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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

Mostafa Hosseini [1], Mahmoud Yousefifard [2], Heidar Aziznejad [3], Farinaz Nasirinezhad [4,*]

[1] Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Physiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[3] The Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran
[4] Physiology Research Center, Department of Physiology, Iran University of Medical Sciences, Tehran, Iran

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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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* Correspondence and reprint requests: Farinaz Nasirinezhad, Physiology Research Center, Department of Physiology, Iran University of Medical Sciences, Shahid Hemmat Highway, Tehran, Iran.
E-mail address: nasirinezhad.f@iums.ac.ir (F. Nasirinezhad).

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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.