International Orthopaedics (2018) 42:2737–2743
https://doi.org/10.1007/s00264-018-3977-9

ORIGINAL PAPER

No differences in the efficacy among various core decompression modalities and non-operative treatment: a network meta-analysis

Byung-Ho Yoon[1] · Young-Kyun Lee[2] · Ki-Choul Kim[3] · Yong-Chan Ha[4] · Kyung-Hoi Koo[2]

Received: 27 February 2018 / Accepted: 4 May 2018 / Published online: 31 May 2018

Abstract

Background Core decompression (CD) has been used to treat early-stage (pre-collapse) osteonecrosis of the femoral head (ONFH) in an attempt to prevent collapse. Recently, other adjunctive treatments including bone grafting (BG) and bone marrow mononuclear cells (BMMC) were combined to traditional CD to improve the results. We assessed the efficacy of various CD modalities and non-operative treatment through a network meta-analysis (NMA).

Methods Nine randomized controlled trials with a minimum two year follow-up were retrieved from PubMed, Embase, and Cochrane Library search. Treatment modalities categorized into five; (1) traditional CD alone, (2) CD combining BG, (3) CD combining BMMC, (4) CD combining BG and BMMC, and (5) non-operative treatment. The rate of conversion to total hip arthroplasty (THA) and the radiologic progression were compared among the five treatments.

Results A total of 453 hips were included in our NMA; 151 hips in CD, 70 hips in CD combining BG, 116 hips in CD combining BMMC, 25 hips in CD combining BG and BMMC, and 91 hips in non-operative treatment. There were no differences in the rate of THA conversion across all five treatment modalities. The pooled risk ratio compared with non-operative treatment for THA conversion was 0.92 (95% CI, 0.19–4.43; $p = 0.915$) in traditional CD; 4.10 (95% CI, 0.37–45.42; $p = 0.250$) in CD combining BG; 0.30 (95% CI, 0.04–2.49; $p = 0.267$) in CD combining BMMC; and 1.78 (95% CI, 0.05–63.34; $p = 0.750$) in CD combining BG and BMMC. No significant differences were found in terms of the radiologic progression across all treatments.

Conclusions In the current NMA, we did not find any differences in the rates of THA conversion and radiologic progression across all CD modalities and non-operative treatment. These results question the assumption that CD changes the natural course of ONFH. Considering that size of necrotic portion is the major determinant of future collapse of the necrotic femoral head and the collapse does not occur in small lesions even without any treatment, a large-scale randomized controlled trial is necessary to confirm the effectiveness of CD.

Level of evidence Level I, meta-analysis.

Byung-Ho Yoon and Young-Kyun Lee equally contributed to this work and should be considered co-first authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00264-018-3977-9) contains supplementary material, which is available to authorized users.

✉ Ki-Choul Kim
puhoo73@hanmail.net

Byung-Ho Yoon
cragy0215@naver.com

Young-Kyun Lee
ykleemd@gmail.com

Yong-Chan Ha
hayongch@naver.com

Kyung-Hoi Koo
khkoo@snu.ac.kr

[1] Department of Orthopaedic Surgery, Inje University College of Medicine, Seoul Paik Hospital, Seoul, South Korea

[2] Department of Orthopaedic Surgery, Seoul National University Bundang Hospital, Seongnam, South Korea

[3] Department of Orthopaedic Surgery, Dankook University College of Medicine, Dongnam-gu, Cheonan-si, Chungcheongnam-do, South Korea

[4] Department of Orthopaedic Surgery, Chung-Ang University College of Medicine, Seoul, South Korea

Keywords Hip · Osteonecrosis · Avascular necrosis · Core decompression · Network · Meta-analysis

Introduction

Since osteonecrosis of the femoral head (ONFH) usually affects young adults, various treatments have been developed to prevent or delay the progress of the disease [1]. Core decompression (CD) has been the most common treatment for that purpose over the past 30 years, because it is simple, minimally invasive, easy to perform, and does not require any special equipment [2]. To enhance bone regeneration, bone graft (BG) and bone marrow mononuclear cells (BMMC) have been combined to traditional CD. However, there has been debate over the efficacies of these modalities because inconsistent outcomes with varying success rates have been reported [3–5].

To date, four meta-analyses have been performed to determine the effectiveness of CD and concluded that CD was effective when it was done in the earliest stage ONFH [6–9]. However, all of these meta-analyses had weak statistical strength because they included non-randomized clinical trials or observational studies and did not evaluate the efficacies of adjunctive CD modalities. Moreover, these analyses pertained to pairwise comparisons between two treatments and did not provide comprehensive and overall evidence about the effectiveness of various CD modalities and non-operative treatment.

The natural course of ONFH has been well studied [10]. The size of necrotic portion is the major determinant of further collapse of the necrotic femoral head. The collapse does not occur in small lesions even without any intervention. Thus, small pre-collapse lesions do not progress to further stage and remain in early stage without collapse of necrotic femoral head. It should be argued that previous studies, which reported preventive effect of CD, might have included small early lesions and resultant selection bias.

The network meta-analysis (NMA) or multiple-treatments meta-analysis is a recently developed methodology that allows the evaluation of multiple treatment modalities. It compares direct and indirect evidences on relative effectiveness of numerous treatments and provides a relative ranking of all treatments in terms of effectiveness with a reliable power [11].

When there are multiple treatments for a certain disease, and only a few pair-wise comparisons between two treatments are available, the NMA allows the estimation of efficacies of the multiple treatments, regardless of whether there have been direct (head-to-head) comparisons including all treatments. As far as the effectiveness of treatments for ONFH is concerned, the NMA application allows direct and indirect comparisons among various treatments.

In an attempt to compare the efficacy of various CD modalities and non-operative treatment in patients with ONFH, we conducted a NMA. The efficacy was investigated by comparing the rates of (1) conversion total hip arthroplasty (THA), (2) radiographic progression, and (3) pain relief.

Materials and methods

Search strategy and selection of studies

This systematic review and network meta-analysis was conducted according to the updated preferred reporting items for systematic review and meta-analysis (Electronic supplementary material (ESM) 1) [12], and guidelines for network meta-analysis [11]. In November 2016, a search was performed on PubMed-Medline, Embase, and Cochrane Library by using key terms (osteonecrosis OR aseptic necrosis OR avascular necrosis AND core decompression).

Two independent reviewers (blinded by authors) screened the titles and abstracts. They also checked the reference lists of all potentially eligible studies and review papers to find out additional relevant publications. Among the searched publications, we selected studies, which met predefined inclusion and exclusion criteria. The inclusion criteria were (1) RCTs on clinical or radiologic results of CD in patients with ONFH and (2) studies reporting at least one of the following main outcomes: the rate of THA requirement, post-operative collapse rate, and clinical success. The exclusion criteria were (1) studies that included traumatic ONFH (2) non-RCT, reviews, protocols, basic science articles, and studies with less than ten subjects. The language was restricted to English. When updated studies, which involved the same cohort of patients in a previously published study, were identified, only the latest study was included in the analysis.

Types of interventions

Treatment modalities categorized into five; (1) traditional CD using 8–10-mm-wide cannula trephine and multiple drillings with a 3-mm Steinman pin, (2) CD combined with allogeneic or autologous BG, (3) CD combined with BMMC, (4) CD combined with BG and BMMC, and (5) non-operative treatments. Non-operative treatments included non-weight bearing with crutches, use of analgesics, physical therapy, and biophysical stimulation.

Data extraction and outcome measure

From every eligible study, we extracted the first author, year of publication, study design, number of patients, enrollment period, patient characteristics, type of treatment, and length of follow-up. The primary outcome of interest was the rate of conversion to THA. The secondary outcome of interest was

the rates of radiographic progression and clinical success. We defined radiographic progression as a collapse of the necrotic femoral head more than 2 mm [13, 14].

Assessment quality and publication bias

Two authors (blinded by authors) independently performed quality assessment with use of the risk of bias assessment tool, which was described in the Cochrane Handbook for Systematic Reviews of Interventions [15]. We assessed publication bias with Begg's funnel plot and Egger's test.

Statistical analyses

Two statistical analyses were performed on the extracted data.

1) Pair-wise meta-analysis

First, we performed a pair-wise meta-analysis on comparative studies [16]. For each study, we calculated the relative risk with 95% confidence interval (CI) by using crude 2 × 2 tables, whenever possible. The Mantel–Haenszel method was used to calculate the odds ratio [17]. Heterogeneity between comparable studies was tested with chi-square (χ^2) and I^2 test. $P > 0.1$ and $I^2 < 50\%$ were criteria of the statistical heterogeneity.

2) Network meta-analysis

After the pair-wise meta-analysis, we performed a NMA to determine comparative efficacy among the five treatments. The probability of superiority, which means the probability that a certain treatment has the highest success rates among the multiple treatments in simulation runs, was calculated. If a treatment had a 70% probability of superiority, it would mean that the treatment had the highest number of success rates out of all treatment modalities in 70% of the simulation runs.

All analyses were performed using the "mvmeta" command [18] of STATA (version 14.0; Stata Corporation, College Station, TX, USA) and self-programmed STATA routines described in Chaimani et al. [19] Corresponding 95% credible intervals (CrIs) were obtained using the 2.5th and 97.5th percentiles of the posterior distribution.

This study was exempted from institutional review board review because it did not involve human subjects.

Results

Description of included studies

We identified nine RCTs: two RTCs comparing CD and non-operative treatment [4, 5], four RTCs of CD versus CD with

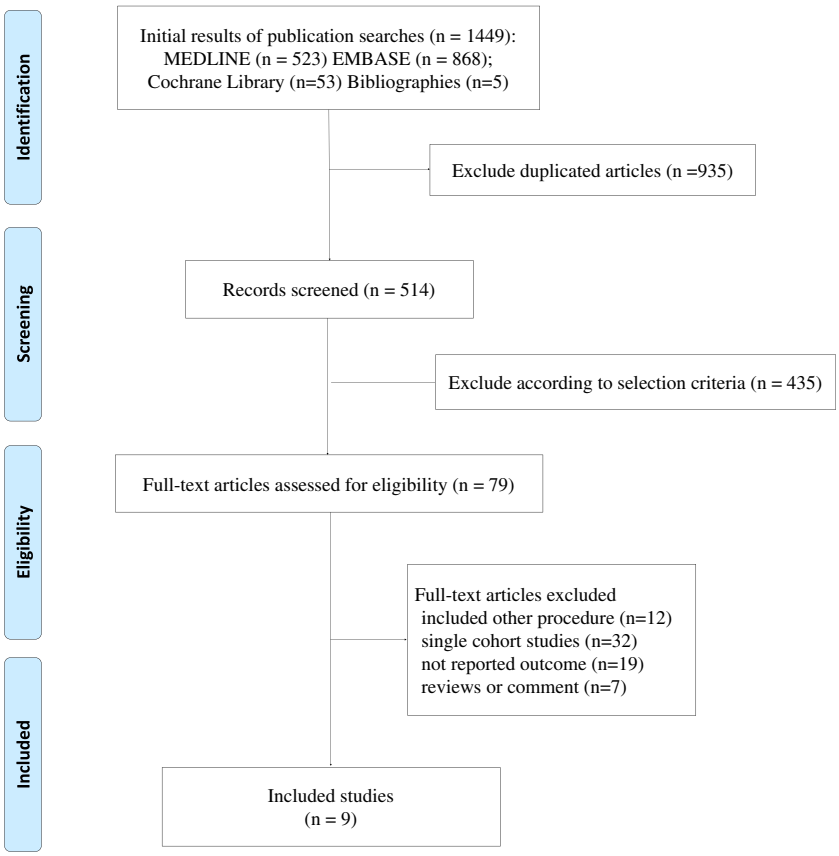

Fig. 1 PRISMA flow diagram details the process of relevant clinical study selection

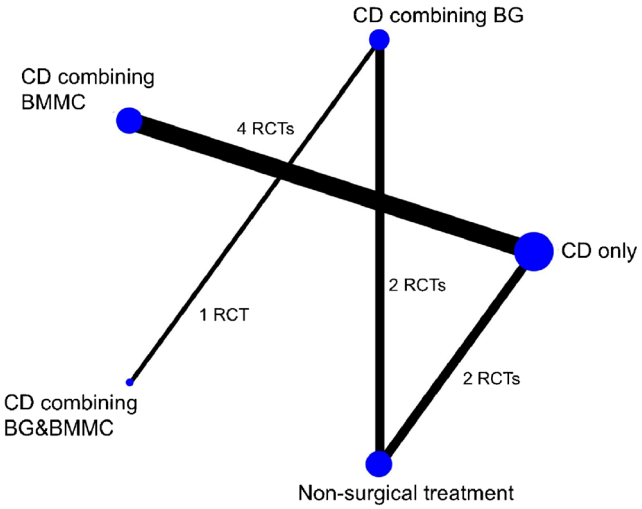

Fig. 2 Network plot depicting direct evidence used in network meta-analysis. Nodes representing the interventions being compared and edges representing the available direct comparisons. Nodes size and line thickness are weighted proportional to number of papers providing direct evidence

BMMC [20–23], two RTCs of CD with BG versus non-operative treatment [3, 24], and one RTC of CD with BG versus CD with BG and BMMC [14] (Figs. 1 and 2). A total of 453 hips were included in our NMA; 151 underwent CD, 70 CD with BG, 116 CD with BMMC, 25 CD with BG and BMMC, and 91 non-operative treatment. The characteristics of included studies are summarized in Table 1.

Conversion to total hip arthroplasty

THA requirement data were provided in all nine studies. The overall rate of THA conversion was 24.2% (110/453 hips). There were no differences in the rate of THA conversion among the five treatments (Fig. 3a). The probability of superiority was 3.8% in CD, 1.5% in CD with BG, 64.5% in CD with BMMC, 24.5% in CD with BG and BMMC, and 5.8% in non-operative treatment.

Radiographic progression

Seven trials [3, 4, 14, 20, 22–24] provided data of radiographic progression. The overall rate of progression was 29.9% (116/387 hips). There were no differences in the rate of the femoral head collapse across the five treatments (Fig. 3b). The probability of superiority was 0.5% in CD, 1.1% in CD with BG, 21.4% in CD with BMMC, 64.1% in CD with BG and BMMC, and 13% non-operative treatment.

Clinical success

Four trials [3–5, 24] involving a total of 185 hips provided relevant data for clinical success while the remaining five studies described the change of pain scores [14, 20–23].

Table 1 Characteristics of included individual studies

Study name	Enrollment period	Country	Group comparison	Conversion to THR (hips)	Radiographic progression (hips)	Mean follow-up (years)	Inclusion criteria	Mean age
Stulberg [4]	1983–1987	USA	A: CD only E: Non-surgical treatment	A: 8/28 (29%) E: 13/22 (59%)	A: 21/28 (75%) E: 11/22 (50%)	2.4	ARCO stages 1–3	38.6
Koo [3]	1990–1992	Korea	B: CD + BG E: Non-surgical treatment	B: 13/18 (72%) E: 13/19 (68%)	B: 14/18 (78%) E: 15/19 (79%)	2	ARCO stages 1–3	45/48
Wang [24]	2001–2002	Taiwan	B: CD + BG E: Non-surgical treatment	B: 9/28 (32%) E: 3/29 (10%)	B: 7/28 (25%) E: 2/29 (7%)	2.1/2.1	ARCO stages 1–3	40/40
Neumayr [5]	1998–2002	USA	A: CD only E: Non-surgical treatment	A: 3/17 (18%) E: 0/21 (0%)	–/–	3.1/3.0	ARCO stages 1–3	25/26
Sen [23]	NA	India	A: CD only C: CD + BMSC	A: 3/25 (12%) C: 1/26 (4%)	A: 4/25 (16%) C: 1/26 (4%)	2/2	ARCO stages 2–3	48/44
Zhao [22]	2004–2006	China	A: CD only C: CD + BMSC	A: 5/44(11%) C: 0/53 (0%)	A: 10/44(23%) C: 2/53 (4%)	5/5	ARCO stages 1–2	34/33
Ma [14]	2009–2010	China	B: CD + BG D, CD + BG, and BMMC	B: 4/24 (17%) D: 2/25 (4%)	B: 8/24 (33%) D: 2/25 (4%)	2/2	ARCO stages 1–2	44/45
Tabatabaee [21]	NA	Iran	A: CD only C: CD + BMMC	A: 3/14 (35%) C: 0/14 (36%)	–/–	2/2	ARCO stages 1–3	31/27
Hauzeur [20]	NA	Belgium	A: CD only C: CD + BMMC	A: 15/23 (65%) C: 15/23 (65%)	A: 9/23 (39%) C: 10/23 (43%)	2/2	ARCO stage 3	49/48

THR, total hip replacement; CD, core decompression; BG, bone graft; BMMC, bone marrow mononuclear cell NA: non-available

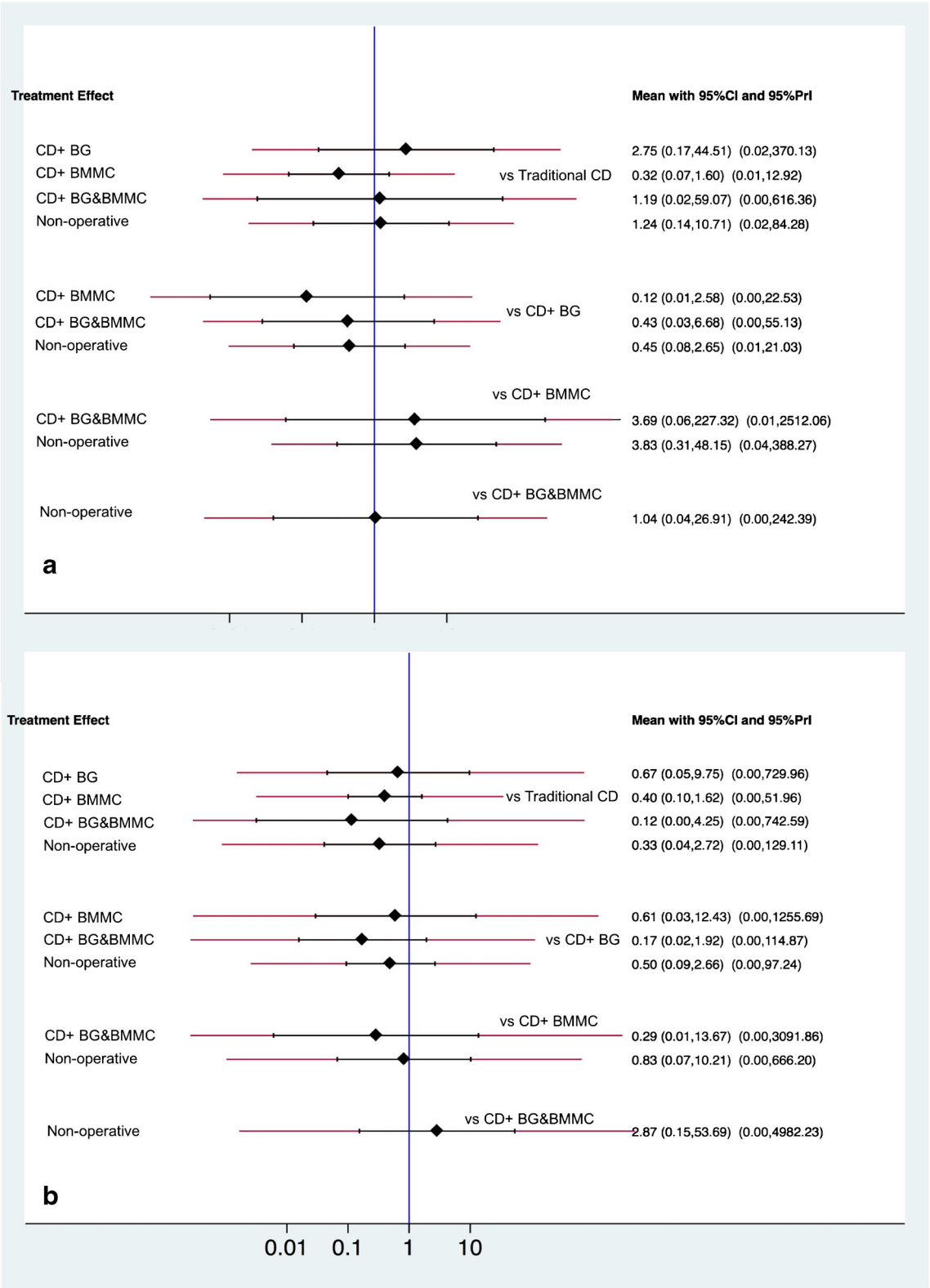

Fig. 3 The interval plot of the odds ratio for the efficacy by **a** the rate of conversion to total hip arthroplasty and **b** radiographic progression rate (black line indicates confidential interval; red line indicates credible interval). The 95% confidential interval included 1, and this means all treatment comparisons failed to reach a statistical significance

Thus, it was not feasible to perform NMA due to a lack of objective comparisons.

Methodological quality of included studies

Subjects were randomized by established allocation sequence of each study, and investigators were all blind to the allocation. Nevertheless, it was unclear whether the included trials met all the quality assessment criteria (Electronic Supplementary material 3), because physicians were not blind to their procedures.

Discussion

In our NMA, there were no significant differences in the rate of THA conversion and femoral head collapse among various CD modalities and non-operative treatment. During the last three decades, CD has been used in early-stage (pre-collapse) ONFH in an attempt to prevent future collapse of the necrotic femoral head, and the CD technique has evolved combining BG and BMMC. However, our results question the fundamental assumption that core decompression changes the natural course of ONFH.

Whether CD prevents future collapse of the necrotic femoral head remains an issue of controversy. While several studies reported excellent results of the procedure [4, 13, 23], other studies showed that it is not superior to non-operative treatments [6–9]. It is difficult to judge the efficacy of CD procedure due to the variety of modern techniques between studies, small number of subjects in each study and a paucity of RCTs. Moreover, the size of necrotic portion, which is the major determinant of future collapse of the necrotic femoral head, has not been stratified in most analyses. Most studies, which supported the efficacy of CD, indicated that the best results were obtained when this procedure was done in the earliest stage of the disease with small lesions [2, 25–28]. Considering that small lesions do not develop femoral head collapse even without any intervention, it should be argued that these studies might have had a selection bias including small early lesions.

The stage of ONFH also could be covariant factor in the analysis of the efficacy of CD. One review demonstrated that more recent studies have conferred better results than older studies, but there were fewer stage III hips in the more recent reports, suggesting that patient selection was an important reason for this improvement [26]. In our study, seven studies had included stage III lesions, so we expected that subgroup analysis based on the ONFH stage would reveal that patient selection was the main determinant of prognosis. However, subgroup NMA could not be performed, because only four studies identified their results according to the stage of disease (the other studies provided stage when enrolled but not at outcome evaluation) and there was too small sample size in each stage.

Although current study is the first NMA comparing conventional CD with recent modalities by summarizing all the available RCTs, our NMA still be interpreted cautiously. Because although various CD modalities have been categorized, the methods of surgical technique or adjuvant procedures within each category are not exactly the same.

Some limitations exist in our NMA study. First, the lesion size was not stratified. Second, the number of subjects in each study was small. Third, NMA includes indirect evidence, which necessitates another level of complexity and assumptions than pair-wise meta-analysis. Fourth, the preventive effect of CD in ONFH remains an issue of controversy. A large-scale RCT with stratification of necrotic extent is warranted to determine whether CD really prevents the disease progression in the patients with ONFH.

Funding There is no funding source.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

Disclosure None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work.

References

1. Chughtai M, Piuzzi NS, Khlopas A, Jones LC, Goodman SB, Mont MA (2017) An evidence-based guide to the treatment of osteonecrosis of the femoral head. Bone Joint J 99-B:1267–1279. https://doi.org/10.1302/0301-620X.99B10.BJJ-2017-0233.R2
2. Learmonth ID, Maloon S, Dall G (1990) Core decompression for early atraumatic osteonecrosis of the femoral head. J Bone Joint Surg Br 72:387–390
3. Koo KH, Kim R, Ko GH, Song HR, Jeong ST, Cho SH (1995) Preventing collapse in early osteonecrosis of the femoral head. A randomised clinical trial of core decompression. J Bone Joint Surg Br 77:870–874
4. Stulberg BN, Davis AW, Bauer TW, Levine M, Easley K (1991) Osteonecrosis of the femoral head. A prospective randomized treatment protocol. Clin Orthop Relat Res 268:140–151
5. Neumayr LD, Aguilar C, Earles AN, Jergesen HE, Haberkern CM, Kammen BF, Nancarrow PA, Padua E, Milet M, Stulberg BN, Williams RA, Orringer EP, Graber N, Robertson SM, Vichinsky EP, National Osteonecrosis Trial in Sickle Cell Anemia Study G (2006) Physical therapy alone compared with core decompression and physical therapy for femoral head osteonecrosis in sickle cell disease. Results of a multicenter study at a mean of three years after

treatment. J Bone Joint Surg Am 88:2573–2582. https://doi.org/10.2106/JBJS.E.01454
6. Hong YC, Zhong HM, Lin T, Shi JB (2015) Comparison of core decompression and conservative treatment for avascular necrosis of femoral head at early stage: a meta-analysis. Int J Clin Exp Med 8:5207–5216
7. Li X, Xu X, Wu W (2014) Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis. Int J Clin Exp Pathol 7:5024–5030
8. Castro FP Jr, Barrack RL (2000) Core decompression and conservative treatment for avascular necrosis of the femoral head: a meta-analysis. Am J Orthop (Belle Mead NJ) 29:187–194
9. Sadile F, Bernasconi A, Russo S, Maffulli N (2016) Core decompression versus other joint preserving treatments for osteonecrosis of the femoral head: a meta-analysis. Br Med Bull 118:33–49. https://doi.org/10.1093/bmb/ldw010
10. Jagadale VS, Cheng EY (2014) Causes of pain in early stage and advanced stage: clinical features and natural course of osteonecrosis. In: Koo KH (ed) Osteonecrosis, 2nd edn. Springer, Berlin, pp 165–170
11. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, Boersma C, Thompson D, Larholt KM, Diaz M, Barrett A (2011) Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR task force on indirect treatment comparisons good research practices: part 2. Value Health 14:429–437. https://doi.org/10.1016/j.jval.2011.01.011
12. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. https://doi.org/10.1136/bmj.g7647
13. Kang P, Pei F, Shen B, Zhou Z, Yang J (2012) Are the results of multiple drilling and alendronate for osteonecrosis of the femoral head better than those of multiple drilling? A pilot study. Joint Bone Spine 79:67–72. https://doi.org/10.1016/j.jbspin.2011.02.020
14. Ma Y, Wang T, Liao J, Gu H, Lin X, Jiang Q, Bulsara MK, Zheng M, Zheng Q (2014) Efficacy of autologous bone marrow buffy coat grafting combined with core decompression in patients with avascular necrosis of femoral head: a prospective, double-blinded, randomized, controlled study. Stem Cell Res Ther 5:115. https://doi.org/10.1186/scrt505
15. Kim KS, Jo JK, Chung JH, Kim JH, Choi HY, Lee SW (2017) Quality analysis of randomized controlled trials in the international journal of impotence research: quality assessment and relevant clinical impact. Int J Impot Res 29:65–69. https://doi.org/10.1038/ijir.2016.48
16. Higgins JPT, Green S (2008) Cochrane handbook for systematic reviews for intervention. version 5.0.0:242–248. The Cochrane Collaboration, London
17. Borenstein M (2009) Introduction to meta-analysis. Effect sizes based on binary data. Wiley, Chichester, p33–39
18. Shim S, Yoon BH, Shin IS, Bae JM (2017) Network meta-analysis: application and practice using Stata. Epidemiol Health 39:e2017047. https://doi.org/10.4178/epih.e2017047
19. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G (2013) Graphical tools for network meta-analysis in STATA. PLoS One 8:e76654. https://doi.org/10.1371/journal.pone.0076654
20. Hauzeur JP, De Maertelaer V, Baudoux E, Malaise M, Beguin Y, Gangji V (2017) Inefficacy of autologous bone marrow concentrate in stage three osteonecrosis: a randomized controlled double-blind trial. Int Orthop. https://doi.org/10.1007/s00264-017-3650-8
21. Tabatabaee RM, Saberi S, Parvizi J, Mortazavi SM, Farzan M (2015) Combining concentrated autologous bone marrow stem cells injection with core decompression improves outcome for patients with early-stage osteonecrosis of the femoral head: a comparative study. J Arthroplast 30:11–15. https://doi.org/10.1016/j.arth.2015.06.022
22. Zhao D, Cui D, Wang B, Tian F, Guo L, Yang L, Liu B, Yu X (2012) Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. Bone 50:325–330. https://doi.org/10.1016/j.bone.2011.11.002
23. Sen RK, Tripathy SK, Aggarwal S, Marwaha N, Sharma RR, Khandelwal N (2012) Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study. J Arthroplast 27:679–686. https://doi.org/10.1016/j.arth.2011.08.008
24. Wang CJ, Wang FS, Huang CC, Yang KD, Weng LH, Huang HY (2005) Treatment for osteonecrosis of the femoral head: comparison of extracorporeal shock waves with core decompression and bone-grafting. J Bone Joint Surg Am 87:2380–2387. https://doi.org/10.2106/JBJS.E.00174
25. Hungerford DS, Jones LC (2004) Asymptomatic osteonecrosis: should it be treated? Clin Orthop Relat Res 429:124–130
26. Marker DR, Seyler TM, Ulrich SD, Srivastava S, Mont MA (2008) Do modern techniques improve core decompression outcomes for hip osteonecrosis? Clin Orthop Relat Res 466:1093–1103. https://doi.org/10.1007/s11999-008-0184-9
27. Mazieres B, Marin F, Chiron P, Moulinier L, Amigues JM, Laroche M, Cantagrel A (1997) Influence of the volume of osteonecrosis on the outcome of core decompression of the femoral head. Ann Rheum Dis 56:747–750
28. Morita D, Hasegawa Y, Okura T, Osawa Y, Ishiguro N (2017) Long-term outcomes of transtrochanteric rotational osteotomy for non-traumatic osteonecrosis of the femoral head. Bone Joint J 99-B:175–183. https://doi.org/10.1302/0301-620X.99B2.BJJ-2016-0417.R2