

Hyaluronate for temporomandibular joint disorders (Review)

Shi Z, Guo C, Awad M



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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
METHODS	3
RESULTS	5
DISCUSSION	11
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	12
REFERENCES	12
CHARACTERISTICS OF STUDIES	15
DATA AND ANALYSES	22
Analysis 1.1. Comparison 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo, Outcome 1 Short term effect on improvement of symptoms (for Bertolami 1993, only patients with DDR included).	23
Analysis 1.2. Comparison 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo, Outcome 2 Short term effect on improvement of clinical signs.	23
Analysis 1.3. Comparison 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo, Outcome 3 Long term effect on improvement of clinical signs.	24
Analysis 1.4. Comparison 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo, Outcome 4 Sensitivity analysis for 1.1-1.3 (intention-to-treat analysis).	24
Analysis 2.1. Comparison 2 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs glucocorticoids, Outcome 1 Short term effect on improvement of symptoms.	25
Analysis 2.2. Comparison 2 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs glucocorticoids, Outcome 2 Short term effect on improvement of clinical signs.	25
Analysis 3.1. Comparison 3 Treatment effects of hyaluronate on single clinical variables, Outcome 1 Treatment effects of hyaluronate on TMJ pain relieving.	26
APPENDICES	26
WHAT'S NEW	27
HISTORY	27
CONTRIBUTIONS OF AUTHORS	27
DECLARATIONS OF INTEREST	28
SOURCES OF SUPPORT	28
INDEX TERMS	28

[Intervention Review]

Hyaluronate for temporomandibular joint disorders

Zongdao Shi¹, Chunlan Guo², Manal Awad³

¹Department of Oral and Maxillofacial Surgery, West China College of Stomatology, Sichuan University, Chengdu, China. ²Dentistry Department, Peking Union Medical College Hospital, Beijing, China. ³College of Health Sciences, American University of Sharjah, Sharjah, United Arab Emirates

Contact address: Zongdao Shi, Department of Oral and Maxillofacial Surgery, West China College of Stomatology, Sichuan University, No 14, 3rd section, Renmin Nan Road, Chengdu, Sichuan Province, 610041, China. shizd0664@yahoo.com.cn. shizd0664@vip.sina.com.

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ABSTRACT

Background

Temporomandibular joint disorders (TMD) refer to a group of heterogeneous pain and dysfunction conditions involving the masticatory system, reducing life quality of the sufferers. Intra-articular injection of hyaluronate for TMD has been used for nearly 2 decades but the clinical effectiveness of the agent has not been summarized in the form of a systematic review.

Objectives

To assess the effectiveness of intra-articular injection of hyaluronate both alone and in combination with other remedies on temporomandibular joint disorders.

Search strategy

Intensive electronic and handsearches were carried out. The Cochrane Oral Health Group's Trials Register (September 2001), CENTRAL (*The Cochrane Library* 2001, Issue 3), MEDLINE (1966 to May 2001), PubMed (up to March 2002), EMBASE (1980 to August 2001), SIGLE (1980 to December 2001), CBMdisc (1983 to July 2001, in Chinese) and Chinese Medical Library were searched. All the Chinese professional journals in the oral health field were handsearched and conference proceedings consulted. There was no language restriction.

Selection criteria

Randomized or quasi-randomized controlled trials (RCTs), with single or double blind design, testing the effectiveness of hyaluronate for patients with temporomandibular joint disorders.

Data collection and analysis

Two review authors independently extracted data, and three review authors independently assessed the quality of included studies. The first authors of the selected articles were contacted for additional information.

Hyaluronate for temporomandibular joint disorders (Review)

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1

Main results

Seven studies were included in the review. Three studies, including 109 patients with temporomandibular disorders, compared hyaluronate with placebo. Long term effects (3 months or longer) are in favour of hyaluronate for the improvement of clinical signs/overall improvement of TMD (RR = 1.71, 95% CI: 1.05, 2.77) from two of the studies (n = 71). However, this conclusion was not stable enough at sensitivity analysis.

Three studies provided data from 124 patients for the comparison of hyaluronate with glucocorticoids (one study also included a placebo group). Hyaluronate had the same short term and long term effects on the improvement of symptoms, clinical signs or overall conditions of the disorders as glucocorticoids.

When comparing the effect of arthroscopy or arthrocentesis with and without hyaluronate, results were inconsistent. Hyaluronate had a potential in improving arthroscopic evaluation scores.

Mild and transient adverse reactions such as discomfort or pain at the injection site were reported in the hyaluronate groups. No quality of life data were reported

Authors' conclusions

There is insufficient, consistent evidence to either support or refute the use of hyaluronate for treating patients with TMD. Further high quality RCTs of hyaluronate need to be conducted before firm conclusions with regard to its effectiveness can be drawn.

PLAIN LANGUAGE SUMMARY

Hyaluronate for temporomandibular joint disorders

There is insufficient evidence to either support or refute the use of hyaluronate for treating patients with temporomandibular joint disorders.

When the joint between lower jaw and the base of the skull is not working well it can lead to movement problems, noises (clicking or grating), muscle spasms or pain (temporomandibular joint disorders (TMD)). Arthritis can also affect the joint. A range of treatment options are available including the injection of substances such as glucocorticoids or hyaluronate into the joint. Hyaluronate is sometimes used for osteoarthritis of the knees or hips. The review found that there is not enough evidence to judge whether hyaluronate injections into the joint are helpful for people with TMD. Reported side-effects were mild and transient. No data on quality of life were reported.

BACKGROUND

Temporomandibular joint disorders (TMD) refer to a group of heterogeneous pain and dysfunction conditions involving the masticatory system. Common signs and symptoms include facial and jaw pain, clicking or crepitus of the temporomandibular joints (TMJ), restriction of mandibular movement, and deviation on opening (Rugh 1985), influencing life quality of the sufferers.

The prevalence of clinical signs and symptoms of TMD have been reported from about 10% to 76%, increasing with age groups, however, TMD is more common in those 20 to 40 years of age (Solberg 1979; Wanman 1986). Usually the prevalence of symp-

oms is less than that of clinical signs. A survey of TMD in the population aged from 15 to 38 years in Chengdu, China revealed that the prevalence of signs was 75.8% whereas prevalence of symptoms was 13.1% (Xu Yinghua 1989).

Synovitis, internal derangement (ID) and osteoarthritis (OA) of the TMJ produce similar common symptoms to those of TMD (de Bont 1986; de Bont 1989; Stegenga 1989; Stegenga 1992). There have been various remedies applied to these problems such as anti-inflammatory drug therapy, occlusal appliance therapy, physical therapy, intra-articular glucocorticoids (CO) injections, arthro-

centesis, arthroscopy and arthroplasty, etc. (Ishigaki 1992; Mohl 1992). The principle approach for the selection of therapies is that those which are easier to use and are without irreversible effects are tried first. Intra-articular injection of CO was widely used as a simple method to treat the intra-articular problems of the TMJ (Kopp 1981; Toller 1977; Wenneberg 1991; Zhang 1985). Unfortunately experimental studies showed evidence that CO might cause necrosis of the articular cartilage (Kikiewicz 1985; Shi 2002(A)), and clinical reports showed evidence that multiple injections of such a drug might cause damage to the TMJ (Chandler 1958; Toller 1977).

Sodium hyaluronate (HS) is one of the natural components of synovial fluid of the joints, playing an important role in lubricating and maintaining the normal internal environment of the joints. HS intra-articular injection showed good effects in experimental models of osteoarthritis in animals (Abatangelo 1989; Kitoh 1992; Neo 1997; Schiavinato 1989; Shi 2002(A)) and traumatic arthritic joints of race horses (Rydell 1970). Since 1970, it has been used for treating human osteoarthritis of knee and hip joints (Peyron 1974). Short term and long term effects of intra-articular injection of HS into the TMJ were first reported by Kopp in 1979 (Kopp 1979). Since then several studies applying HS alone or in combination with other remedies for patients with TMD have been conducted and the results published (Alpaslan 2000; Bertolami 1993; Edwards 1994; Hepguler 2002; Hirota 1998; Kopp 1985; Kopp 1991; Shi 2002(B)). However the sample sizes of the studies are quite small. It is necessary to perform a systematic review to pool the results together to precisely estimate the treatment effect and adverse reactions of HS. This will assist clinicians and patients in making appropriate clinical decisions.

OBJECTIVES

(1) To assess the effectiveness of intra-articular injection of hyaluronate both alone and in combination with other remedies in relieving short and long term symptoms of temporomandibular joint disorders.

(2) To determine number, type and severity of adverse reactions following intra-articular use of hyaluronate.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials (RCTs) (using true or quasi methods of randomization) aiming to test treatment effects of

hyaluronate (HS) intra-articular injections on patients with TMD were identified and included.

Types of participants

Patients of both sexes, aged above 18 years who were diagnosed by clinical and/or imaging criteria (Dworkin 1992; List 1996; Stegenga 1992(B)) with TMD or rheumatoid arthritis of the TMJ regardless of their race, social and economical status, profession or residential locations.

Types of interventions

The treatment group received at least one intra-articular injection of HS alone or in combination with other active treatments for TMD. The control group could receive placebo or glucocorticoids (CO) injections alone or the same active treatments as the test group.

Types of outcome measures

The principal outcome variables collected for analysis were as follows.

(1) Subjective assessments made by the patients such as pain on face and jaw, clicking or crepitation of the TM joints and masticatory dysfunction; clinical assessments made by the observers such as tenderness on the TMJ and masticatory muscles, pain on jaw movement, ranges of mandibular movements, or some indices such as Helkimo anamnestic scores, clinical dysfunction scores etc.

(2) Those variables used in at least one study such as bite force, as one of the physical indicators, improvement of quality of arthroscopic procedures, measurements for quality of life.

(3) Adverse effects of hyaluronate intra-articular injection.

(4) Withdrawals for adverse effects, drop outs and the number lost to follow up.

Search methods for identification of studies

There was no language restriction for inclusion.

Published literature

The following databases were searched for relevant studies.

Cochrane Oral Health Group's Trials Register (most recent search up to September 24, 2001) (Appendix 1).

Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2001, Issue 3).

MEDLINE (1966 to May 2001) (Appendix 2).

PubMed (up to March 2002) (Appendix 3).

EMBASE (1980 to August 2001 week 2) (Appendix 4).

System for Information on Grey Literature in Europe (SIGLE) (1980 to December 2001) ([Appendix 5](#)).

Chinese literature databases such as the Chinese Biomedical Literature Database (CBMdisc - published by the Information Institute of Chinese Academy of Medical Sciences, including medical data indexed from over 900 medical journals, proceedings etc. from 1981 onwards) (1983 to July 2001, in Chinese) and Chinese Medical Library produced by Chinese Cochrane Center.

Handsearching

All the Chinese professional journals within the oral health field from the first issue of publication before 1996 were searched by Zongdao Shi and his colleagues CL Guo, E Chen, WL Zhan, F Xia and L Chen. Fifteen Chinese dental journals were searched:

- *Chinese Journal of Stomatology* (1953 to 2000)
- *Journal of Stomatology* (1981 to 2000)
- *West China Journal of Stomatology* (1983 to 2000)
- *Journal of Practical Stomatology* (1985 to 2000)
- *Journal of Clinical Stomatology* (1985 to 2000)
- *Journal of Comprehensive Stomatology* (1985 to 2000)
- *Journal of Modern Stomatology* (1987 to 2000)
- *Chinese Journal of Conservative Dentistry* (1991 to 2000)
- *Journal of Maxillofacial Surgery* (1991 to 2000)
- *SHSngHSi Journal of Stomatology* (1992 to 2000)
- *Chinese Journal of Dental Material and Devices* (1992 to 2000)
- *Beijing Journal of Stomatology* (1993 to 2000)
- *Chinese Journal of Dental Prevention and Treatment* (1993 to 2000)
- *Chinese Journal of Orthodontics* (1994 to 2000)
- *Chinese Journal of Implantology* (1996 to 2000).

Unpublished literature

In the proceedings of the Third National Symposium on Temporomandibular Disorders which was held in Xiamen, Fujian Province, China from June 16 to 21, 2001, three RCT reports were presented, one by Z Shi which was subsequently published in full ([Shi 2002\(B\)](#)), the other two by [Chu 2001](#) and [Qi 2001](#), *see Description of studies*.

The first authors of all selected articles were contacted to ask if they knew of any unpublished articles examining the role of hyaluronate in the treatment of TMD.

In total two abstracts and 21 articles were identified through the search.

Data collection and analysis

Study identification

Initially the titles, abstracts (where available) and key words of the 23 identified studies were screened by Zongdao Shi (ZS) and independently judged by two review authors (ZS and Chunlan Guo (CG)) to determine whether they were relevant to the systematic review. In total, 13 studies with randomized controlled design (true or quasi) examining the effectiveness of intra-articular injection of hyaluronate (HS) on the patients with clinically or radiographically confirmed TMD or rheumatoid arthritis were identified, in which two were abstracts only ([Chu 2001](#); [Qi 2001](#)). The authors of the 11 selected articles were contacted by letter or email or both to ask if they could offer more detailed information for their published articles, if they knew of any unpublished materials relating to hyaluronate in the treatment of patients with TMDs and how they would anticipate the prospect of using this drug for TMD in the future. Two authors responded, providing important information on methodology and clarified issues regarding the quality assessment of their articles. The review authors are highly appreciative of the honesty of the corresponders (Professor Alpaslan of Gazi University, Turkey and Gu Zhiyuan of Zhejiang University of China). The review author Zongdao Shi as first author of one included randomized controlled trial (RCT) re-analyzed data in order to provide more relevant information for the review, however, he was not involved in the quality assessment of this trial. One RCT by [Gu 1997](#) was excluded because the first author informed the review authors that part of the study sample (20 patients) were reused in a subsequent RCT [Gu 1998](#). The first author could not be contacted for [Qian 1999](#), so the technique being used could not be confirmed. Hence [Qian 1999](#) was also excluded at this stage, leaving nine studies for further consideration.

Various brands of HS were used in different studies. The manufacturers of the HS products were contacted for more information concerning adverse reactions through the Cochrane Oral Health Group (COHG) Co-ordinator. There was no response from the manufacturers by the time the review was submitted for publication. Any new information from manufacturers in the future will be used for updating the review.

Data extraction

Two review authors (ZS and CG) independently extracted data from the included studies. Contents of the data extraction included: details of the study setting, characteristics of the study samples, dosage and course of the interventions, baseline and the outcomes. Disagreement on data extraction was resolved by discussion.

Quality assessment

Three review authors (ZS, CG and Manal Awad (MA)) independently assessed the quality of each study according to the *Cochrane Reviewers' Handbook*. The strengths and weaknesses of the study

design of each included study were analyzed. Disagreements on validity assessment were resolved by discussion.

The main items of the quality assessment were:

- 1) Was the study randomized and the randomization procedure clearly stated?
- 2) How good was the allocation concealment?
- 3) Was the study described as blind?
- 4) Was there a clear description of withdrawals and drop outs?

Data analysis

All the analyses were based on the specific numerical data provided in the published articles. In the cases of missing or confusing data the review authors contacted the first authors to supplement and clarify the data. If the review author failed to get further information then only the complete data were used for meta-analysis.

The follow-up time varied across studies. From the view of clinicians and the sufferers of TMD, it is important to know the clinical effect of hyaluronate in both the short and long term. It is, therefore, clinically important to analyze the effect of treatment in different time periods. For the purpose of this review, a short term effect was defined as an outcome evaluated within 3 months from the first injection of hyaluronate. Long term effects were defined as outcomes evaluated at 6 months or longer.

The outcome variables could be defined in three categories: symptoms which reflect subjective feeling and judgment of the patients, clinical signs reflecting objective judgement of the observers, and other measurements such as bite force, arthroscopic quality, etc. Where possible, effects on single items of symptoms such as pain, noise of the joints or clinical signs such as mouth opening, tenderness of the TMJ or masticatory muscles were to be analyzed. Intention-to-treat analysis was used to assess the effects of hyaluronate on TMD if the follow up or drop outs were clearly reported.

Meta-analysis was conducted to synthesize the effect of hyaluronate across studies. If statistically significant heterogeneity existed, the source for the variability was analyzed and a random-effects model was used. A fixed-effect model was used when data were homogeneous. For binary outcomes, risk ratios (RR) with the 95% confidence intervals were calculated using a fixed-effect model when homogeneity existed across studies, a random-effects model (DerSimonian-Laird method) when heterogeneity existed. For continuous outcomes weighted mean differences and 95% confidence intervals were calculated. Again a fixed-effect model was used when data were homogeneous and a random-effects model if significant heterogeneity was shown. Forest plots were used to illustrate the outcome comparisons.

Sensitivity analysis was carried out upon different assumptions to test the stability of the conclusions.

Publication bias was to be estimated using appropriate statistical methods and the strengths and generalizability of the evidence carefully explained.

Adverse reactions were examined to determine the number, type and severity.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Included studies

(See [Characteristics of included studies](#) table.)

From the extensive searches and following an initial screening, nine randomized controlled trials (RCTs) were identified. Within these nine RCTs, the first author was the same for three studies: [Kopp 1985](#); [Kopp 1987](#); [Kopp 1991](#). Following discussion with the Cochrane Oral Health Group, one study ([Kopp 1987](#)) needed to be excluded: [Kopp 1987](#) did not fulfil the criteria for a randomized controlled trial of crossover design. One RCT was identified which compared hyaluronate with lidocaine ([Gu 1998](#)). This study falls outside the remit of this review with regard to the control group, but meets all other inclusion criteria. A decision to broaden the scope of the review at update has been made and studies comparing hyaluronate with other control groups will be searched for and included. Details of all 16 excluded studies are presented in the [Characteristics of excluded studies](#) table.

As a result, seven studies were included in the data analysis of the review. According to the characteristics of the interventions, three types of comparisons could be defined:

- sodium hyaluronate (HS) versus placebo (PL);
- HS versus glucocorticoids (CO);
- HS plus other basic treatment (e.g. arthroscopy or arthrocentesis) versus basic treatment alone/with placebo.

The study of [Kopp 1991](#) had three treatment groups, hyaluronate (HS), placebo (PL) and glucocorticoids (CO) so appears in two of the following sections.

(I) Studies comparing hyaluronate (HS) and placebo (PL)

There are three studies making comparisons between the therapeutic effects of HS and PL on TMD.

[Kopp 1991](#): A randomized, double-blind placebo-controlled trial was carried out in 41 patients with rheumatoid arthritis involving the TMJ. Patients were divided into three parallel groups: 14 on HS, 14 on CO and 13 on PL. All of the three agents were injected into the upper compartment of the TMJ with volume of 0.7 ml, repeated once 2 weeks later. The concentration of hyaluronate was 10 mg/ml, and methylprednisolone (a glucocorticoid) 40 mg/ml.

The outcomes measured were pain of the TMJ, subjective symptom improvement, clinical dysfunction scores, maximum voluntary mouth opening, tenderness to palpation of the TMJ and muscle regions. The patients were followed up for a period of 4 weeks.

Bertolami 1993: A multicenter randomized, double-blind, placebo-controlled trial was conducted in 121 patients with intracapsular TMJ disorders. The HS group included 80 patients, 35 with reducing displaced disc (DDR), eight with non-reducing displaced disc (DDN), 37 with degenerative joint disease (DJD). The PL group included 41 patients, 15 with DDR, 6 with DDN and 20 with DJD. A single injection of HS (10 mg/ml) or saline into the upper compartment of the TMJ dictated by joint space volume was made and the patients were then followed for 6 months, with weekly checking in the first month and monthly checking for the rest of the follow-up period. Visual analogue scales of noise, noise locations, total and intracapsular scores from both the dysfunction and anamnestic indices, as well as the most clinically relevant variables such as joint noise and mandibular deviation, muscular soreness scores and mandibular protrusion were used as measurement variables for the within and between group outcome comparisons.

Hepguler 2002: A randomized, double-blind, placebo-controlled trial was conducted in patients over 21 years of age. Patients fulfilled standard criteria for DDR and were resistant to conservative therapy for over 2 months. There were 19 patients in both the HS group and PL group. A volume of 0.5 ml of HS (15 mg/ml) or saline was injected into the superior joint compartment of the TMJ and was repeated 1 week later. The patients were reassessed 1 and 6 months after the last injection. Sound and pain intensity of the TMJ and modified Helkimo's clinical dysfunction index were used to measure the clinical outcomes.

(2) Studies concerning comparisons between hyaluronate (HS) and glucocorticoids (CO)

There are three studies comparing the effects of HS and CO on TMD.

Kopp 1985: A randomly allocated, double-blind controlled trial was performed in 33 patients with TMD for whom conservative treatments had failed. Eighteen patients received injections of 1% HS 0.5 ml in the upper compartments of the TMJs twice, 2 weeks apart and 15 patients received CO using the same approach. Follow up was made for up to 4 weeks. The outcomes were evaluated using subjective symptoms which were summarized in a questionnaire containing 10 questions including pain in the TMJ and facial area, difficulties with opening the mouth widely, joint sounds, duration of symptoms, and pain and stiffness in other joints etc, severity of subjective dysfunction scores, clinical dysfunction scores, tenderness to palpation of the TMJs and the muscle, detection of TMJ crepitation and maximum bite force etc.

Kopp 1991: mentioned above.

Shi 2002(B): A randomized, double-blind controlled trial in 67

patients with TMD. Four dropped out (two from each group), leaving 35 in the HS group and 28 in the CO group. In the HS group seven patients had synovitis, 14 DDN and 14 had OA. In the CO group, seven had synovitis, seven had DDN and 14 OA. 1% HS 0.6 ml for test group and 2.5% prednisolone 0.5 ml for control group were mixed with 0.5% bupivacaine 1 ml for an upper compartment injection of the TMJs, once a week for three to four injections. One week after the last injection the patients were re-checked clinically using the following variables: clicking, visual analogue pain scores, pain at jaw movement, function restriction scores, maximum voluntary opening, tenderness scores on the lateral part of the TMJ and mandibular deviation.

(3) Studies concerning comparisons between hyaluronate (HS) with arthroscopy or arthrocentesis in one arm and arthroscopy or arthrocentesis without HS in another arm

There are two studies in this category.

McCain 1989: A randomly allocated, single-blind trial was performed in 33 patients meeting the criteria of the American Association of Oral and Maxillofacial Surgeons for TMJ arthroscopy. TMJ arthroscopies were done in 33 joints with HS and Ringer's saline and 22 with Ringer's saline alone. HS was used in insufflation and irrigation when the arthroscopic procedure was being undertaken. The dosage was 0.5% HS 2.6 ml (range 1 to 5 ml) in average for insufflation, and the mean volume of 24.2 ml (range 6 to 94 ml) for irrigation. Comparisons were based on the number of TMJs instead of the number of cases. Except arthroscopic quality, some symptoms such as pain and clinical signs such as clicking, tenderness were evaluated.

Alpaslan 2001: A randomized, single-blind controlled trial of arthrocentesis (AC) with and without HS injection in 41 TMJs of 31 patients. There were 16 patients with DDR, in whom 2 received AC plus HS, four received AC only; 15 cases with DDN, in whom 11 cases were given AC plus HS and four given AC only. Clinical evaluations were undertaken after the procedure, at day one, and then monthly for the first 6 months and subsequently at months 9, 12, 18 and 24. The treatment groups were compared in terms of intensity of pain, jaw function, maximal mouth opening, clicking and mandibular lateral movement

Excluded studies

(See [Characteristics of excluded studies](#) table for further details.)

From the search strategies, besides the included studies there were 16 additional articles or abstracts identified for which the full copies were obtained. After thorough reading and discussion, these studies were excluded based on the inclusion and exclusion criteria. Although the reasons for exclusion for each study varied, the main points were deficiency of randomization, lack of control group, insufficient reporting, only available as an abstract.

Risk of bias in included studies

Six of the seven included studies examine the treatment of temporomandibular joint disorder, including DDR, DDN and DJD. One randomized controlled trial (RCT) (Kopp 1991) focused on rheumatoid arthritis of the TMJ. All the targeting diseases belong to intracapsular pathology, having the same sorts of symptoms and clinical signs. It was reasonable to group them together within the review.

Four of the included trials used true randomization techniques, such as third party randomization. For three studies the method used to generate the sequence of allocation was not stated (Alpaslan 2001; Kopp 1985; Kopp 1991). Five studies (Bertolami 1993; Kopp 1985; Kopp 1991; Hepguler 2002; Shi 2002(B)) were double blinded, and the other two were single blinded. The inclusion and exclusion criteria of the studies were clearly stated. All included patients had symptoms and/or clinical signs resistant to previously conservative therapies. All studies were conducted following serious ethical considerations, and consent was obtained before allocation to treatment.

Three studies (Alpaslan 2001; Bertolami 1993; McCain 1989) did not fully report the cases that withdrew or were lost to follow up. For this reason, it is difficult to use the intention-to-treat method to estimate the therapeutic effects of HS in comparison to control groups. The other five studies reported drop outs and the number lost to follow up directly or one could obtain the figures from the attached tables.

TMD is a clinical dysfunction disorder relating to psychiatric and social factors. Quite a lot of symptoms of the masticatory system are 'soft' variables not able to be quantitatively expressed. Nevertheless the authors of the included studies made a good effort to use quantitative methods to estimate the size of the therapeutic effects, such as visual analogue scale for scoring pain, severity of the symptoms, impairment of the function and Helkimo indices. Synthesized clinical variables included several items, might cause some problems e.g. readers could not estimate which of the items had changed following the interventions.

Analysis of confounding bias is important in determining the intervention-effect relationship. In reality many factors might result in better functional status. For example, fluctuation of the TMD symptoms over time and natural regression towards normal are common phenomena. Reducing parafunctions of the masticatory system and/or reducing masticatory loading etc. could lead to remission of the symptom and clinical signs of TMD. Further more, other treatments such as occlusal therapy, physical therapy and medication etc. may bring about improvement of TMD. Only a few studies paid attention to and analyzed the confounding biases.

Effects of interventions

Part I: Evaluation of the treatment effects of hyaluronate on TMD by synthesized clinical variables

Short term effect of hyaluronate (HS) in comparison with placebo (PL) on improvement of symptoms of TMD (Comparison 1, Outcome 1.1)

In the study by Kopp 1991, at 4 weeks after the last injection the patients were asked to compare their symptoms with pretreatment condition: if symptom free, much improved, slightly improved, no change or worse. Symptoms improved in 10 out of 14 cases in the HS group and nine out of 13 in the PL group. Symptoms, as measured by a VAS, decreased by a median of 11 mm in the HS group and 8 mm in the PL group. Bertolami 1993 reported that in patients with DDR at least one anamnestic class improved in four patients (12.5%) in the HS group and none improved in the PL group.

Pooling the two trials together made the total number of participants up to 70, 44 receiving HS and 26 receiving placebo. No statistically significant effect in the HS group could be seen (RR = 1.24, 95% CI: 0.72, 2.14). Bertolami 1993 reported that in the patients with DDR, the total and intracapsular scores from the anamnestic indices, as well as the most clinically relevant variables such as joint noise and mandibular deviation showed a consistent and significant improvement for patients receiving HS in comparison with those in the PL group. In patients with DDN, anamnestic scores and intracapsular anamnestic scores showed little within-groups and between-groups differences during weeks one to four. In patients with DJD, the anamnestic scores improved in both groups but without a statistically significant difference between groups. However, there were no detailed numerical data available for meta-analysis for the subgroups of DDR, DDN and DJD.

Short term effect of HS in comparison with PL on improvement of clinical signs or overall improvement of TMD (Comparison 1, Outcome 1.2)

Bertolami 1993 indicated that the clinical dysfunction index derived from Helkimo and co-workers was a semi-quantitative tool to grade severity of pain and dysfunction of the TMJ. In the patients with DDR, 22 out of 30 in the HS group improved for at least one dysfunction class, eight out 14 improved in the PL group. For the patients with DDR the total and intracapsular scores from dysfunction showed a consistent and significant improvement for HS group in comparison with PL group. For the patients with DDN, at least one dysfunction class improved in all cases for HS group and 40% in PL group with significant difference between two groups, intracapsular scores significantly improved in HS group in comparing with PL group. In DJD patients, more patients in the PL group relapsed at least one dysfunction class than in the HS group, but no statistically significant difference was seen between the two groups.

Kopp 1991 showed that clinical dysfunction scores (CDS) decreased by a median of five in both the HS and PL groups. The reduction in CDS was greater than four in eight cases in the HS group and seven cases in the PL group.

Hepguler 2002 used a modified Helkimo index (by Kurita 1997) with four levels to grade the treatment responses:

- total remission - if the index components all went down to the 0 or 1 level;
- partial remission - if one index component was at a level >1;
- unchanged - if none of the components went up or down;
- exacerbated - if one or more of the index components went up.

Total or partial remission showed in 17 patients (89.5%) at 1 month in the HS group, four patients (21%) in the PL group. In a meta-analysis of the three sets of data, heterogeneity was shown ($P < 0.1$), so a random-effects model was used. The overall results included 109 patients; 63 on HS and 46 on PL. No statistically significant difference between groups was shown. But if the heterogeneity was ignored and fixed effects model used, the overall effect became statistically significant.

Long term effect of HS in comparison with PL on improvement of symptoms of TMD

One study reported the long term effect of HS in comparison with PL on improvement of symptoms of TMD. In the article by Bertolami 1993, from Figure 3 and Table 3 of the paper the number of patients with DDR improving at least one anamnestic class at the sixth month could be calculated. 25% (5/20) of the patients in the HS group improved whereas none of the patients in the PL group improved. For patients with DDN no symptom data at 6 months were reported. For patients with DJD the anamnestic and visual analogue scores were significantly improved for both groups but statistically significant differences between group were not detected.

Long term effect of HS in comparison with PL on improvement of clinical signs or overall improvement of TMD (Comparison 1, Outcome 1.3)

In the article by Bertolami 1993, from Figure 1 and Table 3 of the paper, the number of patients with DDR improving at least one dysfunction class at the 6-month visit could be calculated. 70% (14/20) of the HS group improved and 53.8% (7/13) of the PL group improved. For patients with DDN no clinical signs data at 6 months were reported. In patients with DJD, the dysfunction scores improved in both groups but without differences between groups. Unfortunately there are also no numerical data available for analysis of DJD.

In the article by Hepguler 2002, total or partial remission, as indicated by the modified Helkimo's index, were shown in 12

patients (63.2%) at 6 months in HS group, and five (26%) in the PL group.

In total, 71 patients with TMD were checked at 6 months (39 receiving HS and 32 receiving PL). The clinical signs or overall dysfunction of TMD had statistically significantly improved in the HS group when compared to those of the PL group (RR = 1.71, 95% CI: 1.05, 2.77). This suggests that hyaluronate had a long term effect in improving clinical signs of TMD.

Sensitivity analysis of long term effect of HS in comparison with PL on improvement of clinical signs or overall improvement of TMD (Comparison 1, Outcome 1.4)

An intention-to-treat analysis was carried out. Of the two studies, only Bertolami 1993 had different numbers at baseline and 6 month examination. The number of patients with DDR allocated to receive HS was 35 instead of 20, and to receive PL 15 instead of 13. Using these numbers, the meta-analysis showed no statistically significant difference between the two groups (RR = 1.39, 95% CI: 0.51, 3.85). This suggest that the conclusion that hyaluronate had a long term effect in improving clinical signs of TMD is not yet stable.

Short term effect of HS in comparison with glucocorticoids (CO) on improvement of symptoms of TMD (Comparison 2, Outcome 2.1)

There are three studies concerning these comparisons. Kopp 1985 reported that the subjective symptoms were summarized in a questionnaire containing ten questions including items such as pain in the TMJ and facial area, difficulties with opening the mouth widely, joint sounds, duration of symptoms, pain and stiffness in other joints. Severity of subjective dysfunction was graded in two ways: one way by using a subjective dysfunction severity score with five levels: minimal or no discomfort, slight discomfort, moderate discomfort, severe discomfort, very severe discomfort and another way by using visual analogue scale. Thirteen patients out of 18 improved in HS group and nine out of 15 improved in CO group. Compared with baseline, the subjective symptoms represented by the average VAS were significantly reduced for both groups: 30% for HS and 40% for CO. Kopp 1991 reported that the symptoms improved in ten cases in HS group, 13 in the CO group. Symptom, as reported by VAS, decreased by a median of 11 mm in HS, 34 mm in CO groups. Shi 2002(B) reported that 32 cases (91.4%) of the HS group and 25 cases (89.3%) in CO group improved their symptoms of TMD.

Meta-analysis for the three studies with 124 patients in total, 67 on HS and 57 on CO, showed no heterogeneity among the results. The overall effect showed no statistically significant difference between the two groups (RR = 0.99, 95% CI: 0.84, 1.17).

Short term effect of HS in comparison with CO on improvement of clinical signs or overall improvement of TMD (Comparison 2, Outcome 2.2)

For this comparison, the same three studies were included (Kopp 1985; Kopp 1991; Shi 2002(B)). Kopp 1985 indicated that the median clinical dysfunction scores reduced from 8.5 at baseline to 6.5 at week four after the final injection of HS. The reduction was from 12 to three for the CO group. The number of cases improving were 13 out of 18 for HS group and 13 out of 15 for the CO group. Kopp 1991 reported that the clinical dysfunction scores decreased by a median of five in the HS group and six in the CO group. A reduction in clinical dysfunction scores greater than four occurred in eight cases in the HS group and 11 cases for the CO group. Shi 2002(B) reported that function restriction scores decreased more than half of those at baseline in eight cases (22.9%) in the HS group and four (14.3%) in the CO group, with no statistically significant difference between groups ($P > 0.05$). In total 124 cases were included in the meta-analysis: 67 receiving HS and 57 receiving CO. There was no statistically significant difference between the groups in terms of improvements of clinical signs in short term (RR = 0.91, 95% CI: 0.66, 1.25).

Effect of HS with arthroscopy or arthrocentesis in comparison to arthroscopy or arthrocentesis without HS on improvement of symptoms and clinical signs of TMD

In the study by McCain 1989, a variable 'clinical condition' was used but it was unclear what items of symptoms or clinical signs were included in the variable. Hence it was difficult to compare it with the effect of overall symptoms and clinical signs reported by others. However, the effects on some single items of symptoms and clinical signs were presented in two tables. From the tables' data it could be seen that there is no significant difference between the two groups e.g. arthroscopy with HS and arthroscopy without HS in terms of muscular pain or joint pain scores, mean change from baseline for mouth opening etc. Alpaslan 2001 reported that pain was significantly relieved in the patients receiving arthrocentesis (AC) with HS in comparing to AC alone at second month. Also clicking significantly disappeared in patients receiving HS with AC and not in the AC alone group. Jaw function improved significantly irrespective of the diagnosis for the group with HS but only for the subgroup of patients with DDR without HS. Alpaslan 2001 used diagrams instead of numerical data to present the above outcomes so unable to perform meta-analysis to synthesize the data of McCain 1989. Nevertheless Alpaslan 2000 reported good detail on measurements of jaw motion in the follow up period up to 2 years, showing a tendency that HS with AC had a potential in consistently significantly increasing maximal opening in comparing with the AC group, especially beneficial to the patient with closed lock. This may be viewed as a therapeutic effect of hyaluronate.

Effect of HS with arthroscopy or arthrocentesis in comparison to arthroscopy or arthrocentesis without HS on improvement of arthroscopic procedure

McCain 1989 demonstrated that arthroscopic procedures with HS provided statistically significant better evaluation scores, such as less clogging, better visualization, easier control of debris and tissue debridement, control of synovium, and less volume of irrigation fluid than those of the arthroscopic procedure without HS.

Part 2: Evaluation of the treatment effects of hyaluronate on TMD by single clinical variables

It should be noted that the following data might be incomplete, due to the fact that some of the single variables were reported as elements of the synthesized variables, such as the Helkimo's indices and not reported alone. However, it is useful to summarize the reported single clinical variables to disclose more details about the effects of hyaluronate.

Relief of TMJ pain

There are four studies examining the short term effect on pain relief between HS group and placebo (Bertolami 1993; Hegguler 2002; Kopp 1991), or between HS with AC and AC only (Alpaslan 2001). Only one study had numerical data. Kopp 1991 reported that pain of the TMJ eliminated in 25% of the sufferers in HA, and 33.3% in PL groups. The other three studies all stated that the group with HS had a statistically significant better effect on TMJ pain relief than that of the group without HS, however, no numerical data were reported. Bertolami 1993 reported that visual analogue pain scores consistently improved for HS group and relapsed for PL group. Hegguler 2002 reported that pain intensity of the TMJ measured by VAS showed greater reductions at months one and six in the HS group compared with the placebo group and a statistically significant within group difference in the HS group compared with baseline measurements. Alpaslan 2001 showed that intensity of pain decreased significantly in the HS group (in both DDR and DDN patients). Between group analysis showed there was a steady, statistically significant decrease in pain in the HS group between two to 24 months. In the AC only group significant pain relief was achieved for the DDN patients only. Two studies comparing HS to CO reported on pain relief (Kopp 1991; Shi 2002(B)). The study by Shi 2002(B) reported that VAS scores were reduced by more than half of those reported at baseline in 14 cases in the HS group and 11 cases in the CO group, with no statistically significant difference between groups. Kopp 1991 reported that pain of the TMJ was eliminated in three out of 12 cases in the HA group and four out of 12 cases in the CO group. Pooling these two studies showed no statistically significant difference between groups (RR = 0.95, 95% CI: 0.55, 1.65) (Comparison 3, Outcome 3.1).

The above results suggest that HS has a statistically significant effect on TMJ pain relief in most of the studies in comparison

with placebo, although better reporting of data is required. In comparison to CO, HS shows no statistically significant difference in pain relief.

Relief of TMJ sounds

Two studies comparing HS to PL reported on reduction in sounds (Bertolami 1993; Hegguler 2002). Bertolami 1993 reported that for the patients with DDR, noise, as measured on a VAS, decreased in both groups but there was no statistically significant difference between groups. Nevertheless, the noise location showed a greater degree of improvement for HS group than PL group. For the patients with DJD, noise amplitude improved in both groups at same level at month six. Hegguler 2002 reported that the sound intensity of the TMJ measured by VAS showed greater reductions at month one and six in the HS group compared with the PL group with statistically significant within group difference in the HS group compared with baseline measurements. No numerical data were available for meta-analysis.

Alpaslan 2001 reported that clicking disappeared significantly ($P < 0.05$) for patients receiving HS in conjunction with AC. This same effect was not seen in the AC only group. Between group analysis for joint noise showed a statistically significant reduction in the DDN patients (from 2 through to 9 months) in the HS with AC group in comparison to the AC only group.

Two studies making comparisons between HS and CO reported on changes in noise. Kopp 1985 reported that with regard to detection of TMJ crepitation, no statistically significant change was seen in either the HS or CO groups. Shi 2002(B) reported no significant between group differences, with clicking disappearing in a total of eight cases, four in each group.

From the above results it can be seen that the TMJ sounds reduced significantly in two out of three studies in the group with HS. There was no statistically significant difference between HS and CO with regard to reduction in noise.

Mouth opening

Kopp 1991 reported that the maximum voluntary mouth opening increased by a median of 3 mm in HS and 1 mm in PL groups. Bertolami 1993 reported that the patients with DDN improved mouth opening for the HS group up to 5 mm at week five. The maximum difference between the HS and PL group was 8 mm at week five. However, no statistically significant differences either within or between groups were shown at any time point.

McCain 1989 reported no statistically significant differences between groups with regard to mouth opening or range of motion. Alpaslan 2001 indicated that maximal mouth opening increased in both groups but only statistically significant in the HS with AC group.

Kopp 1991 reported that the maximum voluntary mouth opening increased by a median of 3 mm in HS, compared to 6 mm in

the CO group. Shi 2002(B) reported that maximum voluntary opening increased more than 5 mm in 13 patients (37.1%) in the HS group and seven patients (25.0%) in the CO group. No statistically significant between group differences were shown.

TMJ tenderness

Kopp 1991 reported that tenderness to palpation of the TMJs was reduced but not significantly in both HS and PL groups. McCain 1989 showed no statistically significant difference between arthroscopy plus HS and arthroscopy plus PL groups with regard to reduction of TMJ lateral tenderness.

Three articles comparing HS to CO reported on TMJ tenderness (Kopp 1985; Kopp 1991; Shi 2002(B)). Kopp 1985 reported that tenderness on palpation of the TMJs reduced significantly in both HS and CO groups. However, Kopp 1991 indicated that tenderness on palpation of the TMJs reduced significantly only in CO group. Tenderness of the posterial part of the TMJ reduced in both the HS and CO groups, but only significant in the CO group. Shi 2002(B) reported that tenderness scores for the lateral part of the TMJ reduced by more than half of those recorded at baseline in 13 cases (37.1%) in HS group and four cases (14.3%) in the CO group. The between group difference was statistically significant ($P < 0.05$).

Muscular tenderness

Kopp 1991 reported that the number of tender muscle regions decreased in both HS and PL groups but only statistically significantly in the HS group. Bertolami 1993 indicated that for the patients with DDN, the muscle soreness scores significantly improved in the HS group when compared to PL. McCain 1989 reported that there was no statistically significant difference between groups with regard to muscle tenderness.

Kopp 1985 reported that tenderness of the muscle reduced significantly only in the CO group and not the HS group, whereas Kopp 1991 indicated that the number of tender muscle regions decreased significantly in both HS and CO groups.

Deviation of the mandible

Bertolami 1993 reported that for the patients with DDR the mandibular deviation showed a consistent and significant improvement for HS group in comparison with PL group at months one, four, five and six.

Shi 2002(B) reported that the abnormal deviation reduced to within normal limits in 13 cases (37.1%) in the HS group and six cases (21.4%) in the CO group. No statistically significant difference between the groups was observed ($P > 0.05$).

Maximum bite force

Only one study reported on bite force (Kopp 1985). Maximum bite force was increased in both the HS and CO groups, but only significantly increased in the CO group ($P < 0.05$).

Arthroscopic quality

McCain 1989 demonstrated that HS provided statistically significantly better evaluation scores than Ringer's solution for the arthroscopic procedure, such as less clogging, better visualization, easier control of debris, tissue debridement, control of synovium, and less volume of irrigation fluid.

Quality of life

To date, no RCTs in this area report on quality of life.

Part 3: Adverse reactions of intracapsular injection of hyaluronate

Two articles reported detailed information on adverse reactions of HS and control agents. Bertolami 1993 reported that six patients (7.5%) in HS group developed seven adverse events, such as discomfort at the injection site and localized swelling. Five of these events were classed as mild, one moderate and one severe. Shi 2002(B) reported that 13 patients (37.1%) receiving HS had pain on injection into the TMJ, lasting half a day to 3 days. Three patients had open bite in the injection side and weak bite force. All the adverse reactions could be spontaneously relieved.

Number of patients withdrawing due to adverse reactions of HS

Up to now no trials have reported this information.

DISCUSSION

To date, it is 17 years since the first published report of hyaluronate to treat temporomandibular disorders by Kopp et al (Kopp 1985). Following more and more wide use of this agent in TMJ clinical practice, it is critical to know 'does the published/unpublished data provide strong evidence to justify its use?' This systematic review aims to find the answer to this question.

From intensive literature searches, a total of 21 published articles and two abstracts in a Chinese conference proceeding relevant to hyaluronate and TMD, rheumatoid TMJ arthritis were detected. Seven published articles fulfilled the inclusion criteria of the protocol. The authors of the selected articles were consulted to obtain more information for analysis. The manufacturers of different brands of hyaluronate were contacted for more information

through the Cochrane Oral Health Group. Two authors provided valuable information concerning the methods of their studies and some numerical data. No reply was sent back from the manufacturers. Meta-analysis was conducted only when sufficient data were available to synthesize therapeutic effects of hyaluronate on TMD and rheumatoid TMJ arthritis.

In comparison with placebo, hyaluronate showed no statistically significant short term effect on improving clinical signs or overall conditions of temporomandibular joint disorders in three studies. There is some evidence that hyaluronate had a long term effect in improving clinical signs of TMD in comparison to placebo, based on the findings of two well designed, double-blind RCTs (Bertolami 1993; Hegguler 2002). However, this conclusion is not stable when intention-to-treat analysis was used. In comparison with glucocorticoids, hyaluronate had the same short term and long term effects on improvement of symptoms, clinical signs or overall conditions of the disorders. In comparison between arthroscopy or arthrocentesis with or without HS groups, there was no statistically significant difference in terms of short or long term improvement of symptoms in one study but the conclusion were in contrast to another study.

Some single clinical symptoms or signs such as pain, sounds of the joint, mouth opening and tenderness on the TMJ or the muscular regions were shown to have improved for patients receiving HS in some of the included studies. However, due to insufficient reporting of numerical data and inconsistencies in results, no firm conclusions can be drawn with regard to the effect of HS on such outcomes.

Most of the adverse reactions for hyaluronate were mild and transient. The prevalences of the adverse reactions in two reports were 7.5% and 37.1% respectively. The main types were discomfort or pain at the injection site, localized swelling, open bite and weak bite force which resolved spontaneously in a short time.

The included articles were exposed to the following methodological flaws: incomplete reporting of randomization procedure and follow-up results. For a long time follow up, one cannot be sure the remission of the symptoms and clinical signs was a true outcome or reflection of fluctuation of the disorders or owing to co-interventions by other clinicians. The outcomes were usually measured by some composite variables such as Helkimo's anamnestic and dysfunction scores, one cannot be sure which symptom or clinical sign was being improved or exacerbated. Small pooled sample size, various brands, dosages and administrations of hyaluronate, various quality levels of the studies also weaken the validity of the results. Variations in outcome variables made comparison across trials problematic.

Some animal experiments reported by Shi 2002(A) and others have suggested that damaged articular cartilages of the TMJ could be repaired by intracapsular injection of hyaluronate. Nevertheless, the clinical outcomes of hyaluronate are inconsistent. More well

designed randomized controlled trials are needed to establish the effectiveness of hyaluronate for treating patients with TMD.

AUTHORS' CONCLUSIONS

Implications for practice

This review suggests hyaluronate might improve long term clinical signs of TMD and overall improvement of TMD in comparison with placebo, but currently the results are unstable. The effect size of hyaluronate was in the same level with that of glucocorticoids. Some benefits might be gained when using it in combination with arthrocentesis and arthroscopy of the TMJ. The reported adverse reactions of intracapsular injection of hyaluronate are mild and transient. It is recommended that hyaluronate be used as an alternative for the patients with symptomatic TMD and rheumatoid TMJ within the constraints of a well-designed randomized controlled trial (RCT).

Implications for research

The included studies provided positive but weak evidence for using

hyaluronate to treat TMD and rheumatoid TMJ problems. Some methodological flaws and incomplete reporting were the main factors influencing validity and reproducibility of the conclusion. In addition different brands, dosages of hyaluronate and different treatment courses have been used in the included clinical studies. Therefore more RCTs, especially multicenter trials of sufficient sample size, using important but concise and objective outcome variables, including life quality, are needed to establish its true therapeutic effects and if that is shown, find the best dosage and usage for specific clinical conditions of TMD and rheumatoid TMJ problem.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Alpaslan 2001

Methods	Randomized, single-blind controlled trial. Method of randomization not stated. Single-centred with two parallel groups, follow up for 24 months.
Participants	31 patients (41 TMJs) included, 5 males, 26 females. Mean age 27 years. 19 joints with DDR (13 joints on AC+HS; 6 joints on AC only) 22 joints with closed lock (13 joints on AC+HS; 9 joints on AC only).
Interventions	AC with 1ml 1% HS as test intervention (n = 26). AC with saline only as control (n = 15).
Outcomes	Intensity of pain significantly decreased in HS group between 2 to 24 months. The jaw function improved in significant level in HS group from 6 to 24 months. Opening and mandibular lateral movement increased significantly only in the SH group. Clicking disappeared significant only in SH group.
Notes	Single blinded. Drop outs were not mentioned. Additional information obtained from author.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bertolami 1993

Methods	Randomized, double-blind, placebo-controlled trial. Third party randomization. Multicenter with two parallel groups, follow up for 6 months.
Participants	Patients with documented diagnosis of an intracapsular TMJ disorder, severe dysfunction, resistant to conservative therapy for at least 2 months. In HS group 80 patients with mean age 36 years (35 with DDR; 8 with DDN; 37 with DJD). In saline group 41 patients with mean age of 40.7 years (15 with DDR; 6 with DDN; 20 with DJD). Prior to analysis, 14 disqualified.
Interventions	Single injection of HS (10 mg/ml) (n = 80) or saline as placebo (n = 41) into upper compartment of the TMJ dictated by joint space volume.
Outcomes	For the cases with DDR, the total and intracapsular scores from both the dysfunction and anamnestic indices, as well as the most relevant variables e.g. joint noise and mandibular deviation showed a consistent and significant improvement for HS group in comparison with PL group. For the cases with DJD,

Bertolami 1993 (Continued)

	anamnesic and total dysfunction scores improved for both groups and no significant difference between groups. For cases with DDN, at least one dysfunction class improved in all cases for HS group with significant difference between two groups. Anamnestic scores showed little within-groups and between-groups difference during 1 to 4 weeks. Adverse reactions reported.	
Notes	Drop outs were not clearly presented.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hepguler 2002

Methods	Randomized, double-blind, placebo-controlled trial. Third party randomization. Two parallel groups, follow up for 6 months.	
Participants	Patients over 21 years of age, fulfilling standard criteria for DDR and resistant to conservative therapy over 2 months. 19 patients in each group, with average age 31.9 years for HS group and 31.1years for PL group.	
Interventions	0.5 ml HS (15 mg/ml) (n = 19) or saline (n = 19) injected into superior joint compartment of the TMJ, repeated once a week later.	
Outcomes	Sound and pain intensity of the TMJ showed significantly greater reductions at month 1 and 6 in HS group compared with PL group. Modified Helkimo's clinical dysfunction index in the HS group improved 89.5% at month 1 and 63% at months 6 in HS group, which were significantly better than improvements of 21% at month 1 and 24% at months 6 respectively.	
Notes	Confounding bias might exist in long term follow up.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Kopp 1985

Methods	Randomized, double-blind controlled trial. Randomization stratified according to crepitation and severity of symptoms (generation of sequence not stated). Single-centre with two parallel groups, follow up for 4 weeks.	
Participants	Patients with TMD following failure of conservative treatments. 33 patients included (4 male, 29 female). Mean age 46 years.	
Interventions	Injection into upper compartment of TMJ with HS (10 mg/ml) 0.5 ml twice, 2 weeks apart (n = 18). Betamethasone (CO) was administered in same approach and frequency (n = 15).	
Outcomes	Subjective symptoms were improved in 13 out of 18 cases in HS group, 9 out of 13 in CO group. Symptom VAS reduced from baseline 30% for HS, 40% for CO groups. Helkimo's clinical dysfunction scores improved in 13 cases in HS group and 13 in CO group. Tenderness to palpation of the TMJs reduced significantly in both HS and CO groups. Tenderness of the muscle reduced significantly only in CO group.	
Notes	The clinical data were not fully reported.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kopp 1991

Methods	Randomized, double-blind, placebo-controlled trial. Method of randomization not stated. Three parallel groups, follow up of 4 weeks.	
Participants	Patients with rheumatoid disease involving the TMJ. 41 patients included, 2 males with mean age 65 years, 39 females with mean age 56 years. 14 on HS, 14 on CO and 13 on PL (saline placebo).	
Interventions	HS (10 mg/ml) 0.7 ml being injected to upper compartment of the TMJ for twice, 2 weeks apart (n = 14). Methylprednisolone (40 mg/ml) 0.7 ml (n = 14), saline 0.7 ml (n = 13) with the same approach and frequency as hyaluronate respectively. Hyalan insufflation and irrigation when doing arthroscopic procedure, then being washed out; control group receiving same procedures without hylan solution.	
Outcomes	Symptom improved in 10 cases in HS, 13 in CO and 9 in SA groups. The reduction in clinical dysfunction scores greater than 4 for 8 cases in HS, 11 for CO and 7 for SA groups. The mouth opening increased by a median of 3 mm in HS, 6 mm in CO and 1 mm in SA groups. Tenderness to palpation of the TMJs reduced significantly only in CO group. The number of tender muscle regions decreased in three groups but only significantly in HA and CO groups.	

Kopp 1991 (Continued)

Notes	Randomization method was not described.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

McCain 1989

Methods	Randomized, single-blind controlled trial. Randomization scheme established by a predetermined table. Two parallel groups, follow up 8 weeks.	
Participants	33 patients met the inclusion criteria of TMJ arthroscopy, 4 males, 29 females. Mean age 34 years. 22 with both TMJ involved. 33 joints with HS and 22 without HS.	
Interventions	In average 0.5% HS 2.6 ml (range 1 to 5 ml) for insufflation, mean volume for irrigation 24.2 ml (range 6 to 94ml) for arthroscopic procedure as intervention (TMJs = 33). The control group underwent arthroscopic procedure with Ringer's saline only (TMJs = 22).	
Outcomes	Clinical conditions improved in 19 joints (63%) for HS group and 15 joints(81%) for only Ringer's group. No significant difference between groups. No significant difference between groups for mouth opening, range of motion, TMJ and muscular tenderness. HS resulted in significantly better evaluation scores for arthroscopic procedure.	
Notes	Single blindness might reduce justness of the observers. Evaluation clinical outcomes according to joints instead of patients.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Shi 2002(B)

Methods	Randomized, single-blind controlled trial. Two parallel groups, follow up 4-5 weeks.	
Participants	67 patients with clinical symptoms of DDR, DDN or DJD of the TMJ included. In HA group 7 males, 28 females, mean age 38.5 years (7 with synovitis; 14 with DDN; 14 with DJD). In CO group, 5 males, 23 females, mean age 43.1 years (7 with synovitis; 7 with DDR ; 14 with DJD). 4 cases did not complete the treatments/lost to follow up and were excluded.	

Shi 2002(B) (Continued)

Interventions	0.5 ml of HS were mixed with bupivacaine 1 ml for upper compartment injection, once a week for 3-4 times as one course (n = 35). The control group received 2.5% prednisolone 0.5 ml mixed with 0.5% bupivacaine 1 ml, administered as for test group (n = 28).
Outcomes	Pain at jaw movement reduced markedly in 62.9% of the HS group and 28.6% in CO group, with significant difference between groups. Tenderness scores on the TMJ reduced markedly in 37.1% of the HS group and 14.3% of the CO group, with significant difference between groups (P < 0.05). The rates of clicking elimination, function restriction scores reduction and increase of mouth opening, abnormal mandibular deviation returning to normal limits were not significantly different between groups.
Notes	Single blindness affecting clinical evaluation if the variable not objective.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

DDR - reducing disc displacement
DDN - non-reducing disc displacement
DJD - degenerative joint disease

Characteristics of excluded studies [ordered by study ID]

Alpaslan 2000	No randomization or blinding
Chu 2001	Abstract in conference proceedings
Edwards 1994	Descriptive study
Fader 1993	Case report
Gu 1997	Overlap with Gu 1998
Gu 1998	RCT - control group lidocaine (outside remit of review)
Hirota 1998	Descriptive study
Kopp 1987	Inappropriate study design
Lida 1998	Case report

(Continued)

Qi 2001	Abstract in conference proceedings
Qian 1999	The irrigation procedure with hyaluronate not confirmed
Sato 1997	Not an RCT
Sato 1999	Not an RCT
Shibata 1998	Laboratory study
Smith 1989	Laboratory study

DATA AND ANALYSES

Comparison 1. Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short term effect on improvement of symptoms (for Bertolami 1993, only patients with DDR included)	2	70	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.72, 2.14]
2 Short term effect on improvement of clinical signs	3	109	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.80, 3.57]
3 Long term effect on improvement of clinical signs	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.05, 2.77]
4 Sensitivity analysis for 1.1-1.3 (intention-to-treat analysis)	2	88	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.51, 3.85]

Comparison 2. Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs glucocorticoids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short term effect on improvement of symptoms	3	124	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.84, 1.17]
2 Short term effect on improvement of clinical signs	3	124	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.66, 1.25]

Comparison 3. Treatment effects of hyaluronate on single clinical variables

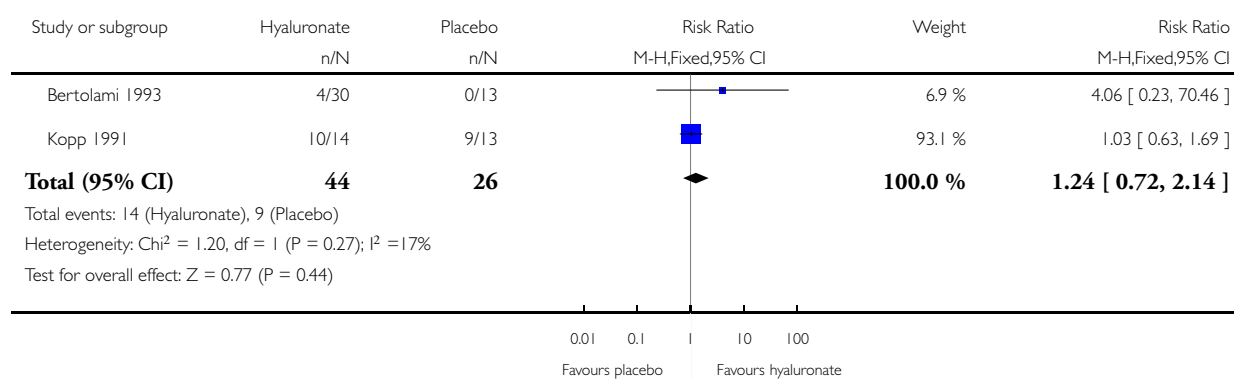
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment effects of hyaluronate on TMJ pain relieving	2	87	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.55, 1.65]

Analysis 1.1. Comparison 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo, Outcome 1 Short term effect on improvement of symptoms (for Bertolami 1993, only patients with DDR included).

Review: Hyaluronate for temporomandibular joint disorders

Comparison: 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo

Outcome: 1 Short term effect on improvement of symptoms (for Bertolami 1993, only patients with DDR included)

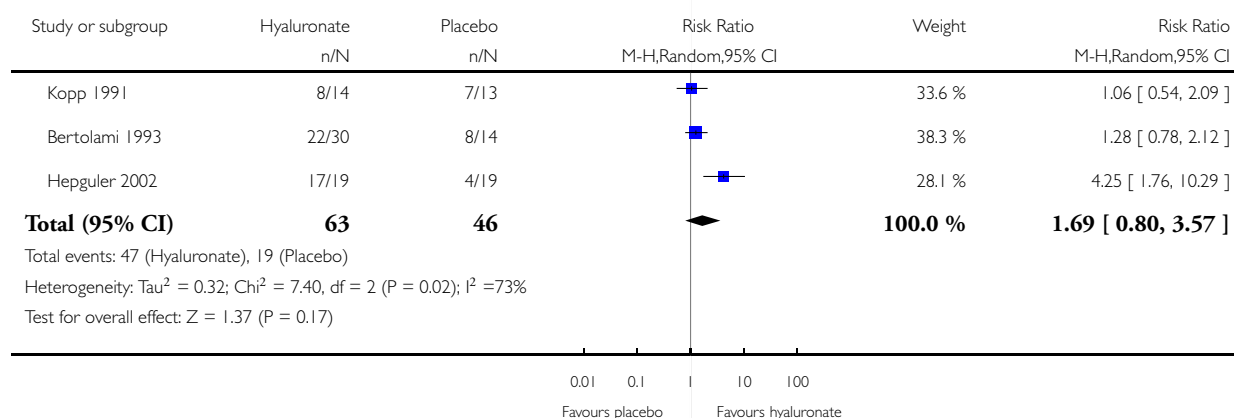


Analysis 1.2. Comparison 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo, Outcome 2 Short term effect on improvement of clinical signs.

Review: Hyaluronate for temporomandibular joint disorders

Comparison: 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo

Outcome: 2 Short term effect on improvement of clinical signs

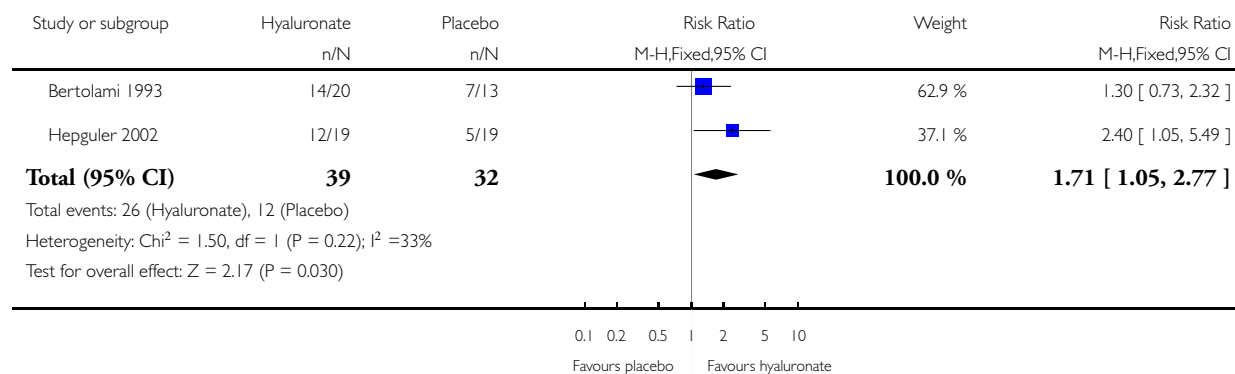


Analysis 1.3. Comparison 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo, Outcome 3 Long term effect on improvement of clinical signs.

Review: Hyaluronate for temporomandibular joint disorders

Comparison: 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo

Outcome: 3 Long term effect on improvement of clinical signs

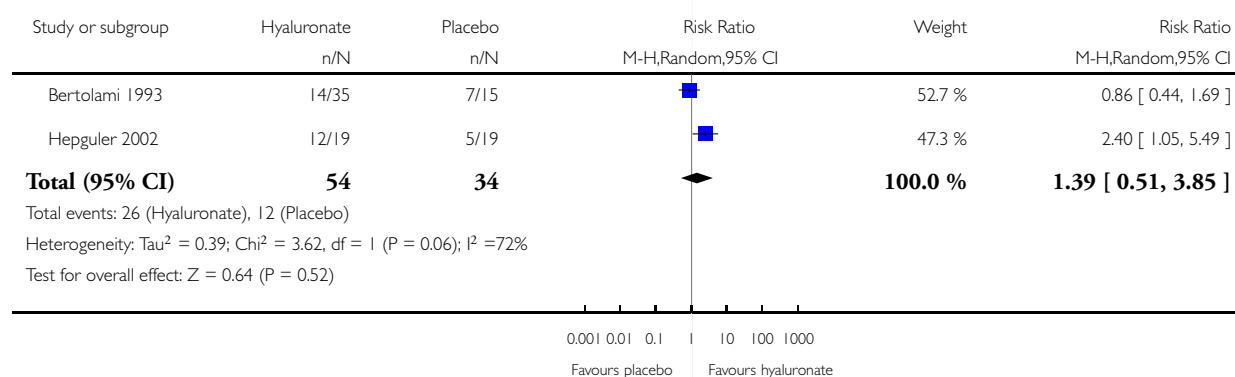


Analysis 1.4. Comparison 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo, Outcome 4 Sensitivity analysis for 1.1-1.3 (intention-to-treat analysis).

Review: Hyaluronate for temporomandibular joint disorders

Comparison: 1 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs placebo

Outcome: 4 Sensitivity analysis for 1.1-1.3 (intention-to-treat analysis)

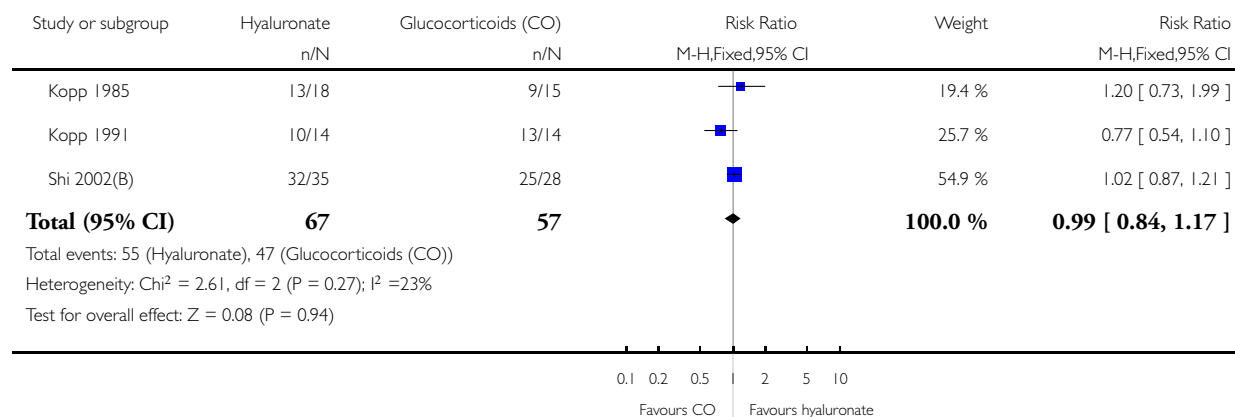


Analysis 2.1. Comparison 2 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs glucocorticoids, Outcome 1 Short term effect on improvement of symptoms.

Review: Hyaluronate for temporomandibular joint disorders

Comparison: 2 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs glucocorticoids

Outcome: 1 Short term effect on improvement of symptoms

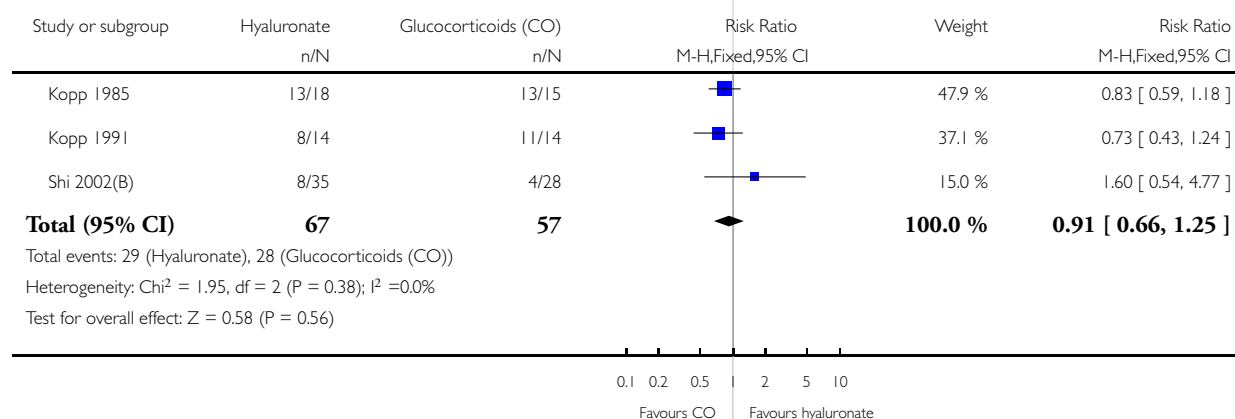


Analysis 2.2. Comparison 2 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs glucocorticoids, Outcome 2 Short term effect on improvement of clinical signs.

Review: Hyaluronate for temporomandibular joint disorders

Comparison: 2 Treatment effects of hyaluronate on synthesized clinical variables: hyaluronate vs glucocorticoids

Outcome: 2 Short term effect on improvement of clinical signs

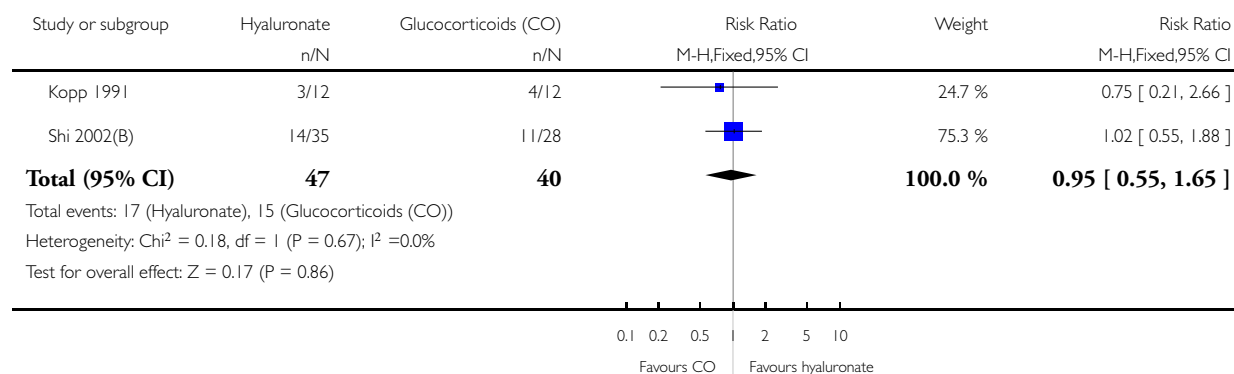


Analysis 3.1. Comparison 3 Treatment effects of hyaluronate on single clinical variables, Outcome 1 Treatment effects of hyaluronate on TMJ pain relieving.

Review: Hyaluronate for temporomandibular joint disorders

Comparison: 3 Treatment effects of hyaluronate on single clinical variables

Outcome: 1 Treatment effects of hyaluronate on TMJ pain relieving



APPENDICES

Appendix 1. Cochrane Oral Health Group's Trials Register search strategy

- #1. TEMPOROMANDIBULAR-JOINT-DISORDERS*:ME
- #2. (((TEMPOROMANDIBULAR and JOINT) or TMJ) AND (DISORDER* OR DYSFUNCTION))
- #3. HYALURONIC-ACID:ME
- #4. HYALURONATE*
- #5. (HYALURONIC next ACID)
- #6. (#1 or #2)
- #7. ((#3 or #4) or #5)
- #8. (#6 and #7)

Appendix 2. MEDLINE search strategy

MEDLINE (searched through WINSPIRSTM, version 4.01, SilverPlatter International, N.Y.); the search strategy was from the optimal search strategy for RCTs (as described in Appendix 5c of the *Cochrane Reviewers' Handbook*) in combination with the following terms relating to the subject area:

- #1. exp temporomandibular joint/
- #2. exp temporomandibular joint disorders/
- #3. temporomandibular and (disorder\$ or dysfunction)
- #4. hyaluronate
- #5. hyaluronic
- #6. hyaluronic acid/
- #7. or/1-3
- #8. or/4-5
- #9. 7 and 8

Appendix 3. PubMed search strategy

The following MeSH terms were used:

(Temporomandibular joint/ OR Temporomandibular joint disorders/) AND Hyaluronic acid

Appendix 4. EMBASE search strategy

#1. exp temporomandibular joint disorder/ or “temporomandibular joint disorder”.mp.

#2. exp temporomandibular joint/or “temporomandibular joint”.mp.

#3. ((Temporomandibular adj joint) or TMJ).mp.

#4. #1 or #2 or #3

#5. exp hyaluronic acid/ or “hyaluronic acid”.mp.

#6. hyaluronate.mp.

#7. #5 or #6

#8. #4 and #7

#9. exp randomized controlled trial/

#10. “RANDOM\$”.mp.

#11. randomi?\$.mp.

#12. (crossover\$ or cross-over\$).mp.

#13. factorial\$.mp.

#14. placebo\$.mp.

#15. or/#9-#14

#16. controlled clinical trial\$.mp.

#17. #15 or #16

#18. #8 and #17

Appendix 5. SIGLE search strategy

(temporomandibular and (hyaluronate OR hyaluronic acid))

WHAT'S NEW

Last assessed as up-to-date: 13 November 2002.

16 September 2008	Amended	Converted to new review format.
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HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 1, 2003

CONTRIBUTIONS OF AUTHORS

Contact review author: Professor Zongdao Shi. Initiation of the systematic review, writing the protocol, searching various electronic databases and handsearching Chinese professional journals, contacting the first authors of the included articles, collecting and evaluating the included data, completing the meta-analysis, writing and revising the systematic review.

Co-author: Chunlan Guo. Helped with handsearching the Chinese professional journals, extracting data from the included articles, evaluating and scoring the quality of the included articles.

Co-author: Manal Awad. Helped in reviewing the protocol, evaluating and scoring quality of the included articles.

DECLARATIONS OF INTEREST

Zongdao Shi is among the authors of one of the included studies, however, he was not involved in the quality assessment of this trial.

SOURCES OF SUPPORT

Internal sources

- West China School of Stomatology, Sichuan University, China.
- Chinese Cochrane Center, China.

External sources

- Project of Development of Systematic Review supported by Chinese Medical Board of New York, USA.
- Cochrane Oral Health Group, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Glucocorticoids [administration & dosage]; Hyaluronic Acid [*administration & dosage]; Randomized Controlled Trials as Topic; Temporomandibular Joint Disorders [*drug therapy]

MeSH check words

Humans