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Original Article

Effectiveness of various hip preservation treatments for non-traumatic osteonecrosis of the femoral head: A network meta-analysis of randomized controlled trials

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ABSTRACT

Background: Non-traumatic osteonecrosis of the femoral head (ONFH) is a refractory osteonecrosis disease caused by an abnormal blood supply to bone tissue. However, therapeutic hip preservation strategies are diverse, and the therapeutic outcomes are not ideal.
Objective: A network meta-analysis was performed to assess the effect of hip preservation treatments on non-traumatic ONFH.
Methods: We searched public electronic databases through May 15, 2017 using the following keywords: "femoral head necrosis osteonecrosis"; "femoral head osteonecrosis"; "osteonecrosis of femoral head"; "avascular necrosis of femoral head"; "necrosis of femoral"; and "random*". The primary outcome in the present analysis was the treatment failure rate. Secondary outcomes included the Harris hip and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.
Results: We included 21 articles assessing a total of 1415 hips in our analysis. In the network meta-analysis, the treatments were ranked by the surface under the cumulative ranking curve (SUCRA). Core decompression (CD) plus cytotherapy was most likely to reduce the treatment failure rate (SUCRA score = 18.9%), followed by alendronate treatment (SUCRA score = 17.8%), cocktail treatments (SUCRA score = 15.6%), extracorporeal shock wave therapy (ESWT) plus alendronate (SUCRA score = 15.4%), and avascular biomaterials plus cytotherapy (SUCRA score = 13.8%) in a frequentist framework; similar results were obtained in a Bayesian framework. For the secondary outcomes, ESWT was most likely to improve the Harris hip score (SUCRA score = 33.7%), followed by ESWT plus alendronate (SUCRA score = 33.1%) and cocktail (SUCRA score = 19.6%) treatments in a frequentist framework. A traditional analysis showed that the effect of CD plus cytotherapy was significantly better than the effect of CD alone in improving the WOMAC score (SMD, −6.01; 95% CI, −7.81 to −4.22; $p < 0.001$).
Conclusion: CD plus cytotherapy is a relatively superior treatment for reducing treatment failure rates in early and intermediate ONFH patients, and ESWT is the most effective treatment for improving Harris hip scores.

1. Introduction

Non-traumatic osteonecrosis of the femoral head (ONFH, also called avascular necrosis of the femoral head and aseptic necrosis of the femoral head) is a common but refractory osteonecrosis disease caused by an abnormal blood supply to bone tissue that results in bone tissue death, structural remodeling, and collapse [1]. At present, the pathogenesis is unclear [2]. Pain is the most common ONFH symptom; pain usually occurs after bearing weight in the early stage, whereas persistent pain and claudication occur in the later stage of ONFH.

The principle of ONFH treatment is to terminate the progression of the lesion and to restore the ability to bear weight and engage in daily activities. The main therapeutic strategies for ONFH include bisphosphonate [3], hyperbaric oxygen (HBO) therapy [4], electrical stimulation [5], and extracorporeal shock wave therapy (ESWT) [6]. Core decompression (CD) is commonly used to reduce pressure in

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the bone and to improve perfusion and relieve symptoms [7]. With the development of new technology, cytotherapeutic treatments, such as bone marrow mononuclear cell implantation, have also been studied in clinical practice [8]. Total hip arthroplasty (THA) is eventually necessary if the necrotic process of the disease is not controlled.

Systematic analyses of ONFH treatment have been conducted previously, but only specific types of treatment have been summarized [4,9–13]. In several studies, cytotherapy was shown to be a safe and effective treatment that slowed disease progression, with a low femoral head collapse rate. However, due to the use of different cell sources and characteristics, the cell processing methods need to be standardized [9–11]. ESWT is also commonly used in ONFH therapy to improve motor function and relieve pain; moreover, ESWT can alleviate bone marrow edema and partially reverse bone tissue necrosis [12]. HBO can increase blood and tissue oxygen levels by increasing the oxygen partial pressure, which can also achieve beneficial clinical treatment effects [4]. Bisphosphonate is not recommended for ONFH treatment due to its less pronounced effects and potential side effects [13]. Although some treatments have a therapeutic effect on ONFH, a comparative study of these treatments is lacking. We hypothesized that one treatment strategy should have a higher success rate and better symptom-relieving effects in OFNH therapy than the other strategies. This study analyzed the various ONFH hip preservation treatments tested in randomized controlled trials (RCTs) using a network analysis to guide the selection and application of clinical treatments.

2. Methods

2.1. Search strategy

A systematic literature search was conducted by two investigators (second and third authors' name) in the PubMed, Embase, and Cochrane Library databases to identify RCTs published prior to May 15, 2017.

A combination of the following search terms was used: “femoral head necrosis osteonecrosis”, “femoral head osteonecrosis”, “osteonecrosis of femoral head”, “avascular necrosis of femoral head”, “necrosis of femoral”, and “random*”. The language was restricted to English. We sought additional references through a manual search of the bibliographies of relevant publications.

2.2. Selection criteria

Two authors (second and third authors' name) independently reviewed the titles and abstracts of potentially eligible publications. The studies included in this meta-analysis met the following criteria: (1) the study had a prospective RCT design; (2) the study included ONFH patients; (3) the patients received two or more different types of treatment as a comparison; and (4) at least one of the following outcomes was included in the study: the number of treatment failures in patients/hips (including formal head collapse and the need for THA); the Harris hip scores; or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.

The exclusion criteria were as follows: (1) the study did not have a prospective RCT design; (2) the study included non-ONFH patients or high-risk patients without ONFH onset; (3) the study compared similar types of treatment or was a dose-related study; (4) the study involved traditional Chinese medicine or other drugs with unclear compositions; and (5) the study focused on undesired outcomes. Non-peer reviewed studies, such as conference reports and dissertations, were also excluded due to their lack of reliability.

2.3. Date extraction and quality assessment

The following information was extracted independently from each eligible study by two investigators (Second and third authors' name): name of first author; publication year; sample size; number of hips; type of patients; intervention treatment; type of intervention; control treatment; type of control; and follow-up. We assessed the methodological quality of the included trials using the recommended Cochrane Collaboration tool [14]. Studies were graded as having a “low risk”, “unclear risk”, or “high risk” of bias across the seven specific domains.

2.3.1. Outcome assessment

The primary outcome was the treatment failure rate. The secondary outcomes were the Harris hip and WOMAC scores. The treatment failure rate indicates the frequency that hips underwent collapse of the femoral head or required THA. If these two results were both reported but were different, we used the value with the greater number of results because THA and collapse were both considered treatment failure. The Harris Hip Score includes four subscales to assess pain, joint activity, absence of deformity, and range of motion. The maximum score is 100, and a higher score indicates a better treatment result. The WOMAC scores includes three subscales to assess pain, stiffness, and physical function, and a lower score indicates a better patient condition.

2.4. Statistical analysis

We performed a random-effects network meta-analysis within a frequentist framework with STATA (version 13.0, StataCorp LLC, TX, USA) and within a Bayesian framework with the GeMTC R package (version 3.2.3, The R Development Core Team/R Foundation for Statistical Computing, Vienna, Austria). A consistency model was adopted in all analyses. We summarized the network meta-analysis results with standardized mean differences (SMDs) or odds ratios (ORs) and their credible intervals (CrIs). In the Bayesian network meta-analysis, the pooled estimates were obtained using the Markov chain Monte Carlo method. Three Markov chains were run simultaneously with different arbitrarily chosen initial values [15]. For all treatments, we estimated the probability of the treatment being at each possible rank for each intervention using the surface under the cumulative ranking curve (SUCRA). Comparison-adjusted funnel plots were used to determine whether small-study effects were present in our analysis.

We also performed a traditional pairwise meta-analysis using a random-effects model, which is a conservative methodology that accounts for between-trial heterogeneity within each comparison if the comparisons are not suitable for analysis via network meta-analysis. SMDs were calculated as the effect sizes for continuous outcomes, and ORs were calculated for dichotomous outcomes, both with 95% confidence intervals (CIs). All tests were two-tailed, and a p value less than 0.05 was considered significant.

3. Results

3.1. Literature search

Overall, 1002 citations were identified in the database search after duplicate removal. We excluded 953 reports after the titles and abstracts were screened. The full texts of the remaining 49 articles were assessed, and 28 articles were excluded for the following reasons: 10 were not RCTs; five reported on unrelated diseases, including Legg-Calve-Perthes disease (because this disease occurs in children and is self-limited and self-healing), bone

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