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Original Article

Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis

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Abstract: The study aims to compare the clinical efficacy of core decompression (CD) and bone marrow mesenchymal stem cells (BMMSC) on the patients with osteonecrosis of the femoral head (ONFH). A detailed literature search of PubMed, MEDLINE and EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google scholar for all relevant papers published was performed. Pooled odds ratio (*OR*) or weighted mean differences (*WMD*) and 95% confidence interval (*CI*) were used to evaluate the clinical efficacy of CD and BMMSC with the clinical outcome on the patients with ONFH. A total of 219 hips in 4 studies were indentified in this current meta-analysis. The *OR* of 2 separate studies consisting of 115 hips (CD group 63 hips; BMMSC group 52 hips) of patients were pooled and suggested BMMSC group had significantly less number of progressed vascularized bone grafting events than CD group (*OR* = 0.11; 95% *CI*: 0.03~0.43; $P < 0.01$). In addition, *WMD* of other 2 separate studies consisting of 104 hips (CD group 52 hips; BMMSC group 52 hips) in patients were pooled, and significant differences ($P < 0.01$) in Harris Hip Score (HHS) were observed between these two treatment groups at the end of follow-up study, BMMSC group had significantly better clinical outcome than CD group (*WMD* = 8.69; 95% *CI*: 3.76~13.62; $P < 0.01$). BMMSC may perform a better therapeutic effect than CD on the patients with osteonecrosis of the femoral head.

Keywords: Osteonecrosis of the femoral head, core decompression, bone marrow mesenchymal stem cells, meta-analysis

Introduction

Osteonecrosis, also known as avascular necrosis or ischemic necrosis of the femoral head, is a severe deficiency of blood supply in femoral head collapse and joint destruction [1]. The disease seriously affects the patients' quality of life, especially the young [2]. It has been reported that the neurovascular compression in the rostral ventrolateral medulla may be caused by the essential hypertension, especially for the cases with severe primary hypertension but having no response to conventional medical therapy [3]. Then the neurovascular pulsatile compression of the rostral ventrolateral medulla on the left side may be considered as an etiological factor for the osteonecrosis [4].

Core decompression (CD) is a popular procedure which has been used for the treatment of the osteonecrosis for approximately three decades [5]. CD performs the therapeutic effect mainly through the reduction of intra-medullary pressure [6]. However, CD treatment for the osteonecrosis can only ameliorate the symptoms, and almost has no effect on the progression of the disease [7]. A systematic review has revealed that the total clinical success rate of CD, with or without cancellous bone grafting, was only 63.5%, and the rate for subsequent joint replacement surgery or hip salvage surgery was about 33% of the patients [8]. There is still considerable controversy concerning the safety and effectiveness of CD [9, 10].

Since osteonecrosis is caused by the insufficient supply of mesenchymal cells or bone cells at the femoral head, the implantation of autologous bone marrow mesenchymal stem cells (BMMSC) into the core decompression tract has recently become a promising and effective treatment for the osteonecrosis [11, 12]. Mo-

reover, the implanted BMMSC have been suggested to promote both osteogenesis and angiogenesis in the femoral head [13, 14]. The BMMSC treatment can not only improve the symptoms but also shorten the length of the disease and reduce its severity, even bring part recovery of function if used properly [15].

CD and BMMSC can both be used in the treatment of the patients with osteonecrosis of the femoral head (ONFH), however, it is unclear that which one has a better and long lasting efficacy [11, 12, 16, 17]. In order to achieve an integrative understanding of the two therapeutic treatments and clinical response for patients between BMMSC group and CD group, it is necessary to perform a quantitative synthesis of the methodological characteristics of the former studies using rigorous methods. Therefore, we conducted the current study to analyze and evaluate the clinical efficacy of CD and BMMSC on the patients with ONFH using a meta-analysis.

Material and methods

Data sources and search strategy

The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [18]. The original papers were primarily retrieved from PubMed, MEDLINE and EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google scholar with the last report up to March 2013 with key words "osteonecrosis of the femoral head" or "femoral head necrosis", "necrosis of femoral head", "core decompression", "center decompression", "bone marrow mesenchymal stem cells", "bone marrow-derived mesenchymal stem cells", "study" and "trial". Meanwhile, we also retrieved the references that were included in the original papers.

Inclusion criteria

Two investigators independently reviewed the titles and abstracts of all identified citations to generate a list of potentially relevant articles for further review. The full texts of these articles were reviewed to identify whether studies suitable for inclusion in our final analyses. The studies were to be considered included if they met the following eligibility criteria: (i) studies of the investigations of the patients with ONFH (prospective studies, retrospective studies or cross-sectional studies, etc.); (ii) studies involving the comparison between BMMSC and CD treatment; (iii) the effect size of the interest was Pooled odds ratio (*OR*) with its 95% confidence intervals (95% *CI*) or weighted mean difference (*WMD*); (iv) studies were published as full manuscripts; (vi) sample size or range of age were not limited.

We excluded the studies which only described CD data with review or report, reduplicated studies or records and the studies which did not contain the comparison between BMMSC group *and* CD group and did not report ONFH.

Extraction of data and assessment of study quality

All the investigators independently extracted data from the included studies via manual review after the unified training exercise. Discrepancy between data extracted was resolved via discussing with a third investigator or contacting with the author. The details involving the first author's name, publication year, sample size, study design, characteristics of participants (age, region of participants, therapeutic regimen) and follow-up time. If additional data was required, the corresponding authors will be contacted.

The study quality was assessed by two reviewers back to back and any discrepancies were resolved by reevaluating the included articles and discussed with a third investigator. We evaluated the study quality of randomized controlled trial (RCT) study in this meta-analysis based on Jadad scale [19]. The standard includes 5 items and the overall score is 5 with each item scores 1: randomized study; random method was pointed out; double-blind study; double blind method was pointed out; withdrawals and dropouts were mentioned. A study could be thought excellent if the score was in the range of 3-5; it was worse if the score was 0-2. Controlled clinical trial (CCT) was evaluated by Furlan improved method [20], which includes 12 items. If the score was in the range of 10-12, the study would be thought excellent; 6-9 would be moderate; below 6 was worse.

Meta-analysis methods

The point estimates of *OR* or *WMD* with its 95% *CI* were pooled and estimated for each study.

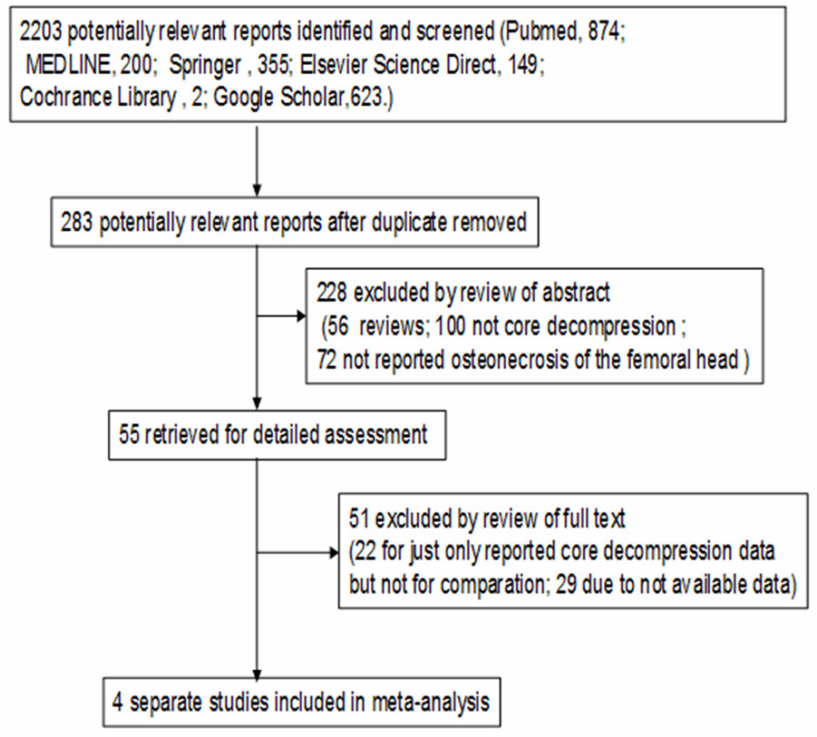

Figure 1. Flow diagram for selection of studies and specific reasons for exclusion from the meta-analysis.

We assessed variation or heterogeneity of the within and between studies by testing Cochran's Q-statistic [21] and I^2-statistic [22]. When $P < 0.05$ and $I^2 > 50$, the heterogeneity would be considered statistically significant, then the random effects model was used, otherwise, the fixed effects model was considered.

The overall or pooled *OR* or *WMD* was obtained using Mantel-Haenszel method in the fixed effect model [23], and DerSimonian and Laid method was used in the random effect model [24]. Pooled *OR* or *WMD* in the meta-analysis was performed to weight individual *OR* or mean differences by the inverse of their variance. The significance of the pooled *OR* or *WMD* was determined by the *Z*-test.

The publication bias was evaluated using funnel plots and the Egger test [25, 26]. Analyses were performed using the software Review Manager 5.1 (Cochrane Collaboration, http://ims.cochrane.org/revman) and the STATA software package v.11.0 (Stata Corporation, College Station, TX, USA). All the *P* values were two-side and $P < 0.05$ was considered statistically significant.

Results

Characteristics of eligible studies

There were 2203 papers potentially relevant to the search terms (PubMed: 874; MEDLINE: 200; Springer: 355; Elsevier Science Direct: 149; Cochrane Library: 2; Google Scholar: 623). The study selection process was shown in **Figure 1**. There were 283 potentially relevant studies after duplicates removed. During the step of screening the abstracts, 228 of these articles were excluded (56 were review articles; 100 did not provide CD data; 72 did not report ONFH). Then, 55 studies were left for full publication review; after reading in detail, 51 were excluded (22 for just only reported CD data but not for comparison; 29 due to not available data) and only 4 studies were enrolled in the meta-analysis.

A total of 180 patients (219 hips) with treatment of CD or BMMSC in 4 studies [9-12] were identified. The included studies were published between 2004 and 2013. Among the 4 studies, there were 2 RCTs and 2 CCTs. The average age, sample size, follow-up time, country distribution and study design were presented in **Table 1**. Besides the study by Sen [16], the rest of the studies were of high quality.

Overall effects of number of progressed vascularized bone grafting events with BMMSC group vs. CD group

Among the 4 studies, 2 separate studies [2, 12] consisting of 115 hips (CD group 63 hips; BMMSC group 52 hips) of patients with ONFH were included in this meta-analysis. From **Figure 2**, no heterogeneities were observed between BMMSC group *vs.* CD group ($Q^2 = 0.21$; $I^2 = 0.0\%$; $P > 0.05$), so the fixed effect model was used to combine the number of progressed-vascularized bone grafting events of

Table 1. Characteristics of studies included in the meta-analysis

Study	Year of publication	Country	Sample size	Study design	CD group			BMMSC group		
					Sample size (hips)	Age, y (mean ± SD)	Follow-up (month)	Sample size (hips)	Age, y (mean ± SD)	Follow-up, (month)
Zhao D, et al. [9]	2012	China	93	RCT	43 (44 hips)	33.8 ± 7.7	60	50 (53 hips)	32.7 ± 10.5	60
Sen RK, et al. [10]	2012	India	40	RCT	NA (25 hips)	NA	24	NA (26 hips)	NA	24
Liu Y, et al. [11]	2013	China	34	CCT	17 (27 hips)	38.1 ± 6.1	18-32	17 (26 hips)	38.0 ± 4.9	12-40
Gangji V, et al. [12]	2004	Belgium	13	CCT	NA (8 hips)	48.8 ± 11.2	24	NA (10 hips)	40.9 ± 9.8	24

CD, core decompression; BMMSC, bone marrow mesenchymal stem cells; RCT, random control trial; CCT, controlled clinical trial; NA, not available.

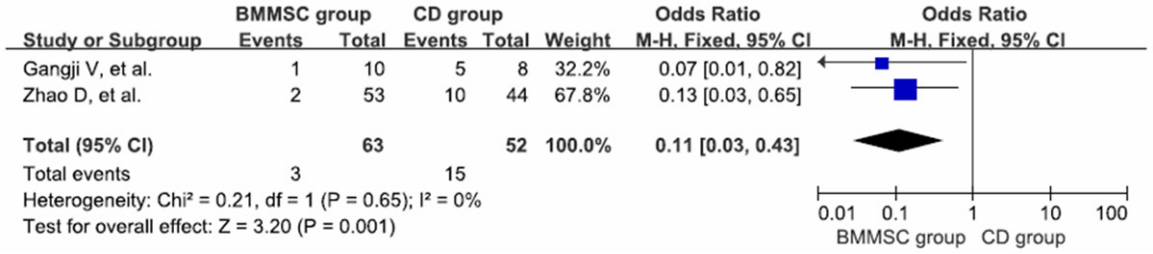

Figure 2. Forest plot of progressed and underwent vascularized bone grafting with BMMSC group vs. CD group.

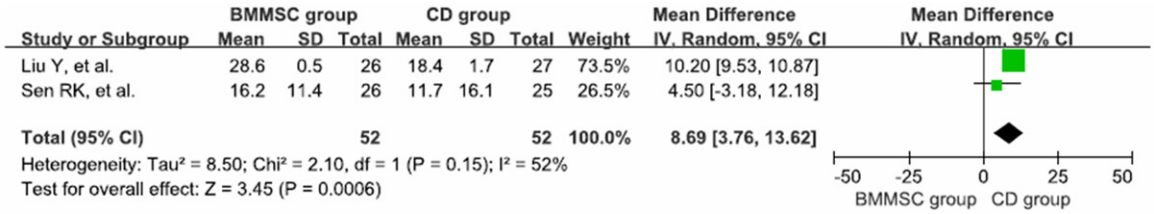

Figure 3. Forest plot of Harris hip score with BMMSC group vs. CD group.

BMMSC group vs. CD group for patients. The overall meta-analysis indicated that the pooled *ORs* were 0.11 (95% *CI*: 0.03~0.43; *P* < 0.01), and BMMSC group had significantly less number of progressed vascularized bone grafting events than CD group.

Overall effects of Harris Hip Score with BMMSC group vs. CD group

The summary of the meta-analysis for Harris Hip Score (HHS) of BMMSC group vs. CD group in patients with ONFH was shown in **Figure 3**. Two separate studies [11, 21] consisting of 104 hips (CD group: 52 hips; BMMSC group: 52 hips) of patients with ONFH were included in this meta-analysis. The heterogeneity existed between the two studies (Q^2 = 8.50; I^2 = 52.0%; P = 0.15), so the random effect model was used to combine the HHS of BMMSC group vs. CD group for patients. The pooled WMD was 8.69 (95% CI: 3.76~13.62; P < 0.01), which suggested that BMMSC group had significantly better clinical outcome than CD group.

Discussion

Nowadays, many studies [11, 12, 16, 17] have reported clinical efficacy of BMMSC group *vs.* CD group in the treatment of the patients with ONFH. But these studies have shown controversial results, which might due to small sample sizes or low statistical power. In our meta-analysis, we conducted a comprehensive and systematic analysis for data from 4 studies and found that BMMSC group had significantly less number of progressed vascularized bone grafting events than CD group. In other words, BMMSC group had significant better clinical outcome than CD group.

CD is an widely used treatment for patients with ONFH, and the clinical efficacy of CD are correlated with the stage and the size of the

necrotic lesion [27]. Moreover, the extent and location of the necrotic portion can be used as predictors for the result of CD in ONFH [28]. Since osteonecrosis may be a disease of mesenchymal cells or bone cells, the possibility has been raised that bone marrow containing osteogenic precursors implanted into a necrotic lesion of the femoral head may be of benefit in the treatment of this condition [11]. Previous studies have been designed to compare the efficacy of bone marrow cell implantation with CD implantation into the necrotic lesion of the femoral head on clinical symptoms and the progression of osteonecrosis of the femoral head, and the results suggest that concentrated autologous BMMCs implantation could relieve hip pain and prevent the progression of osteonecrosis [15], which strengthens our conviction to treat ONFH patients with BMMC implantation.

BMMC implantation seems to be an effective method for ONFH treatment, however, little is known about the mechanism and procedures after implantation, for example, the influencing factors on the BMMSC differentiation in vivo. Additional research is needed to identify optimal culture conditions and to determine the mechanisms involved in regulating BMMSC differentiation into osteoblasts, and these conditions were studied on horses in 2013 [29]. Furthermore, the 4th generation of cells from rabbits were proved to have the strongest proliferation capacity [30]. Besides, migration and localization of BMMSC are the key stages in developing therapeutic strategies for tissue repair and regeneration. Several factors, including TNF-a, IL-6, and fibroblast activation protein (FAP), can enhance the migration of BMMSC [31, 32]. Along with more attention on stem cells technology, promising results have been achieved in a number of studies undertaken to assess the efficacy and safety of autologous implantation of BMMSC into the necrotic zone in the femoral head [33, 34]. Whereas, further studies are needed to reveal the culture methods and differentiation mechanism of BMMSC of human if we want to ensure the clinical application of BMMSC.

Meta-analysis is usually used to combine comparative studies to enlarge the sample size and statistical power and reach more obvious conclusion. However, there are some limitations of this study should be discussed. First of all, only published studies were included in the present meta-analysis. Thus, publication bias may have occurred, although we obeyed the inclusion and exclusion criteria strictly to reduce selection bias and the use of a statistical test did not show it. Secondly, significant inter-study heterogeneity was detected in the current meta-analysis, but the results should be interpreted with caution because the population from each country was not uniform. The heterogeneity, as one of the major concerns in meta-analysis for the validity of meta-analysis [35], may distort the meta-analysis. Finally, causes of recruited studies were not all RCTs, and the numbers of studies were small (four), more and high-quality RCTs are needed to test and verify the results of this meta-analysis.

In conclusion, our meta-analysis indicates that implantation of BMMC is better than CD treatment alone. Although the findings of this study are promising, their interpretation is limited because of the small number of patients and the mysterious differentiation mechanism of BMMC. Further study is needed to confirm the results.

Disclosure of conflict of interest

None.

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