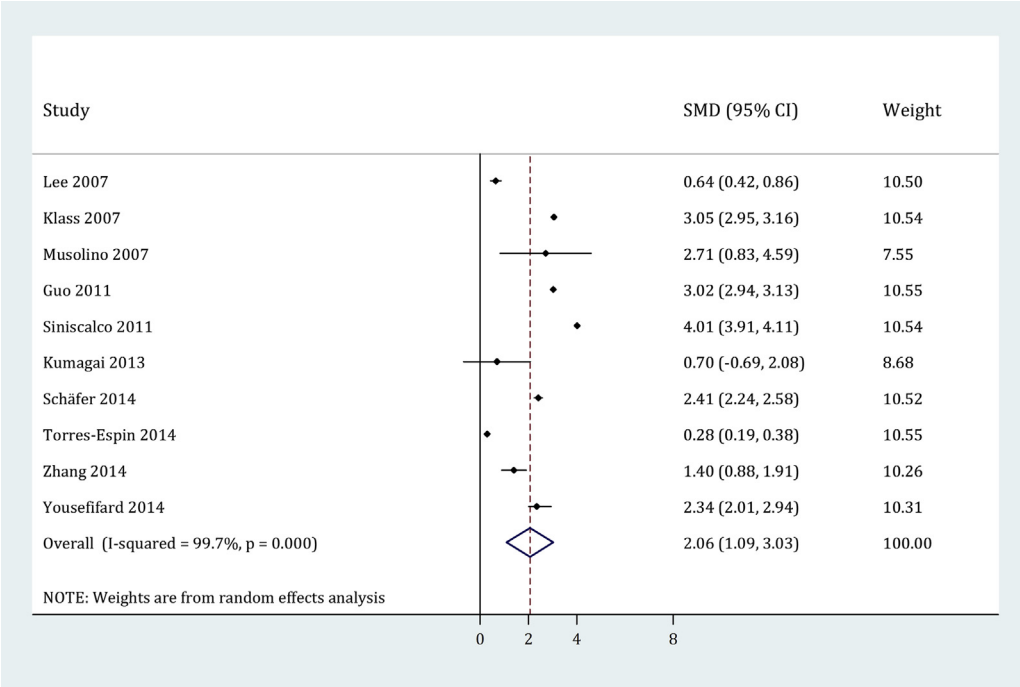

Figure 2. The effect of BMMSC transplantation on mechanical allodynia.

seen on allodynia and hyperalgesia. Therefore, there may be a species difference between rat and mouse. Further studies are required to confirm this hypothesis.

Currently, there are 2 experimental animal models of neuropathic pain, including peripheral and central models [51-53]. Subgroup analysis showed that BMMSC transplantation leads to more improvement in allodynia induced in the peripheral model compared with in the central model. This finding is partly due to the different mechanism of neuropathic pain in the central and peripheral models. In peripheral models, altered ion channel expression triggers enhanced membrane resonance, rhythmogenesis, and ectopic spiking with increased cellular excitability, which are the most important mechanisms of inducing the neuropathic pain. Sprouting of myelinated nerve fibers into lamina II, increased glutamate release, evoking fast

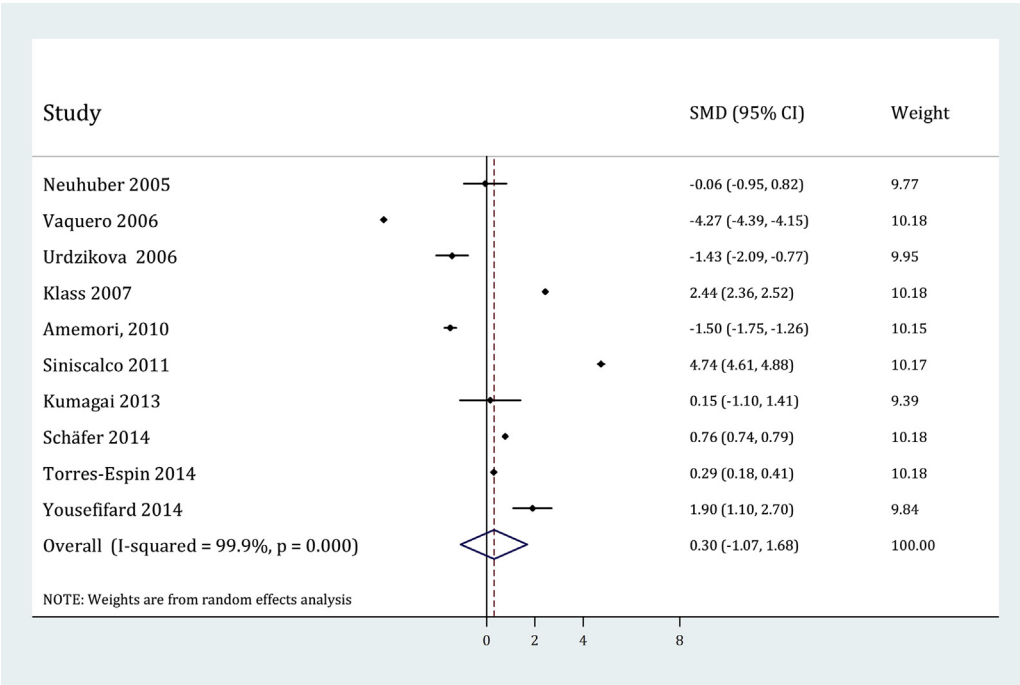

Figure 3. The effect of BMMSC transplantation on heat hyperalgesia.

excitatory synaptic potentials, expression of brain-derived neurotrophic factor and substance P, neuroplasticity changes in central pain descending regulatory systems, and astrocytes and glial cell activation are the most important mechanisms in central models. BMMSC transplantation provides a protective effect for the host cells. Efficacy of this supportive role may be greater in reversing the pathophysiological changes in the peripheral model [54-56].

The development of secondary spinal cord damage sets in the early minutes after injury and continues for weeks or months. The mechanisms involved in secondary spinal cord damage consist of apoptosis, astroglial scar launch, central cavitation, central chromatolysis, compression and vertebral column instability, deficient expression of myelin associated genes after spinal cord injury, demyelination of residual axons, derangements in ionic homeostasis, glutamatergic excitotoxicity, immune cells invasion and release of cytokines, inflammation, and ischemia/reperfusion-induced endothelial damage, etc. [57]. BMMSCs have immunomodulatory properties [18,58-60] and, when administered at the right time, may help in minimizing neural inflammation and immune-mediated injuries. Early cell therapy might decrease proliferation or hypertrophy of glial cells (gliosis) and enhance recovery by bioactive molecules, modulation of cytokine production, and growth factors. Also, the angiogenic effect of these cells may help the revascularization of spinal cord [61,62]. In this regard, our findings also showed that onset of stem cell therapy during the first days after injury (fewer than 4 days) causes more improvement in allodynia and hyperalgesia. Accordingly, it seems rational to suggest that the optimal time point for transplantation is fewer than 4 days after the lesion. A similar result was reported in another systematic review, which stated that the optimal time point for transplantation of stem cells in spinal cord injury is 3 days after the lesion for intralesional site and 5 to 7 days for intrathecal injection [63].

Median stem cell transplantation dose in the eligible studies was 2.25×10^6 cells/kg. We categorized the number of transplanted cells into 2 groups (based on 3×10^6 cell dose/kg). This cut point was selected because it is near the typical number of transplanted cells currently administrated in clinical trials (1 to 3×10^6 cell dose/kg) [29,64,65]. Our result demonstrated that stem cell therapy in doses of 3×10^6 or higher is associated with greater improvement in allodynia. The correlation between the number of transplanted cells and recovery after spinal cord injury was reported in 2 studies. The studies demonstrated a dose-dependent influence of BMMSCs on recovery after spinal cord injury [66,67]. BMMSCs display immunosuppressive properties in a dose-dependent manner [58,68]. Subsequently, the development of secondary damage was reduced and survival rate of transplanted cells increased.

Strengths and Limitations

In the present study, 3 points have improved the quality of our meta-analysis. First, we assessed both central and peripheral models of neuropathic pain. Second, we calculated SMDs as the effect size estimate using Hedges' g to compare across articles and to correct for bias caused by small sample size. Third, subgroup analysis was performed stratified by animal gender, type of neuropathy, delivery route, graft type, time between injury and intervention, number of transplanted cells, and follow-up period, because heterogeneity is expected in most meta-analyses. In addition, we conducted an extensive search and used a comprehensive analytical approach that allowed the inclusion of studies presenting not only means and SD, but also other values, such as medians, thus improving the exhaustiveness of the results.

Our review and meta-analysis have a number of limitations. First, some of the original studies did not describe the blinding status of the observer. Moreover, residual confounding (confounding from unknown variables), as in meta-analyses, may introduce considerable bias, and the direction of this bias is unpredictable. Second, the possible source of heterogeneity between the studies was not clear. Therefore, it was decided to use a random-effects model, which gave more conservative results. In addition, we ran a meta-regression and stratified meta-analysis by partitioning of heterogeneity.

CONCLUSION

The present systematic review with meta-analysis seem to suggest that BMMSC transplantation improved allodynia but had no significant effect on hyperalgesia. The effectiveness of BMMSCs on neuropathic pain is higher if they are transplanted for peripheral pain, in fewer than 4 days, and in a dose of equal to or more than 3×10^6 cells per kg.

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