Osteoarthritis and Cartilage xxx (2014) 1–8

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Evaluation of the therapeutic effect of treatment with intra-articular hyaluronic acid in knees for Kashin-Beck disease: A meta-analysis

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ARTICLE INFO

Article history:
Q1 Received 16 January 2014
Accepted 16 April 2014

Keywords:
Intra-articular hyaluronic acid (IAHA)
Kashin-Beck disease (KBD)
Meta-analysis

SUMMARY

Objective: To assess the efficacy and safety of intra-articular hyaluronic acid (IAHA) injection in knee joints of patients with Kashin-Beck disease (KBD).

Methods: We searched nine electronic databases as well as unpublished data from inception until November 30th 2013 using a combination of search terms for KBD and hyaluronic acid (HA). For dichotomous data, odds ratios (OR) and 95% confidence intervals (CI) were estimated. For continuous data, standard mean difference (SMD) was used for outcomes pooled on the difference scale using a "random-effects" or "fixed-effects" model. We also compared the mean and standard deviation of cytokine levels in post-treatment.

Results: The seven eligible trials included 954 IAHA and 495 control patients. The methodological quality of included trials was low. The overall effectiveness of the IAHA group and control group were 93.7% and 62.9%, respectively. IAHA group resulted in very large treatment effects compared to pre-treatment values in 12 months, with SMD values ranging from 1.19 ~ 2.64 (all $P < 0.05$). Compared to controls, SMDs in IAHA group ranged from 0.19 to 0.64 at 1 week to 1 month (all $P > 0.05$) and 0.68 ~ 1.47 at 2 months to 12 months (all $P < 0.05$). There was significant improved of HA, cluster of differentiation44 (CD44), keratan sulfate (KS), IL-1β, tumor necrosis factor-α (TNF-α) and NO (nitric oxide) contents in serum compared with that in the post-treatment and healthy control in non-KBD area (all $P < 0.05$).

Conclusion: IAHA for the treatment of KBD was safe and efficacious at 12 months with low and transient adverse reactions. However, more high-quality randomized controlled trials (RCTs) are needed to confirm its therapeutic effect.

Introduction

Rationale

Kashin-Beck disease (KBD) is a chronic, endemic, deformation osteoarthropathy with unclear etiology and pathogenesis until now[1–4]. Its clinical characteristics are arthralgia, deformation and limited mobility, and its pathological characteristics are necrosis, degeneration, and degradation of articular cartilage and growth plate cartilage. The severe cases show short stature, disability and even loss of life skills[5–7]. KBD was widely distributed in 377 endemic counties in China with 642,000 KBD patients diagnosed in 2011, and a further 37,917,000 individuals at risk according to China health statistics yearbook in 2011[8]. An epidemiological survey estimated that KBD in children have been controlled effectively. Therefore, the treatment of KBD has attracted greater attention from Chinese health authorities. Two meta-analysises[9,10] of selenium for the prevention and treatment of KBD in children concluded that current evidences from randomized controlled trials (RCTs) and non-RCTs consistently suggested the benefits of selenium supplementation for prevention and treatment of KBD in children. Furthermore, NSAIDs and steroids[11–13], selenium supplementation[14–18], physiotherapy[19] and various joint debridement techniques[20–22] can relieve symptoms in short-term. However they cannot repair cartilage lesion and prevent disease progression, there is currently no effective treatment for KBD.

Hyaluronic acid (HA) is one of the main components of articular cartilage and synovial fluid. Intra-articular hyaluronic acid (IAHA) has been widely employed in the medical management of

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http://dx.doi.org/10.1016/j.joca.2014.04.012

osteoarthritis (OA) of the knee. But the validity of IAHA remains considerable controversy. Among the eight meta-analyses and systematic-reviews performed to date[23–30], four trails drew positive conclusions[23–26] that IAHA was an effective and safe treatment for OA. Two trails[27,28] had a small effect when compared with intra-articular placebo, which might have been overestimated due to publication bias. But Arrich J[29] and Bannuru R R[30] came to the conclusion that IAHA had not been confirmed to show the beneficial effects. As adult KBD is a specific type of OA, the clinical management of KBD may be educated by insights gained from the management of OA[31]. Thus, HA has been used to treat KBD, which showed that HA can markedly improve the function of the knee and relieve the symptoms of KBD. However, to date no systematic review of the relevant data has been conducted.

Objectives

The objective of this meta-analysis is to synthesize the results from included studies, to assess the efficacy of IAHA for the treatment of KBD; to compare the effectiveness of the treatment for KBD and OA; and to determine the changes in cytokine levels in adult KBD in the pre-and post-treatment. This meta-analysis aims to assess whether the published evidence justifies the use of IAHA in KBD.

Materials and methods

We conducted this meta-analysis complied with the PRISMA (*P*referred *R*eporting *I*tems for *S*ystematic reviews and *M*eta-*A*nalyses) statement[32] as closely as possible, the aim of the PRISMA Statement is to help us report a meta-analysis to assess the benefits of IAHA for KBD.

Eligibility criteria

We included RCTs comparing the efficacy of IAHA with vitamin C, drugs or other treatment for the treatment of KBD in adult more than 18 years of age. Every included study should contain extractable data for at least one of the outcome measures (Table I) and a report for KBD clinical trials. KBD had to have been diagnosed by clinical and X-ray diagnosis criterion (GB 16003-1995)[33]. In this meta-analysis all trials included were required to have more than 1 month's follow-up. Non-standard outcome measures and duplicate published articles were excluded.

Information sources

We carried out a search of all publications between inception and November 30th, 2013 using nine electronic databases, which included Google scholar, ISI Web of knowledge, Medline, Springer Link, Cochrane Controlled Trial Register, Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technique Journals Database (VIP), The Chinese Biomedical Database (CBM) and Wan Fang data. All dates and languages were included.

Table I
Hierarchy of outcome measures

1. Global knee pain score (visual analog or Liken scale)
2. Lequesne index
3. The Western Ontario and McMaster Universities Arthritis Index (WOMAC)
4. Function score for index joint (visual analog or Liken scale)
5. Overall response rate (WS/T79-1996, WS/T79-2009)

Search strategy

The key search terms of "Kashin-Beck disease" or "KBD" or "Urov" and "hyaluronic acid" or "hyaluronan" or "hyaluronate" or "HA" both in English and Chinese were used with the restricted language of English and Chinese respectively, and all searches were limited to human clinical trials. We also searched the references of review cited for additional articles by hand. Unpublished and ongoing trials were added by contacting the authors.

Study selection

Eligibility of studies was identified independently by two reviewers (CT Xia and H Fang) in three stages. Firstly, title and abstracts from all search results were screened for eligibility in duplicate. Secondly, studies were excluded if title and/or abstract had an obvious violation of the inclusion criteria. The lastly, full-text articles were obtained for all studies matching the inclusion criteria or with unclear eligibility. Any disagreement was resolved by consensus, if necessary, with the help of the senior authors (X Guo).

Data collection process

Two reviewers (CT Xia and H Fang) extracted data from each trial in duplicate and entered into a predefined datasheet. And then the third investigator (FF Yu) checked data consistency, any discrepancy identified was discussed until consensus.

Data items

Data was extracted using structured data extraction tables including the contents: trial design, inclusion and exclusion criteria, subject's general data, characteristics of HA, usage of HA and controls, lost to follow-up, the outcome measures of effect (mean, standard deviation and effective rate). If research literature did not include the exact data, we consulted the original author by e-mail.

Methodological quality evaluation

The risk of bias of included studies was accessed using the Jadad score[34] with the following items: (1) reporting of a randomization method, (2) allocation concealment, (3) blinding method, and (4) completeness of follow-up (Table II). And then the risk of bias was divided into low and high grades by Jadad score. The quality assessment was carried out independently by two researchers (CT Xia and H Fang) with parallel cross check. Any disagreement was resolved by consensus (FF Yu) (Table III). Q2

Data synthesis Q3

Data analysis was performed using StataSE version 11 (STATA Corp, College Station, TX). For non-continuous variables results we used odds ratios (OR) and 95% confidence intervals (CI) for the effect size according to the intention-to-treat (ITT) principles. For continuous variables we used the standard mean difference (SMD) and 95% CI for the effect size in each time window: (1) pre-treatment to post-treatment SMD for IAHA and (2) SMD for IAHA vs controls. For reference, SMD values of 0.2, 0.5, 0.8, and 1.0 are defined as small, medium, large, and very large, respectively[35]. The pooled effect was first calculated at each time point separately using a random effects model with the DerSimonian-Laird method[36]. We used forest plots with 95%CI to present the pooled data. And then the "random-effect" model was used to take meta-

Please cite this article in press as: Yu FF, et al., Evaluation of the therapeutic effect of treatment with intra-articular hyaluronic acid in knees for Kashin-Beck disease: A meta-analysis, Osteoarthritis and Cartilage (2014), http://dx.doi.org/10.1016/j.joca.2014.04.012