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Review

Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: A meta-analysis

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HIGHLIGHTS

- Intraarticular corticosteroid is more effective on pain relief than intraarticular hyaluronic acid in short term (up to 1 month), while it reverses up to 6 months.
- Intraarticular corticosteroid and hyaluronic acid benefit similarly for knee function improvement.
- Both two methods are relatively safe.

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ABSTRACT

Objective: A meta analysis to compare efficacy and safety of intraarticular hyaluronic acid (HA) and intraarticular corticosteroids (CS) in patients with knee osteoarthritis.
Method: Potential studies were searched from the electronic databases included PubMed, Embase, web of science and the Cochrane Library up to August 2016. High quality randomized controlled trials (RCTs) were selected based on inclusion criteria. RevMan 5.3 were used for the meta-analysis.
Results: 12 RCTs containing 1794 patients meet the inclusion criteria. Visual analog scale (VAS) score in CS group decrease more than HA group up to 1 month ($p = 0.03$) and it shows equal efficacy at 3 months ($p = 0.29$); HA is more effective than CS at 6 months ($p = 0.006$). To Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, there is no significant difference for two groups at 3 months ($p = 0.29$); HA shows greater relative effect than CS at 6 months ($p = 0.005$). No significant difference is found on proportion of rescue medication use after initiation of treatment ($p = 0.58$) and proportion of withdrawal for knee pain ($p = 0.54$). HA and CS exhibit equal efficacy on improvement of active range of knee flexion at 3 months ($p = 0.73$) and 6 months ($p = 0.43$). More topical adverse effects occurred in intraarticular HA group when compared with intraarticular CS group.
Conclusion: Intraarticular CS is more effective on pain relief than intraarticular HA in short term (up to 1 month), while HA is more effective in long term (up to 6 months). Two therapies benefit similarly for knee function improvement. Both two methods are relatively safe, but intraarticular HA causes more topical adverse effects compared with intraarticular CS.

1. Introduction

Knee osteoarthritis (OA) is a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and decreased quality of life, characterised by loss of cartilage, remodeling of adjacent bone and associated with inflammation [1]. A large proportion of US adults aged 60 and older have radiographic knee OA (37.4%) and symptomatic radiographic knee OA (12.1%); or

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an estimated 13.3 million persons have radiographic knee OA, 4.3 million persons suffer symptomatic radiographic knee OA [2]. Knee OA is a progressive disease, knee pain and loss of function are main symptoms, which can lead to disability, joint replacement and low quality of life. In advance of effective disease-modifying medical interventions for knee OA, treatments are mainly symptomatic essentially, mainly including intraarticular HA and intraarticular CS [3].

HA is a natural glycosaminoglycan and a component of synovial fluid which act as a lubricant and elastic shock absorber during joint movements. Both concentration and molecular weight of HA decreases in osteoarthritic joints [4]. Intraarticular HA can restore the effect of synovial fluid, protect against cartilage erosion, reduce synovial inflammation [4,5]. Moreover, HA have direct and indirect analgesic effect on the joints [5]. Although numerous clinical studies [6–9] and systematic review [10] have shown benefits (e.g., improvements in knee pain and function, longer time to knee arthroplasty) on knee OA, several studies [11–13] reported increased risk of local or serious adverse events after viscosupplementation of the knee. The safety of intraarticular HA remains controversial.

Intraarticular CS is a long-standing treatment for OA, and the first clinical trial of intraarticular CS in knee OA was performed in 1958 by Miller and colleagues [14]. Corticosteroids have marked anti-inflammatory and immunosuppressive effect, besides, CS can increase both relative viscosity and concentration of HA [15] in arthritic knee. While there is a debate on the effective time of intraarticular CS. Some studies [14,16,17] suggest a short-term (up to 12 weeks) effect for knee OA, whereas there are also papers [18,19] report that a significant improvement can be sustained up to 24 weeks.

In spite of the efficacy and cost-effectiveness of treatment modalities for knee OA are frequently debated and guidelines have changed over time, intraarticular CS and HA remain common treatment for knee OA [3]. Among the efficacy and safety between intraarticular HA and intraarticular CS, there still haven't reached a consencus. In a recent network meta-analysis, Trojian et al. [20] propose that intraarticular HA is superior to intraarticular CS. Conflicts also exist in guidelines. Osteoarthritis Research Society International [21] recommend both intraarticular HA and intraarticular CS for patients with knee OA, while American College of Rheumatology [22] and National Institute for Health and Care [1] just recommend the use of intraarticular CS. Thus, we conduct a meta analysis to compare efficacy and safety of intraarticular HA and intraarticular CS in patients with knee OA.

2. Materials and methods

2.1. Search strategy

Two reviewers performed an electronic literature search for randomized controlled trials (RCTs) comparing the efficacy or safety of intraarticular hyaluronic acid injections with intraarticular corticosteroid injections in the management of knee osteoarthritis. The electronic databases include PubMed, Embase, web of science and the Cochrane Library up to August 2016. The following terms were used as key words:knee osteoarthritis, gonarthrosis, hyaluronic acid (and trade names for hyaluronic acid), viscosupplementation and corticosteroid (and the trade name for corticosteroid).

In addition, further articles were obtained by reviewing references of the selected articles. The detail retrieval process is shown in Fig. 1.

2.2. Inclusion criteria

We included published RCTs that used human beings and compared the efficacy or safety of intraarticular HA with intraarticular CS to treat knee OA. Each RCT wad required to contain at least one outcome, including the visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), proportion of rescue medication use after initiation of treatment, proportion of withdrawal for knee pain, range of motion of the knee, and adverse events. Eligible studies were assessed independently by two authors. In case of disagreement, a consensus was reached through discussion between two authors.

2.3. Data extraction

Two reviewers independently retrieve the relevant data from articles using a standard data extraction form. The publication date, author, study design, number and demographics of participants, HA/CS dose, regimen and frequency, withdrawal rate, follow up time, and outcome measures were extracted for each trial. Where necessary, means and standard deviation were approximated from the figures in the studies. Besides, we calculated missing standard deviations from other available data such as standard errors, or the formula in Cochrane Handbook for Systematic Reviews of Interventions [23]. The data were extracted independently by two reviewers, and any disagreement was discussed until a consensus was reached.

2.4. Quality assessment

Two reviewers independently assessed the quality of the RCTs by using modified Jadad scale [24,25]. Maximum score is 7 points, studies with a total score of $\leq$3 points were considered as low quality studies, while a total score of $\geq$4 points were considered high-quality. It includes generation of allocation sequence, allocation concealment, blind method, and description of withdrawals and drop-outs of the RCTs.

2.5. Statistical and subgroup analysis

We used Review Manager Software for windows (Version 5.3. Copenhagen:The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to perform the meta-analysis. For continuous variable outcomes, mean difference (MD) and 95% confidence interval (CI) were used to assess it. For dichotomous outcomes, relative risks (RR) with a 95% CI were presented. Heterogeneity between studies was assessed by I^2 and χ^2 test. While I^2<50% and P>0.1, we used a fixed-effects model to evaluate, otherwise, a random-effects was used. Besides, subgroup analysis was performed to explore the source of heterogeneity when heterogeneity existed.

3. Results

3.1. Search results

From the databases and other sources (e.g.references), we identified a total of 105 studies, of which 77 were excluded by title and abstract. Among the rest of 28 studies, 14 studies [26–39] meet the inclusion criteria after reading the full text in details. Nevertheless, two [38,39] of the 14 studies didn't report sufficient information for data extraction and analysis. Therefore, the meta-analysis was performed on the basis of 12 studies (Fig. 1). The included 12 studies were all RCTs and published between 1995 and 2016. A total of 1794 participants (673 males, 1121 females) were included. Overall, 971 participants were randomly allocated to HA