Effectiveness of Intra-Articular Injections of Sodium Hyaluronate or Corticosteroids for Intracapsular Temporomandibular Disorders: A Systematic Review and Meta-Analysis

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Aims: To assess the effectiveness of intra-articular injections of sodium hyaluronate (NaH) or corticosteroids (CS) for treatment of intracapsular temporomandibular disorders (TMD). **Methods:** Single- or double-blinded randomized controlled trials (RCTs) on the effectiveness of NaH or CS injections, compared to each other or to placebo, for the treatment of intracapsular TMD due to osteoarthritis and/or internal joint derangement were analyzed in this systematic review and meta-analysis. Electronic searches of MEDLINE through the PubMed, Web of Science, and Cochrane Library databases were conducted on March 17, 2015, and an updated search was conducted on June 7, 2017. Three reviewers independently extracted the data and assessed the risk of bias of included studies. **Results:** An initial search yielded 245 studies, and 5 additional studies were identified through cross referencing. A total of 22 studies were identified as relevant based on the abstracts, but only 7 RCTs met the inclusion criteria. Six of the included studies had unclear risk of bias, and one had high risk of bias. Four studies were eligible for meta-analysis. Pooled results showed no significant difference in short- or long-term pain improvement with NaH compared to CS. The number of responders to NaH was significantly more than placebo in one study, but not significantly higher than CS in another study. **Conclusion:** Although there was no significant difference between the effectiveness of NaH and CS intra-articular injections, there was some evidence that NaH was better than placebo. Further research is needed to determine the minimum effective dose and long-term side effects of both injections. *J Oral Facial Pain Headache 2018;32:53–66. doi: 10.11607/ofph.1783*

Keywords: *corticosteroid, hyaluronic acid, intra-articular injection, sodium hyaluronate, temporomandibular disorders*

Temporomandibular disorders (TMD) are clinical conditions resulting from extra- and/or intracapsular disorders of the temporomandibular joints (TMJs). Extracapsular disorders are conditions affecting the structures surrounding the TMJ, while intracapsular disorders are conditions affecting the structures within the TMJ.[1] TMJ internal derangement is present in approximately 80% of symptomatic TMD patients.[2] The incidence of degenerative joint disease (ie, osteoarthritis [OA]) of the TMJ in the United States is unknown, but the prevalence of patients seeking treatment for OA of the TMJ is higher than the number of individuals seeking treatment for TMJ pain or dysfunction.[3] OA affects women more than men,[4] and because its incidence increases with age,[5] it is becoming an increasingly important health problem in older populations.

Intracapsular TMD are commonly managed by conservative therapies (eg, counseling, avoidance, physiotherapy, occlusal splints, and anti-inflammatories). If symptoms and functions do not improve with conservative therapies, the clinician may consider intra-articular injections of corticosteroids (CS) or sodium hyaluronate (NaH), alone or in conjunction with arthroscopic lavage, prior to resorting to invasive surgical interventions.[6]

Table 1 Electronic Database Searches

Database	Search strategy
PubMed	TMJ OR TMD OR (Temporomandibular Joint) OR (Temporomandibular Joint Disorders) OR CMD OR (Temporomandibular Joint Dysfunction Syndrome) OR (TMJ disc derangement) OR (TMJ disc displacement) OR (Myofascial Pain Syndrome)) AND (corticosteroids OR hydroxycorticosteroids OR glucocorticosteroids OR mineralocorticosteroids OR "hyaluronic acid" OR hyaluronate OR "sodium hyaluronate" OR Hyaluronan *Filters*: Language: Limit to English; Age: Limit to adults; Species: Limit to Humans.
Web of Science	TOPIC: (Temporomandibular Joint) OR (Temporomandibular Joint Disorder*) OR CMD OR (Temporomandibular Joint Dysfunction Syndrome) OR (TMJ disc derangement) OR (TMJ disc displacement) OR (Myofascial Pain Syndrome) OR TMD OR TMJ AND TOPIC: Corticosteroids OR hydroxycorticosteroids OR glucocorticosteroids OR mineralocorticosteroids OR (hyaluronic acid) OR hyaluronate OR (sodium and hyaluronate) OR Hyaluronan AND TOPIC: injection
The Cochrane Library	#1 (Temporomandibular Joint) OR (Temporomandibular Joint Disorder) OR CMD OR (Temporomandibular Joint Dysfunction Syndrome) OR (TMJ disc derangement) OR (TMJ disc displacement) OR (Myofascial Pain Syndrome) OR TMD OR TMJ #2 Corticosteroids OR hydroxycorticosteroids OR glucocorticosteroids OR mineralocorticosteroids OR "hyaluronic acid" OR hyaluronate OR "sodium hyaluronate" OR Hyaluronan #3 Injection #1 and #2 and #3

TMJ = temporomandibular joint; TMD = temporomandibular disorders; CMD = craniomandibular disorders.

Inflammatory and nociceptive mediators are present in the synovial fluid of TMJs with intracapsular disorders.[7] CS prevent the release of arachidonic acid by inhibiting phospholipase A2, which in turn prevents the formation of proinflammatory cytokines and nociceptive mediators.[8] The concentration and molecular weight of endogenous hyaluronic acid are reduced in arthritic synovial fluid of the knee,[9] which in turn results in increased inflammatory mediators. The rheologic homeostasis of TMJ synovial fluid is restored with intra-articular injection of exogenous NaH.[10,11] The functional mechanism of action of NaH is directly dependent on the molecular weight and concentration of hyaluronic acid. Of the hyaluronic acid–based viscosupplements used in the studies included in this systematic review, Hyalgan has the lowest molecular weight (500,000 to 730,000 Daltons) and SYNVISC the highest (6,000,000 Daltons). NaH of high molecular weight yields greater analgesic therapeutic properties than NaH of low molecular weight.[12]

Intra-articular injections of CS or NaH are currently being utilized to treat intracapsular TMD.[13–19] The aim of this systematic review and meta-analysis was to assess the effectiveness of intra-articular injections of NaH or CS for the treatment of intracapsular TMD.

Materials and Methods

Selection Criteria

Studies were limited to randomized controlled trials (RCTs) on TMJ intra-articular injections of CS or NaH, compared to each other or to placebo, in adult patients diagnosed with OA and/or internal derangement of the TMJ. Other terms used to describe these conditions were also included in the search strategy (eg, temporomandibular joint disorders, temporomandibular joint dysfunction syndrome, TMJ disc derangement, TMJ disc displacement, and craniomandibular dysfunction [CMD]).

The clinical PICO (problem, intervention, comparison, outcome) question was defined as follows:

- Problem (P): Adults diagnosed with osteoarthritis and/or internal derangement of the TMJ
- Intervention (I): CS or NaH TMJ injection without arthrocentesis
- Comparison (C): Placebo, CS, or NaH
- Outcome (O): Change in pain score with treatment and number of patients with reported improvement of symptoms

Case reports, clinical guidelines, abstracts of conference proceedings, pilot studies, and systematic reviews were not analyzed. RCTs not available in English, studies including rheumatoid arthritis patients, and studies on arthrocentesis (which was considered a different intervention) with NaH or CS injections were excluded.

Search Methods for Identification of Studies

The search strategies described in Table 1 were applied to all database searches. Briefly, the following databases were searched on March 17, 2015:

- MEDLINE via PubMed (search restricted to English language, humans, and adults)
- The Web of Science, which included conference proceedings (gray literature)
- The Cochrane Library

Three review authors (M.M., V.C., and G.R.) screened titles and abstracts and performed full-text reviews, as needed. An update of the search was

performed on June 7th, 2016, but did not produce any new relevant articles. The same three authors independently scanned all reference sections of reviews, systematic reviews, and all included articles to make sure that no relevant studies were missed from the initial search.

Data Collection and Management

Data were gathered independently by the three review authors. Data included the characteristics of the participants, inclusion and exclusion criteria, interventions, control groups, and outcomes. Risk of bias assessment was performed by the same three authors. Disagreements were resolved by group discussion with a fourth author (R.E.).

The primary outcome assessed was change in the severity of facial or jaw pain measured on a 0- to 10-cm or 0- to 100-mm visual analog scale (VAS) (0 = no pain; 10 cm or 100 mm = worst pain). Secondary outcomes included the number of responders (ie, patients with self-reported total or partial remission of symptoms after treatment)[16–18] and change in mandibular function (ie, range of mandibular movement, measured in mm).

The Helkimo index assesses the severity of TMD based on the evaluation of three subindices: the anamnesis index, the clinical dysfunction index, and the occlusal index.[20–22] The anamnesis index is based on subjective symptoms reported by the patient and has three different levels (free, mild, and severe dysfunction). The clinical dysfunction index evaluates the function of the masticatory system according to the presence and/or severity of clinical symptoms (range of mandibular movement, TMJ function impairment, muscle tenderness during palpation, TMJ pain during palpation, and pain during mandibular movement). The occlusal index evaluates the patient's dental occlusion based on the number of existing teeth, number of teeth in occlusion, occlusal interferences, and joint interferences.[20–22]

The modified Helkimo clinical dysfunction index evaluates pain on movement of the mandible, TMJ pain, maximal mouth opening, signs of TMJ noise and disc derangement, and muscle pain in masticatory muscles. Treatment response with this index is measured as[23]:

- Total remission: Index components all went down to the 0 or 1 level
- Partial remission: Index component was at a level greater than 1
- Unchanged: None of the components went up or down
- Exacerbated: One or more of the index components went up

Evaluation and Management of Risk of Bias

Evaluation and management of risk of bias was performed based on the method described in the Cochrane Handbook for Systematic Reviews of Interventions.[24] A risk of bias table was completed for individual studies.

Measurement of Treatment Effect

Two meta-analyses were conducted: one for change in VAS pain from baseline to posttreatment (primary outcome), and one for number of patients with improved symptoms (secondary outcome). Authors of studies with missing outcome data were contacted to supply these data, and only those studies with complete outcome data were included in the meta-analyses.

Standardized differences in means (SDM) and 95% confidence intervals (CI) were reported for change in VAS pain with treatment, since the authors used different scales (10-cm or 100-mm VAS). Risk ratios (RR) with 95% CI were reported for the number of patients with improved symptoms (dichotomous variable; yes/no improvement). Subgroup analyses were conducted for NaH compared to CS, NaH compared to placebo, and CS compared to placebo. Cochran's (or Q) test[25] and the I^2 statistic[26] were used to test for statistical heterogeneity. When statistically significant heterogeneity (Q P value < .10) was found regarding the effect estimates, the results of the meta-analysis were based on the random-effects model; otherwise, they were based on the fixed-effects model. All analyses were performed using comprehensive meta-analysis v2 software (BioStat).

Levels of Evidence and Summary of Review Findings

Quality of evidence assessment and summary of the review findings were conducted with the software Grading of Recommendations Assessment, Development, and Evaluation (GRADE) profiler (Grader) by using the Cochrane Collaboration and GRADE Working Group recommendations.[24]

Results

The initial database search described in Table 1 yielded 275 publications, 30 of which were duplicate studies (Fig 1). The reference sections of these studies were manually searched, resulting in five additional references. Based on the abstracts of these 250 studies, 22 studies were identified as relevant for the systematic review, and the other 228 were excluded for the following reasons (Table 2): abstract only (n = 1); animal studies (n = 16); studies on juvenile idiopathic arthritis (n = 22); different condition (ie,

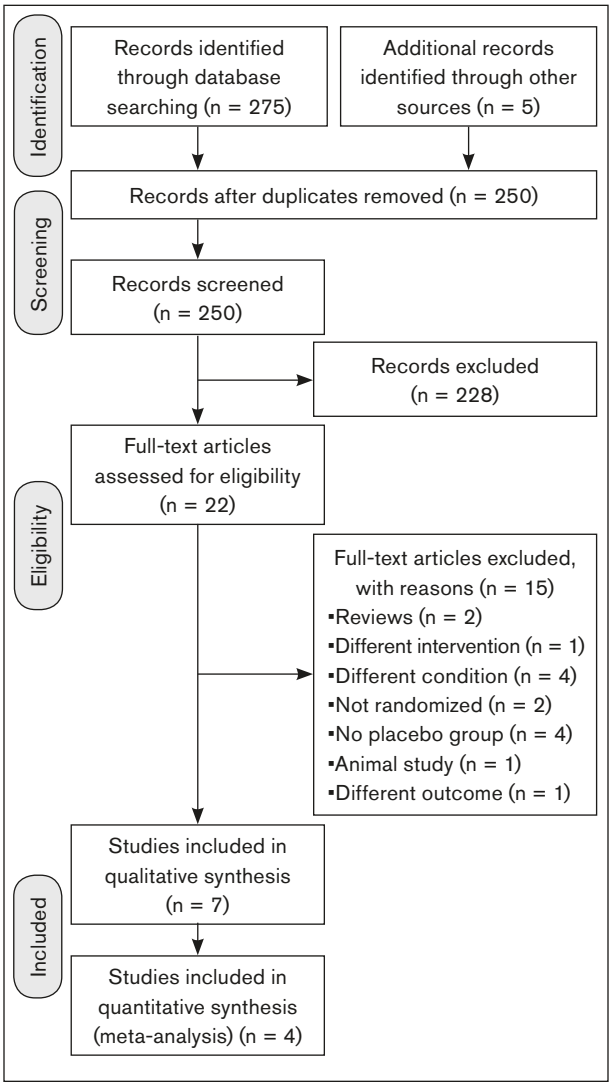

Fig 1 PRISMA[27] flow diagram representing search results.

neck pain, leukemia, fibromyalgia, low back pain, myofascial pain) (n = 83); different intervention (ie, occlusal splints, botulinum toxin, acupuncture, trigger point injections, IGF-1) (n = 27); no control group or placebo group (n = 9); not an RCT (ie, case report, case series, comparative study) (n = 21); opinion/editorial (n = 1); not in English (n = 3); duplicate entry (n = 2); review (n = 19); or studies on the efficacy of arthrocentesis with or without NaH or CS (n = 24).

The full texts of the 22 studies were obtained and analyzed for inclusion independently by three reviewers. Of the original 22 studies, 15 were rejected after a full-text review (Table 3), and of the remaining 7 studies, only 4 reported outcome data that could be used for meta-analyses. The flowchart for criteria and inclusion is presented in Fig 1 based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[27]

An update of the search in June of 2017 provided no new relevant RCTs (Table 4 shows reasons for exclusion of the references retrieved in June 2017).

Included Studies

Seven RCTs[13–19] were included in this systematic review (Table 5). A total of 372 (282 F, 111 M) subjects were included. As Kopp et al utilized the same subjects in a follow-up study[17] as in their original study,[18] the subjects in the follow-up study were not included in the count of 372 subjects. The total number of participants in each study varied from 33[18] to 121.[13] Participants were all adults ranging from 21 to 77 years of age. The majority of the subjects were female, and only the study by Tang et al[19] had an even gender distribution.

The diagnostic criteria used for TMD varied among investigators. Bertolami et al[13] used the Helkimo index with three specific conditions: *(1)* degenerative joint disease; *(2)* displaced disc with reduction; and *(3)* displaced disc without reduction. Bjorland et al[14] and Tang et al[19] included patients with osteoarthrosis of the TMJ and myofascial pain according to the Research Diagnostic Criteria for TMD (RDC/TMD).[28,29] Gencer et al[15] used Wilkes' classification[30] and confirmed the diagnosis of TMJ degeneration with a computed tomography (CT) scan. Hepguler at al[16] used reduced displaced disc and the modified Helkimo index for inclusion criteria.[20–22] Kopp et al[17,18] used pain localized to the TMJ of at least 6-month duration, joint tenderness to palpation, and the Helkimo index[20–22] (Table 3).

Three studies compared NaH to CS,[14,17,18] three compared NaH to placebo (physiologic saline solution),[13,16,19] and one compared NaH and CS to placebo.[15] Betamethasone was used by four studies for intra-articular CS injection,[14,15,17,18] and different compositions and brands were used for NaH injection, including 1% NaH (MedChem Products),[13] SYNVISC,[14] Hyalgan,[15,19] Hylartil,[17,18] and Orthovisc.[16]

The frequency of NaH injections compared to physiologic saline solution varied among the studies, from a single injection[13] to multiple injections (ie, five[19] with 1-week intervals between injections). The frequency of CS injection varied from one injection[15] to two injections[14,16–18] at 2-week intervals (Table 6).

Outcomes

Of the three studies[15,16,19] that compared NaH to placebo, only Gencer et al[15] reported the mean and standard deviation (SD) VAS pain at baseline and follow-up. Tang et al[19] did not report posttreatment data for the placebo group, and Hepguler et al[16] did not report SD for the treatment and placebo groups, nor *P* values comparing both groups. Based on these omissions, these studies[15,16,19] could not be included in the meta-analyses, but were included in the qualitative analyses.

Table 2 Excluded Studies After Screening of Titles and Abstracts

Study (search on March 17, 2015)	Reason for exclusion
Aktas et al,[39] 2010	Different intervention (arthrocentesis + NaH)
Alpaslan and Alpaslan,[40] 2010	Different intervention (arthrocentesis + NaH)
Alpaslan et al,[41] 2000	Different intervention (arthrocentesis + NaH)
Alpaslan et al,[42] 2003	Different intervention (arthrocentesis)
Alpaslan et al,[43] 2001	Different intervention (arthrocentesis + NaH)
Appelgren et al,[44] 1998	Different intervention (arthrocentesis + CS)
Guarda-Nardini et al,[45] 2005	Different intervention (arthrocentesis + NaH)
Guarda-Nardini et al,[46] 2008	Different intervention (arthrocentesis)
Guarda-Nardini et al,[47] 2012	Different intervention (arthrocentesis + NaH)
Guarda-Nardini et al,[48] 2012	Different intervention (arthrocentesis + NaH)
Guarda-Nardini et al,[49] 2012	Different intervention (arthrocentesis + NaH)
Guarda-Nardini et al,[50] 2011	Different intervention (arthrocentesis + NaH)
Guarda-Nardini et al,[51] 2014	Different intervention (arthrocentesis + NaH)
Guo and Revington,[52] 2009	Different intervention (arthrocentesis, lavage)
Huddleston et al,[53] 2012	Different intervention (arthrocentesis + CS)
Manfredini et al,[54] 2009	Different intervention (arthocentesis + NaH)
Manfredini et al,[36] 2012	Different Intervention (arthocentesis + NaH or CS)
Manfredini et al,[33] 2013	Different intervention (arthocentesis + NaH)
Manfredini et al,[55] 2013	Different intervention (arthocentesis + NaH)
Sanromán et al,[56] 2004	Different intervention (arthrocentesis, arthroscopy)
Sato et al,[57] 1997	Different intervention (arthrocentesis + NaH)
Su et al,[58] 2014	Different intervention (arthrocentesis + NaH)
Tabrizi et al,[59] 2014	Different intervention (arthrocentesis + CS)
Ungor et al,[60] 2014	Different intervention (arthrocentesis)

NaH = Sodium hyaluronate; CS = corticosteroid.

Table 3 Studies Excluded After Full-Text Review

Study (search on March 17, 2015)	Reason for exclusion
Alstergren et al,[61] 1996	Not an RCT
Charalambous et al,[62] 2004	Different condition (knee arthritis)
Edwards,[63] 1994	Not an RCT, pilot study with 5 patients
Gu et al,[64] 1998	No placebo group (NaH vs lidocaine)
Gu et al,[65] 1998	No placebo group (prednisolone and lidocaine vs lidocaine alone)
Guarda-Nardini et al,[66] 2005	No placebo group (NaH vs bite plane vs no treatment)
Hirota,[67] 1998	Different topic (arachidonic acid metabolites or cytokines)
Kopp et al,[37] 1991	Different condition (rheumatoid arthritis)
Li et al,[68] 2015	No control group (NaH, superior vs inferior joint space)
Møystad et al,[38] 2008	Different outcome (osseous changes with computed tomography)
Oliveras-Moreno et al,[69] 2008	No placebo group (NaH vs methocarbamol 380 mg and paracetamol 300 mg)
Rydell and Balazs,[70] 1971	Animal study
Shi et al,[71] 2003	Systematic review
Toller,[72] 1976	Literature review
Vallon et al,[73] 2002	Follow-up of an RCT (NaH vs CS vs saline), not randomized

NaH = sodium hyaluronate; CS = corticosteroid; RCT = randomized controlled trial.

Table 4 Excluded Studies After Updated Search in June 2017

Study	Reasons for exclusion
Bouloux et al,[74] 2017	Different intervention (arthrocentesis vs arthrocentesis + CS)
Fernandez-Ferro et al,[75] 2017	Different intervention (arthroscopy + PRGF vs arthroscopy + NaH)
Goaiato et al,[35] 2016	Systematic review
Hegab et al,[76] 2015	No placebo group (PRP or NaH)
Cömert Kiliç et al,[77] 2016	Different intervention (arthrocentesis + NaH vs arthrocentesis + CS vs arthrocentesis + placebo)
Korkmaz et al,[78] 2016	No placebo group (single NaH injection vs double injection vs splint vs no treatment [self-selected])
Marty et al,[79] 2016	Literature review, not in English (French)
Ozdamar et al,[80] 2017	Different intervention (arthrocentesis vs arthrocentesis + NaH)
Patel et al,[81] 2016	Different intervention (arthrocentesis vs arthrocentesis + NaH)

NaH = sodium hyaluronate; CS = corticosteroid; PRGF = plasma rich in growth factors; PRP = platelet-rich plasma.

Table 5 Summary of Eligible RCTs

Reference	Year, country, sample size	Interventions	Mean ± SD age (range) Gender distribution of participants, n
Bertolami et al[13]	1993, USA, N = 121	NaH (n = 80) Saline (n = 41)	NaH: 36 y, 72 F/8 M Placebo: 40.7 y, 35 F/7 M
Bjørnland et al[14]	2007, Norway, N = 40	NaH (SYNVISC) (n = 20) CS (Celestone Chronodose) (n = 20)	NaH: 53.4 ± 12.9 y, 19 F/1 M CS: 50.0 ± 13.3 y, 15 F/5 M
Gencer et al[15]	2014, Turkey, N = 100	NaH (n = 25) Betamethasone (n = 25) Tenoxicam (n = 25) Saline (n = 25)	Range: 18–65 y NaH: 36.27 y, 14 F/11 M CS: 38.25 y, 14 F/11 M TX: 40.50 y, 14 F/11 M Saline: 40.41 y, 13 F/12 M
Hepguler et al[16]	2002, Turkey, N = 38	NaH (n = 19) Saline (n = 19)	NaH: 31.94 ± 12.67 y, 13 F/6 M Saline: 31.10 ± 11.25 y, 13 F/6 M
Kopp et al[18]	1985, Sweden, N = 33	NaH (n = 18) Betamethasone (n = 15)	Range: 26–77 y NaH: 47.55 ± 14.68 y, 16 F/2 M CS: 45.06 ± 11.97 y, 13 F/2 M
Kopp et al (follow-up)[17]	1987, Sweden, N = 33	NaH (n = 18) Betamethasone (n = 15)	Range: 26–77 y NaH: 48 ± 15 y, 11 F/1 M CS: 50.57 ± 10.98 y, 7 F/0 M
Tang et al[19]	2010, China, N = 60	NaH (n = 20) Saline (n = 20) Healthy controls saline (n = 20)	NaH: 43 (28–57) y, 11 F/9 M Saline: 44 (25–63) y, 10 F/10 M Healthy controls: 41 (27–55) y, 10 F/10 M

NaH = sodium hyaluronate; CS = corticosteroid; TMJ = temporomandibular joint; F = Female; M = Male; MRI = magnetic resonance imaging; OA = osteoarthritis; RDC/TMD = Research Diagnostic Criteria for TMD; saline = physiologic saline solution.

Table 6 Dosages and Side Effects Reported in Included Studies

Study	Treatment groups	Number of injections and dosage
Bertolami et al[13]	NaH (n = 80) Saline (n = 41)	Single injection, amount injected dictated by joint space volume
Bjørnland et al[14]	NaH (n = 20) CS (n = 20)	Two injections of NaH or CS 14 days apart; 0.7–1 mL Xylocaine with adrenaline was used as a local anesthesic on the skin.
Gencer et al[15]	NaH (n = 25) CS (n = 25) Tenoxicam (n = 25) Saline (n = 25)	Single injection of NaH, CS, TX, or saline; 0.5 mL
Hepguler et al[16]	NaH (n = 19) Saline (n = 19)	Two injections of NaH or saline 1 wk apart; 0.5 mL
Kopp et al[18]	NaH (n = 18) CS (n = 15)	Two injections of NaH or CS with 2-wk interval; 0.5 mL
Kopp et al (follow-up)[17]	NaH (n = 18) CS (n = 15)	Two injections of NaH or CS with 2-wk interval; 0.5 mL
Tang et al[19]	NaH (n = 20) Saline in TMJ patients (n = 20) Saline in healthy controls (n = 20)	5 injections of NaH or saline once a wk for 5 wk; 1 mL

NaH = sodium hyaluronate; CS = corticosteroids; TX = Tenoxicam; saline = physiologic saline solution.

Three studies[15,16,19] reported changes in pain levels on a 10-cm VAS, while the other four studies[13,14,17,18] used a 100-mm VAS. One study[15] reported changes at 1 week and 6 weeks, and four[13,14,16,18] reported changes at 1 month after intra-articular injection. Four articles[13,14,16,17] reported VAS pain at 1

Inclusion criteria	Risk of bias
1) ≥ 21 y 2) Diagnosis of intracapsular TMJ disorder 3) Exhibit severity at Helkimo dysfunction Class II or higher (severe dysfunction) 4) Prove refractory to conservative therapies for at least 2 mo	Unclear
1) > 20 y 2) Subjective pain from the TMJ at function and at rest for > 1 year, restricted mandibular function 3) Radiographic evidence of OA of the TMJ 4) Patients tried conservative treatments, such as information and reassurance, nonsteroidal anti-inflammatory drugs, physiotherapy, and occlusal splints, without alleviation of symptoms	Unclear
1) Patients with symptoms of jaw pain, limited or painful jaw movement, or clicking or grating within the joint 2) TMD diagnosis confirmed by computed tomography 3) Wilke's diagnosis: Late intermediate (IV) and late (V) stage	Unclear
1) > 21 y 2) Fulfilled diagnostic criteria for reducing displaced disc of the TMJ: TMJ pain (variable), clicking, reciprocal clicking, jaw deviates toward side of click until click occurs then returns to midline, MRI shows displaced disc that reduces on opening 3) Resistance to conservative treatment for at least 2 mo	Unclear
1) Pain localized to the TMJ of at least 6 months' duration and tenderness to palpation of the joint (TMJ arthritis) 2) Failure of conservative treatment, such as occlusal adjustment, bite plates, and/or physical exercises	Unclear
Same as Kopp et al[18]	High
1) Patients diagnosed with OA 2) Unsuccessfully treated by conservative therapy (jaw exercises, physiotherapy, and occlusal splint) 3) Fulfilled criteria for OA of the TMJ according to the RDC/TMD: Presence of arthralgia (TMJ pain with lateral and/or posterior palpation plus self-reports of pain during maximum unassisted/assisted opening and/or lateral excursion, coarse crepitus in the joint, and radiographic degenerative changes)	Unclear

Side effects
A total of 13 adverse events occurred in 10 patients. The majority were mild in nature, self-limiting, and of short duration and consisted primarily of discomfort at the injection site and/or localized swelling. The duration of the event was generally 1 day. NaH group: 7 events in 6 patients (5 mild, 1 moderate, 1 severe) Saline group: 6 events in 4 patients (4 mild, 2 severe)
No permanent facial nerve damage or infection was observed. NaH group: TMJ pain after injections (n = 4), ear pressure (n = 1), open bite (n = 1) CS group: Ear pressure (n = 2), open bite (n = 1), generalized rashes (n = 2)
Not stated; however, the authors reported in Methods that 5 min after the procedure, the patient was examined for signs of facial palsy, and manual mobilization of the jaw was performed to improve mouth opening.
Not stated
Not stated
Not stated
Not stated

month and/or 6 months after intra-articular injection. Only Kopp et al[17] compared VAS changes at 1 year and 2 years (Table 7).

Risk of Bias

The risks of bias for the included studies are summarized in Table 8 and Fig 2.

Table 7 Baseline and Posttreatment Pain Intensity with NaH Compared to CS

		Mean ± SD outcome in NaH group (no. of participants)		Mean ± SD outcome in CS group (no. of participants)		
Study	Scale/follow-up	Mean ± SD	n	Mean ± SD	n	*P* value
Bjørnland et al[14]	0–100 mm VAS B, 1 mo, 6 mo	B: 70 ± 16.2 1 mo: 32 ± 25.6 6 mo: 14 ± 16.2	20	B: 73 ± 18.1 1 mo: 42 ± 27.8 6 mo: 31 ± 31.7	20	1 mo: .409 6 mo: .084
Gencer et al[15]	0–10 cm VAS 1 wk, 6 wk	1 wk: 3.18 ± 0.9 6 wk: 3.41 ± 1.2	25	1 wk: 4.13 ± 1.5 6 wk: 4.51 ± 1.0	25	6 wk: .632
Kopp et al[18]	0–100 mm VAS B, 4 wk	B: Median 53 mm 4 wk: Median 37 mm (*P* < .01)	18	B: Median 57 mm 4 wk: Median 24 mm (*P* > .05)	15	4 wk: .278
Kopp et al (follow-up)[17]	0–100 mm VAS B, 1 y 2 y	B: Median 49 mm 1 y: Median 38 mm (cross-over patients included) (*P* < .05) 2 y: Median 33 mm (*P* < .05)	12	B: Median 60 mm 1 y: Median 35 mm (*P* < .05) B: Median 60 mm 2 y: Median 17 mm (cross-over patients included) (*P* < .05)	12 10	1 y: .511 2 y: .787

SD = standard deviation; NaH = sodium hyaluronate; CS = corticosteroid; VAS = visual analog scale; B = baseline.

Table 8 Summary of Risk of Bias for Eligible Studies

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other potential bias	Overall bias
Bertolami et al[13]	?	–	?	–	–	–	?
Bjørnland et al[14]	?	–	?	–	–	?	?
Gencer et al[15]	–	?	?	–	–	?	?
Hepguler et al[16]	?	–	?	–	–	–	?
Kopp et al[18]	?	?	?	–	–	–	?
Kopp et al[17] (follow-up)	?	?	?	+	–	–	+
Tang et al[19]	?	?	?	–	–	–	?

+ = high risk of bias; – = low risk of bias; ? = unclear risk of bias.

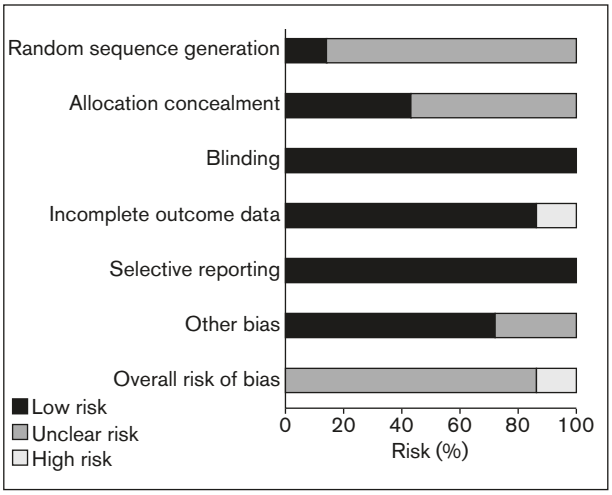

Fig 2 Graph of summary of risk of bias for eligible studies.

Random Sequence Generation. Only one study[15] described how randomization was generated (ie, computer-generated sequence). No other studies reported the method for randomization and were therefore judged at unclear risk of bias.

Allocation Concealment. Three studies were judged at low risk of bias because they concealed the sequence of randomization by using sealed envelopes[14] and clear colorless fluids,[13,16] which are indistinguishable by visual inspection. The studies by Bertolami et al[13] and Hepguler et al[16] used coded syringes that were randomized by the manufacturer and then used sequentially with no identification known to the participating clinicians, examiners, or investigators. The other four studies[15,17–19] did not describe their allocation concealment and were therefore judged at unclear risk of bias.

Blinding. No study described in detail how the patients, investigators, outcome assessors, and data analysts were blinded to the treatment allocation, and therefore all studies were rated at unclear risk of bias.

Incomplete Outcome Data. Six studies[13–16,18,19] were rated at low risk for incomplete outcome data. The exception was the study by Kopp et al,[17] a follow-up study with large dropouts. In this study, the dropout rate at year 1 was 50% and 46.7% for NaH and CS, respectively. However, 100% and 85.7% of participants who received NaH and CS at the 1-year follow-up, respectively, attended the 2-year follow-up.

Selective Reporting. All studies were considered at low risk of bias for selective reporting.

Other Potential Bias. One study was considered at unclear risk of bias due to gender distribution

imbalance at baseline.[14] No co-interventions were reported in any of the included studies during treatment. Gencer et al[15] studied patients who received etodolac and had an unfavorable response to it; risk of bias for this study[15] was considered unclear.

Summary of Risk of Bias. The study by Kopp et al[17] was rated at high risk of bias due to large dropouts. All other studies were rated at unclear risk for this parameter.

Effects of Interventions

Primary Outcome. Six studies reported posttreatment VAS pain. Three of these studies compared NaH to CS,[14,17,18] two compared NaH to placebo,[13,16] and one compared NaH to either CS or placebo.[15]

Comparison of Change in VAS Pain Score Between NaH and CS. Three studies[14,15,18] reported VAS pain at baseline and at 4 to 6 weeks follow-up (ie, short-term pain) (Table 7). No statistically significant heterogeneity was found among these three studies (Q test $P = .361$; $I^2 = 2\%$), so the fixed-effects model was used to compute the overall pooled results, which showed no statistically significant difference in short-term posttreatment pain with NaH compared to CS injections (SDM = −0.040; 95% CI = −0.395 to 0.315; $P = .825$) (Fig 3).

To determine the effects of long-term pain (6 months to 2 years), the data from Kopp et al[17] at 1 year was pooled with 6-month data from Bjørnland et al[14] (Table 7). There was statistically significant heterogeneity (Q test $P = .034$; $I^2 = 78\%$), so the random-effects model was used. The meta-analysis showed no statistically significant difference in long-term posttreatment pain with NaH compared to CS (SDM = −0.058; 95% CI = −1.055 to 0.939; $P = .909$) (Fig 4).

No significant differences in VAS pain were found when the 6-month data by Bjørnland et al[14] and the 2-year data by Kopp et al[17] were analyzed in a sensitivity analysis (SDM = 0.032, 95% CI = −1.168 to 1.233, $P = .958$).

Comparison of Change in VAS Pain Score Between NaH and Placebo. Of the four studies[13,15,16,19] that compared NaH to placebo, only Gencer et al[15] reported the mean and SD VAS pain score at baseline and at follow-up. The study by Tang et al[19] did not follow up on the VAS pain changes for the placebo group, and Hepguler et al[16] did not report the SD for the treatment and placebo groups or a *P* value comparing both groups. Bertolami et al[13] did not report VAS intensity of pain changes. Therefore, of the four studies, only the study by Gencer et al[15] was eligible for meta-analysis.

Secondary Outcomes. *Number of Patients with Reported Improvement of Symptoms with NaH. NaH vs CS.* In their initial study[18] and in their follow-up study,[17] Kopp et al reported the number of patients who had improvement of symptoms. There was no significant difference between NaH and CS at the 1-month ($P = .470$), 1-year ($P = .511$), or 2-year follow-ups ($P = .787$). The mean combined effect showed no significant difference between NaH and CS (RR = 0.994; 95% CI = 0.540 to 1.830; $P = .985$) (Fig 5).

NaH vs Placebo. Only Hepguler et al[16] reported the number of patients who had improvement of symptoms at 1 month ($P = .001$) and 6 months ($P = .038$) with NaH vs placebo. The mean combined effect of NaH at 1 month and 6 months was statistically significantly better than placebo (RR = 3.194; 95% CI = 1.357 to 7.518; $P = .008$) (Fig 6).

CS vs Placebo. Gencer et al[15] did not report the number of patients with improvement of symptoms.

Helkimo Clinical Dysfunction Score and Mandibular Function. NaH vs Placebo. Bertolami et al[13] reported a significant improvement in total dysfunction score ($P \leq .001$) and total intracapsular dysfunction score ($P \leq .05$) when NaH was used from 1 month to 5 months. Hepguler et al[16] found a statistically significantly greater reduction in Helkimo clinical dysfunction index with NaH compared to placebo.

NaH vs CS. Kopp et al[18] reported statistically significant reduced clinical dysfunction for both NaH ($P < .05$) and CS ($P < .01$) groups. Bjørnland et al[14] found a statistically significant improvement in range of mandibular movement for both NaH and CS groups. However, neither of the two studies[14,18] showed significant differences between groups.

Side Effects

Only two studies[13,14] reported the side effects of intra-articular injections (Table 6). Bertolami et al[13] reported discomfort at the injection site and/or localized swelling, which they described as mild and of short duration (generally 1 day). Side effects were reported by 7.5% of patients receiving NaH and by 9.8% of patients receiving saline. Bjørnland et al[14] reported that 20% of patients experienced severe pain after injection with NaH at rest or with mandibular movement. The CS patients presented with ear pressure, open bite, and generalized rashes, but none had pain after injection. According to the authors,[14] complications, however temporary, may have influenced the overall outcome of the study, particularly with regard to assessment of pain intensity.

Levels of Evidence and Summary of the Review Findings

The summary of the outcomes and side effects reported by the authors are presented in Tables 6 and 9, respectively. Although a few of the papers showed NaH as more effective than CS in terms of pain or side effects for certain conditions, the level of evidence was

Study	Statistics for each study				SDM and 95% CI
	SDM	Lower limit	Upper limit	*P* value	
Bjørnland et al[14]	−0.262	−0.884	0.360	.409	
Gencer et al[15]	−0.136	−0.691	0.419	.632	
Kopp et al[18]	0.383	−0.309	1.074	.278	
Total	−0.040	−0.395	0.315	.825	

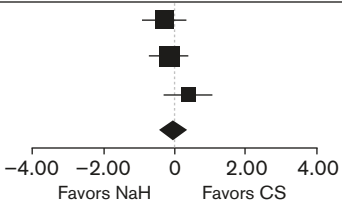

Fig 3 Results of RCTs comparing short-term (4 to 6 weeks) change in pain score for patients receiving intra-articular injections of NaH vs CS. SDM = standardized difference in means; CI = confidence interval.

Study	Statistics for each study				SDM and 95% CI
	SDM	Lower limit	Upper limit	*P* value	
Bjørnland et al[14]	−0.556	−1.188	0.076	.084	
Kopp et al[17]	0.461	−0.233	1.156	.193	
Total	−0.058	−1.055	0.939	.909	

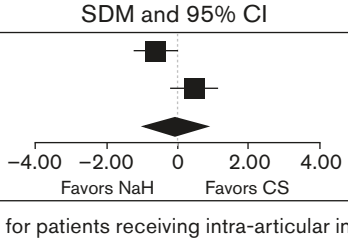

Fig 4 Results of RCTs comparing long-term (6 months to 1 year) change in pain score for patients receiving intra-articular injections of NaH vs CS. SDM = standardized difference in means; CI = confidence interval.

Study	Time point	Statistics for each study				RR and 95% CI
		RR	Lower limit	Upper limit	*P* value	
Kopp et al[18]	1 mo	1.204	0.728	1.990	.470	
Kopp et al[17]	1 y	0.778	0.368	1.645	.511	
Kopp et al[17]	2 y	0.933	0.566	1.539	.787	
Kopp et al[17,18]	Combined	0.994	0.540	1.830	.985	

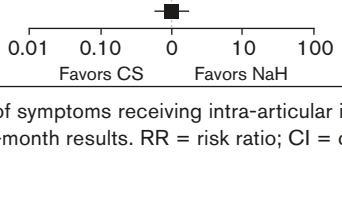

Fig 5 Results of RCTs comparing the number of patients with reported improvement of symptoms receiving intra-articular injection of NaH vs CS. Kopp et al[17] is a 1- and 2-year follow-up of Kopp et al,[18] which reported 1-month results. RR = risk ratio; CI = confidence interval.

Study	Time point	Statistics for each study				RR and 95% CI
		RR	Lower limit	Upper limit	*P* value	
Hepguler et al[16]	1 mo	4.250	1.755	10.290	.001	
Hepguler et al[16]	6 mo	2.400	1.050	5.488	.038	
Hepguler et al[16]	Combined	3.194	1.357	7.518	.008	

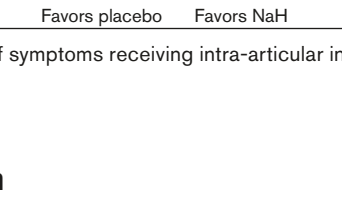

Fig 6 Results of RCTs comparing the number of patients with reported improvement of symptoms receiving intra-articular injections of NaH vs placebo. RR = risk ratio; CI = confidence interval.

considered low. According to the GRADE levels of evidence and summary of findings, the level of evidence for short- and long-term changes in pain was low due to the risk of bias (ie, unclear or high risk), imprecision due to the small number of studies reporting these outcomes, and the small sample sizes of the studies analyzed (< 400 participants in total) (Table 10).

Discussion

RCTs on intra-articular injection of NaH or CS for intracapsular disorders due to OA and/or internal derangement of the TMJ were evaluated in this systematic review and meta-analysis. Four RCTs compared NaH to CS,[14,15,17,18] and three compared it to placebo.[13,16,19]

Table 9 Summary of Outcomes Reported in Included Studies

Study	Intervention	Summary of outcomes	Conclusion by the authors
Bertolami et al[13]	NaH (n = 80) Saline (n = 41)	DJD: No difference in TMJ dysfunction, pain, or physical measurements between treatment groups DDN: Significant between-group differences in dysfunction index and VAS pain and function scores were seen after 1 month; however, beyond this time point, sample size was too small DDR: Significant improvements in the NaH group compared to the saline group throughout the 6-month test period in: (a) Total anamnestic index ($P < .05$) (b) Total intracapsular anamnestic score, sum of mobility, TMJ function, TMJ pain, and movement pain variables ($P < .05$) (c) Visual analog TMJ noise ($P < .01$). At the 2- and 3-month examinations, twice as many patients treated with NaH (90%) showed improvement in temporomandibular dysfunction compared to patients given placebo.	DJD: NaH = saline DDN: NaH > saline DDR: NaH > saline
Bjørnland et al[14]	NaH + xylocaine (n = 20) CS + xylocaine (n = 20)	Both groups of patients had less pain intensity at the 6-month follow-up, and there was significantly less pain intensity in the group of patients who received NaH compared with CS ($P = .001$). Injections in the TMJ of NaH or CS may reduce pain and improve function in patients with osteoarthritis. The injections were more effective in patients with only TMJ pain compared to patients suffering from both TMJ and myofascial pain.	NaH > CS (pain)
Gencer et al[15]	NaH (n = 25) CS (n = 25) Tenoxicam (n = 25) Saline (n = 25)	The NaH group showed significantly better pain relief scores compared to the other groups at 1 wk and 6 wk ($P < .05$). TX and CS groups' pain scores were better than saline group values ($P < .05$ for both TX and CS). TX group at 1 wk displayed better pain scores than CS group ($P < .05$). The pain relief effect of TX was noted to decrease significantly between 1 wk and 6 wk ($P < .05$). The same pattern was not observed in NaH, CS, and saline groups between 1 wk and 6 wk ($P > .05$).	NaH > TX > CS > saline
Hepguler et al[16]	NaH (n = 19) Saline (n = 19)	Evaluation of patients by modified Helkimo's clinical dysfunction index in the NaH group showed significant improvement at 1 mo and 6 mo compared to saline ($P < .001$ and $P < .05$, respectively).	NaH > saline
Kopp et al[18]	NaH (n = 18) CS (n = 15)	NaH and CS reduced subjective symptoms and clinical signs significantly, and no statistically significant difference in effect could be found between drugs in this regard. The patients who had crepitus in the joints injected with CS achieved a smaller reduction in clinical dysfunction score compared to the patients without crepitus, which indicates that the prognosis of intra-articular CS injection is poor in patients who have advanced OA of the TMJ.	NaH = CS (symptoms and signs)
Kopp et al (follow-up)[17]	NaH (n = 18) CS (n = 15)	NaH and CS were equally effective in treating patients with chronic arthritis of TMJ, but NaH might be the best alternative due to reduced risk for side effects.	NaH = CS (pain) NaH > CS (side effects)
Tang et al[19]	NaH (n = 20) Saline in OA patients (n = 20) Saline in healthy controls (n = 20)	NaH decreased uPA activity and levels of uPA, soluble uPAr, and PA inhibitor 1 levels in synovial fluid collected before and after treatment in TMJs of OA patients ($P < .05$), and there was no difference after saline injection. Within the NaH group, the VAS score was significantly reduced after treatment ($P < .05$), but not in the saline group. VAS changes correlated with changes in uPA and uPAR levels, as well as with uPA activity.	NaH > saline (pain)

NaH = sodium hyaluronate; CS = corticosteroids; TX = Tenoxicam; DJD = degenerative joint disease; DDN = disc displacement without reduction; DDR = disc displacement with reduction; OA = osteoarthritis; VAS = visual analog scale; uPA = urokinase-type PA ; uPAr = uPA receptor.

The majority of the subjects had OA of the TMJ, and only one study[16] used disc displacement with reduction as the main diagnosis. All subjects received one to two intra-articular injections into the superior joint space at either 1- or 2-week intervals. The total amount of the injected drug varied from 0.5 mL[15,16,18] to 1 mL.[14,19] One study[13] did not specify the exact amount of injected medication and was dependent on the joint space volume.

The overall strength of the evidence was low due to the small number of studies, small sample sizes (< 400 participants), and the presence of risk of bias.

Overall Completeness and Applicability of Evidence

Three main databases were searched: MEDLINE through PubMed, Web of Science, and The Cochrane Library. Access to EMBASE was not available to the

Table 10 Summary of Findings for Quality of Evidence (GRADE)

Outcomes	No. of Participants (studies), follow-up	Quality of the evidence (GRADE)	Anticipated absolute effects Risk difference with NaH (95% CI)
Change in VAS pain (short term)	123 (3) 4–6 wk	⊕⊕⊖⊖ LOW[a,b] due to risk of bias, imprecision	The mean change in short-term pain in the NaH group was 0.040 standard deviations lower (0.395 lower to 0.315 higher) than in the CS group, favorable to NaH.
Change in VAS pain (long term)	64 (2) 6–12 mo	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	The mean change in long-term pain in the NaH group was 0.058 standard deviations lower (1.055 lower to 0.939 higher) than in the CS group, favorable to NaH.

VAS = visual analog scale; RCT = randomized controlled trial. GRADE Working Group grades of evidence: High quality = further research is very unlikely to change the level of confidence in the estimate of effect; moderate quality = further research is likely to have an important impact on the level of confidence in the estimate of effect and may change the estimate; low quality = further research is very likely to have an important impact on the level of confidence in the estimate of effect and is likely to change the estimate; very low quality = review authors are very uncertain about the estimate. [a]All RCTs at unclear or high risk of bias. [b]Only three studies included in meta-anlysis, small sample size (< 400 participants in total). [c]Only two studies included in meta-anlysis, small sample size (< 400 participants in total).

review authors. Included studies and reviews were hand searched for eligible RCTs. Open-label studies were not included in this systematic review. The participants in the seven eligible studies included in this systematic review were patients who failed to improve with conservative treatments. The results of this review are applicable to individuals of 21 years and older who present with intracapsular TMD and are resistant to conservative therapies; they do not apply to patients with general arthritis, connective tissue disease, a history of treatment with immunosuppressive drugs, any organ diseases, and/or general infection.

Agreements and Disagreements with Other Studies or Reviews

The systematic review by De Souza et al[31] analyzed studies on different interventions for OA of the TMJ (ie, NaH vs CS, diclofenac sodium vs occlusal splint, and glucosamine vs ibuprofen). The authors found weak evidence that the effectiveness of NaH and CS are equivalent.[31] Escoda-Francolí et al[32] reviewed studies that compared different dosages of NaH and CS intra-articular injections in conjunction with arthrocentesis. In this systematic review, the PICO question excluded arthrocentesis studies. Balazs et al[12] tried to establish the best chemical composition of NaH that proved most beneficial. Manfredini et al[33] analyzed the studies on the efficacy of intra-articular injection of NaH vs placebo, CS (either alone or through arthrocentesis), the use of analgesics (paracetamol plus methocarbamol), and oral appliance therapy. The present findings agree with their conclusions[33] that NaH injections are superior to placebo, with outcomes similar to CS injections. Machado et al[34] carried out an extensive search analyzing the effects of NaH vs CS in the treatment of internal derangement of the TMJ and found that both were seemingly effective; however, they provided no meta-analysis nor a summary of the quality of the evidence. Goiato et al[35] used a PICO question different from the present study and included in their systematic review studies on arthrocentesis,[36] subjects with rheumatoid arthritis,[37] and assessment of bone changes after injections,[38] which had been excluded in the present systematic review. Thus, prior reviews concur that there is no difference in the effectiveness of NaH or CS intra-articular injections for OA and/or TMJ internal derangement. However, the quality of the evidence is low.

Conclusions

Although there was no statistically significant difference in the effectiveness between NaH and CS injections to treat intracapsular TMD, there was some favorable evidence that NaH is better than placebo. Nonetheless, the quality of evidence resulting from this systematic review is low due to high or unclear risk of bias, heterogeneity in outcomes, small sample size, and small number of studies included in the meta-analysis. Therefore, high-quality RCTs on the effectiveness of NaH compared to CS or placebo with large sample sizes and long-term follow-up are still lacking.

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