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# Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: A systematic review

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ABSTRACT

*Introduction:* Hyaluronic acid (HA) is a commonly prescribed intra-articular (IA) therapy for knee osteoarthritis (OA). While a single series of IA-HA has been well studied, the efficacy and safety of repeated courses of IA-HA injection therapy in knee OA patients have not been evaluated as frequently.
*Methods:* A literature search was conducted using MEDLINE, EMBASE and PubMed databases. The primary outcome measure was knee pain reduction after each treatment course and/or last reported follow-up visit. Secondary outcomes were treatment-related adverse events (AEs) and serious adverse events (SAEs).
*Results:* A total of 17 articles (7 RCTs and 10 cohort studies) met the pre-defined inclusion criteria. Of the RCTs, six were double-blind with two trials including open label extension studies, and one was single-blind. Studies ranged from investigating a single reinjection cycle to four repeat injection cycles. Eleven studies evaluated one reinjection, five studies evaluated ≥2 repeated courses of IA-HA, and one study allowed either one or two repeated courses. All studies reported pain reduction from baseline in the IA-HA treatment group throughout the initial treatment cycle, and either sustained or further reduced pain throughout the repeated courses of treatment. The study with the longest follow-up repeated IA-HA injection every 6 months for 25 months. Pain decreased after the first course and continued to decrease until the end of the study, with an approximate 55% reduction in pain compared to baseline. Common AEs were joint swelling and arthralgia; there were no reported SAEs. All repeated courses were well tolerated, and the number of documented AEs and SAEs was similar to the primary injection regimens.
*Conclusion:* Repeated courses of IA-HA injections are an effective and safe treatment for knee OA. Repeat courses were demonstrated to maintain or further improve pain reduction while introducing no increased safety risk.


## Introduction

Knee osteoarthritis (OA) is most often a slowly progressive joint disorder characterized by cartilage degeneration and inflammation [1]. Knee OA commonly results in knee pain and decreases patients' mobility (e.g., walking and stair climbing) [2]. Hyaluronic acid (HA) is a glycosaminoglycan that occurs naturally within the synovial fluid of the knee, providing lubrication of the joint and protecting the cartilage from mechanical degradation [3]. HA has been shown to provide anti-inflammatory and chondroprotective effects, increase proteoglycan and HA synthesis, and reduce nerve impulses and nerve sensitivity associated with OA pain [4]. In knee OA, HA is reduced both in molecular weight and concentration. HA is a common intra-articular (IA) therapy for the relief of pain due to knee OA [5].

Evidence suggests HA has significant short-term efficacy (≤6 months) for treating knee OA pain. A recently published network meta-analysis found that IA-HA is an effective and safe short-term treatment option for pain due to knee OA, and IA-HA was more efficacious than NSAIDs, IA-corticosteroids and IA-placebo [6]. Another recently published systematic review and network meta-analysis also concluded that IA-HA showed significant improvement from baseline pain [7]; however, the relative effectiveness of the long-term use of IA-HA through repeat courses of treatment remains to be determined. Therefore, our goal was to conduct a comprehensive systematic review of the literature to determine the efficacy and safety of repeated courses of IA-HA treatment.

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## Methods

### *Literature search*

We conducted a systematic and comprehensive literature search of the MEDLINE, EMBASE and PubMed databases (Appendix 1). The inclusion criteria were (1) randomized controlled trials, (2) cohort studies with IA-HA as the primary treatment, (3) studies that provide at least 1 repeat course of IA-HA, (4) studies that measured knee pain as an outcome, and (5) articles published in English.

### *Data abstraction*

We abstracted details on the study characteristics, details about the HA product used (manufacturer, production method (Bio-HA [biologically derived/non-animal stabilized] or AD [avian-derived]) and molecular weight (indicated as high if ≥3000 kDa, moderate if <3000 and ≥1500 kDa, or low if <1500 kDa), the timing of injections, reported pain outcomes, safety data (the number of treatment-related adverse events (AEs) and treatment-related serious adverse events (SAEs)), and the authors' conclusions. Data from the repeated courses of treatment population were used whenever possible.

### *Outcomes*

The primary outcome of our systematic review was reduction in knee pain at the last reported follow-up visit. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores were extracted whenever reported. If WOMAC pain scores were not reported, an *a priori* hierarchy of outcomes was used to extract the next-most relevant outcome measure. The hierarchy used was taken from a previous meta-analysis, and is as follows: WOMAC pain, Visual Analog Scale (VAS) pain with activity/walking, VAS pain weight bearing, VAS pain at rest, Other Pain outcomes (Knee Injury and Osteoarthritis Outcome Score (KOOS), Musculoskeletal Outcomes Data Evaluation and Management System (MODEMS), Index of Severity for Osteoarthritis for the Knee (ISK) assessment), and WOMAC Total Score.

Secondary outcomes were the number of treatment-related AEs and treatment-related SAEs. These were defined as an AE or SAE related to treatment determined by the investigator. Only the number of treatment-related AEs and SAEs reported for the repeated courses of treatment population were recorded.

### *Data analysis*

Descriptive statistics were used to report study characteristics using counts and percentages for categorical and dichotomous variables, and means with ranges for continuous variables. Due to the heterogeneity in the data types reported, which varied among assessed values, absolute changes from baseline, relative changes from baseline and response rates, we were unable to pool study results. Therefore, data are presented descriptively.

## Results

### *Search strategy*

Our literature search identified 2808 articles, with 1847 of these articles deemed relevant for title review (Fig. 1). Following sequential screening of titles, abstracts, and full texts, 12 articles met the pre-defined inclusion criteria [8–19]. An updated literature search was conducted on April 12, 2017; five additional articles met the pre-defined inclusion criteria [21–25].

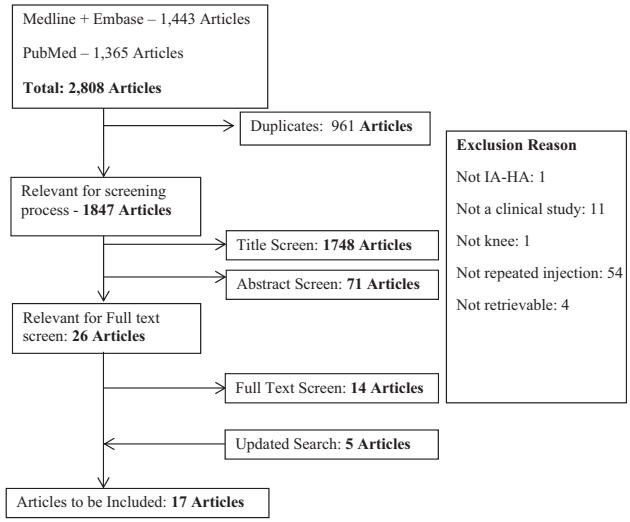


**Fig. 1.** Screening process.

### *Study characteristics*

Seven RCTs and 10 prospective studies were included in the analysis. The majority of studies were published in the last decade (52.9%; Table 1) and in Europe (52.9%; Fig. 2). Of the RCTs, six were double-blind with two trials including open label extension studies and one was single-blind. All 10 prospective studies were open label, with the most frequent follow-up period being 52 weeks (range: 26–174).

### *Treatment details and courses*

Nine studies used high molecular weight HA, eight utilized a low molecular weight HA product and one study [9] evaluated a moderate weight HA versus a high molecular weight HA (Table 2). The majority of IA-HA products were produced via avian-derived molecules (ADHA) ($n = 11$), or by bacterial fermentation (Bio-HA) ($n = 6$), and one study did not report the product characteristics [21] (not related [NR]) ($n = 1$). Atamaz et al. [9] compared a Bio-HA product to an ADHA product.

The number of injections per treatment course ranged from one to five. The number of treatment courses varied between studies, ranging from one additional course of treatment up to five repeated courses of treatment. Altman et al. [8], Atamaz et al. [9], Kolarz et al. [11], Benazzo et al. [22], Heger et al. [23], Kolarz et al. [11], Leighton et al. [24], Neustadt et al. [13], Pal et al. [14], Raynauld et al. [16], Strand et al. [18] and Waddell et al. [19] conducted clinical trials with one repeated course. Raynauld et al. [16] conducted a study with either one or two repeated courses. Abate et al. [21], Jubb et al. [10] and Pham et al. [15] conducted double-blind RCTs with three repeated courses of treatment, and Navarro-Sarabia et al. [12] and Scali [17] conducted studies (patient- and evaluator-blinded RCT and prospective study, respectively) with five repeated treatment courses. Petrella and Wakeford [25] conducted a longitudinal retrospective study and analysis of participants who received additional courses of IA-HA treatment.

### *Efficacy of repeated injections of IA-HA*

All included studies reported statistically significant reductions in pain during the initial IA-HA treatment cycle (Table 3). A further

**Table 1**
Study characteristics. IA-HA: intra-articular hyaluronic acid, KL: Kellgren-Lawrence, NA: not applicable, NR: not reported, RCT-randomized clinical trial

| Trial author(s) | Country | Study design | Blinding | No. of subjects | OA severity (KL) | IA-HA product name | No. of injections per course | No. of repeated treatment courses | Length of follow-up (weeks) |
|---|---|---|---|---|---|---|---|---|---|
| Abate et al. (2015) [21] | Italy | Prospective study | Open label | 15 | 1,2,3 | NR | 3 First, 1 subsequently | 3 | 61 |
| Altman et al. (2011) [8] | USA | RCT + open label extension | Double-blinded Open label | 219 | 2,3 | Euflexxa | 3 | 1 | 26 |
| Atamaz et al. (2006) [9] | Turkey | RCT | Single-blinded | 40 | 2,3 | Orthovisc, Synvisc | 4 | 1 | 52 |
| Benazzo et al. (2016) [22] | Italy | Prospective study | Open label | 49 | 2,3 | Hymovis | 2 | 1 | 52 |
| Heger et al. (2016) [23] | Germany | Prospective study | Open label | 314 | 1,2,3 | Hyalgan | 3 | 1 | 26 |
| Jubb et al. (2003) [10] | UK | RCT | Double-blinded | 408 | 2,3 | Hyalgan | 3 | 2 | 52 |
| Kolarz et al. (2003) [11] | Austria | Prospective study | Open label | 15 | 1, 2, 3 | Hyalgan | 5 | 1 | 52 |
| Leighton et al., 2013 [24] | Canada, UK, Sweden | RCT + open label extension | Double-blinded Open label | 163 | 2,3 | Durolane | 1 | 1 | 52 |
| Navarro-Sarabia et al. (2011) [12] | Spain | RCT | Double-blinded | 306 | 2, 3 | Adant | 5 | 3 | 174 |
| Neustadt (2003) [13] | USA | Prospective study | Open label | 13 | 2,3,4 | Hyalgan | 5 | 1 | 104 |
| Pal et al. (2014) [14] | India | Prospective study | Open label | 11 | 1,2,3 | Synvisc | 1 | 1 | 52 |
| Pham (2004) [15] | France | RCT | Double-blinded | 301 | 1,2,3,4 | NRD101 HA | 3 | 2 | 52 |
| Petrella and Wakeford (2015) [25] | Canada | Retrospective chart review | Retrospective case–control open label | 1263 | 1,2,3,4 | Hyalgan | 1 or 3 | 1 | NR |
| Raynauld et al. (2005) [16] | Canada, USA, Australia | RCT | Randomized open label | 48 | NR | Synvisc | 3 | 1 or 2 | 52 |
| Strand et al. (2016) [23] | USA | RCT + open label extension | Double-blinded Open label | 125 | 1,2,3 | Gel-200 | 2 | 1 | 26 |
| Scali (1995) [17] | Argentina | Prospective study | Open label | 75 | NR | Hyalart | 5 | 4 | 130 |
| Waddell et al. (2005) [19] | USA | Prospective study | Open label | 71 | 2,3,4 | Synvisc | 3 | 1 | 52 |

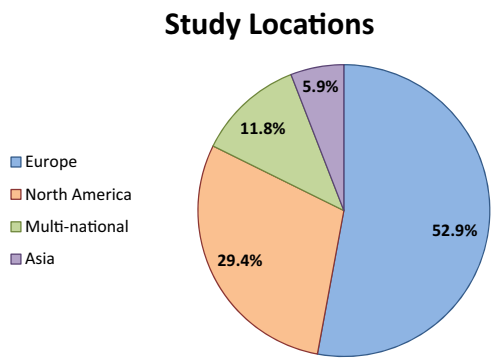


**Fig. 2.** Study locations.

reduction in pain or maintained reduction in pain was also reported in each study throughout the repeated courses of treatment. Two studies [10,15] included a comparator in the retreatment phase. Jubb et al. [10] observed a significant between-group difference in efficacy after each injection cycle compared to placebo, whereas Pham et al. [15] did not observe a significant difference between IA-HA and placebo reinjection after 52 weeks.

*Studies with one repeated course of IA-HA*

Altman et al. conducted an open label extension study which included participants who completed the double-blinded FLEXX Trial [8]. In this open label extension study, participants received three weekly IA-HA (Euflexxa) injections and were followed for 26 weeks. Participants observed an average reduction in pain in the VAS score of 3.5 mm from baseline. Leighton et al. [24] also conducted a double-blinded RCT with an open label extension study. Participants who received a single injection of IA-HA (Durolane) in the open label extension after initial therapy showed significantly higher WOMAC pain responder rates at 39 and 52 weeks ($P < 0.001$)) and a further decrease in WOMAC pain scores compared to baseline measurements. Strand, Lim and Takamura also conducted a 13-week double-blind RCT and 13-week open label extension study using Gel-200 IA-HA treatment versus saline [18]. They found that multiple courses of IA-HA treatment resulted in a statistically significant reduction in pain from baseline in the RCT and in the open label extension study, with greater pain relief in the retreatment phase. Mean scores and changes from baseline were significantly different in the between-group analysis ($p < 0.001$). Atamaz et al. [9] conducted a single-blinded RCT: group 1 received an initial 3-course injection regimen of IA-HA (Orthovisc, Synvisc), followed by a repeat course of a single injection at the 6-month follow-up. Group 2 received physical therapy agents (PTA) such as infrared, short-wave diathermy pulsed patterns and interferential therapy five times a week for 3 weeks. Significant reductions in pain were observed at 12 months in both treatment groups.

There were eight open label studies with one repeated course of IA-HA treatment. All eight prospective studies reported a continued reduction in pain over the multiple courses of treatment. Benazzo et al. conducted a multicentre study. Participants who received a regimen of two weekly IA-HA injections (Hymovis) and a repeat cycle at 6 months demonstrated a significant improvement at week 52 in WOMAC A1 pain sub scores ($P < 0.001$) [22]. Heger et al. [23] evaluated repeat treatment of IA-HA (Hyalgan) at 26 weeks. Verbal Pain Questionnaire (VPQ) scores decreased significantly at 26 weeks compared with baseline for participants that received repeat treatment (initial treatment was 6 months ago) or that received an initial treatment of IA-HA ($P < 0.001$). Kolarz et al. [11] administered one repeated course of IA-HA treatment (Hyalgan) to 15 participants. There were improvements in all pain parameters (VAS pain on movement, VAS pain at rest) compared with the baseline values over the second course of treatment and follow-up periods. Of note, 5 of 15 participants were lost to follow-up at month 6 (12). Participants in the observational study conducted by Neustadt [13] received five weekly IA-HA injections (Hyalgan) and the majority (67%) of participants exhibited a significant reduction in pain 6 weeks after their repeat treatment course. Waddell et al. [19] gave three weekly injections of IA-HA (Synvisc) to participants and followed participants for 24 months. Only participants that had a clinical benefit (≥20 mm improvement from baseline in physician VAS) from the first course of treatment were given a second course of injections at a mean time of 19.6 months following their first injection course. They found that all pain efficacy parameters significantly improved at

**Table 2**
Treatment characteristics. ADHA: avian-derived. Bio-HA: biologically derived/non-animal stabilized. Cntrl: control. IA-HA: intra-articular hyaluronic acid. N/A: not applicable. Trmt: treatment. Molecular weight: high if ≥3000 kDa, moderate if < 3000 and ≥1500 kDa, or low if < 1500 kDa

| | Molecular weight | | Structure (x-linked) | | Production method | |
|---|---|---|---|---|---|---|
| Trial | Group 1 (Trmt) | Group 2 (Cntrl) | Group 1 (Trmt) | Group 2 (Cntrl) | Group 1 (Trmt) | Group 2 (Cntrl) |
| *One repeated course of IA-HA* | | | | | | |
| Altman (2011) [8] | High | N/A | No | N/A | Bio-HA | Saline (FLEXX trial) Bio-HA (extension) |
| Atamaz et al. (2006) [9] | Moderate | No | No | No | Bio-HA | N/A |
| | High | No | Yes | No | ADHA | N/A |
| Benazzo et al. (2016) [22] | High | N/A | No | N/A | Bio-HA | N/A |
| Heger et al. (2016) [23] | Low | N/A | No | N/A | ADHA | N/A |
| Kolarz et al. (2003) [11] | Low | N/A | No | N/A | ADHA | N/A |
| Leighton et al. (2013) [24] | Low | N/A | No | N/A | Bio-HA | N/A |
| Neustadt (2003) [13] | Low | N/A | No | N/A | ADHA | N/A |
| Pal (2014) [14] | High | No | Yes | No | ADHA | N/A |
| Petrella and Wakeford (2015) [25] | High | N/A | No | N/A | ADHA | N/A |
| Raynauld (2005) [16] | High | NA | Yes | NA | ADHA | NA |
| Strand et al. (2016) [18] | High | Gel-200 | Yes | Yes | ADHA | ADHA |
| Waddell et al. (2005) [19] | High | N/A | Yes | N/A | ADHA | N/A |
| *≥Two repeated courses of IA-HA* | | | | | | |
| Abate et al. (2015) [21] | Low | N/A | No | N/A | NR | N/A |
| Jubb (2003) [10] | Low | N/A | No | N/A | ADHA | N/A |
| Navarro-Sarabia (2011) [12] | Low | N/A | No | N/A | Bio-HA | N/A |
| Pham (2004) [15] | High | N/A | No | N/A | Bio-HA | N/A |
| Scali (1995) [17] | Low | N/A | No | N/A | ADHA | N/A |

**Table 3**
Summary of trial results. IA-HA: intra-articular hyaluronic acid, NaHA: sodium hyaluronate, OARSI: osteoarthritis Research Society International, PBS: phosphate-buffered saline, PTA: physical therapy agents, RCT: randomized controlled trial, VAS: visual analog scale, WOMAC: Western Ontario and McMaster Universities osteoarthritis index

| Trial | Pain outcome measures | Summary of results |
|---|---|---|
| *One repeated injection course of IA-HA* | | |
| Altman (2011) [8] | WOMAC (pain)<br>VAS (walking pain) | Participants who continued with IA-BioHA in the open label extension maintained their improvement from baseline, with an average reduction in pain in the VAS score of −3.5 mm. |
| Atamaz et al. (2006) [9] | VAS (spontaneous day pain)<br>Night pain, pain at rest, pain on movement and pain on touch assessed by four-point scoring system (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = strong pain) | There was significant improvement from baseline for all pain measurements in both groups during follow-up; however, there was no significant between-group difference. The improvement of pain (at night, at rest) was greater in the PTA group, although no difference between groups was found in subgroup analyses. |
| Benazzo et al. (2016) [22] | WOMAC (pain) | Significant improvements in WOMAC A1 pain sub scores were observed. Participants treated with two cycles of IA-HA maintained reduction in knee pain 52 weeks after initial treatment. |
| Heger et al. (2016) [23] | Verbal Pain Questionnaire (VPQ) | VPQ scores decreased significantly at 26 weeks compared with baseline. Repeat courses of IA-HA were effective with a favorable safety profile for knee OA. |
| Kolarz et al. (2003) [11] | VAS (pain on movement)<br>VAS (pain at rest)<br>Likert ordinal pain scale (0 = no pain to 4 = very severe pain) | Significant improvements were observed in all pain efficacy parameters compared with baseline values. VAS score for pain on day 35 ($N = 14$) decreased by 22% from baseline, and decreased by 46% by the end of the 12-month follow-up ($N = 6$). |
| Leighton et al. (2013) [24] | WOMAC (pain) | Patients who received NASHA in the open label extension showed an additional decrease in WOMAC pain at 26 weeks compared to the initial blinded treatment phase. |
| Neustadt (2003) [18] | VAS (pain)<br>Night pain, and pain on walking (categorical assessment) | Thirteen patients received a repeated injection course of IA-HA, and the majority (67%) of knees improved in pain after a repeat treatment course. |
| Pal (2014) [14] | WOMAC (walking pain)<br>WOMAC (pain) | After repeat injection, statistically significant decreases were observed in both WOMAC pain sub scores. |
| Petrella and Wakeford (2015) [25] | VAS (pain)<br>6-minute walk test (6MWT) | Significant improvements in VAS pain and 6MWT were observed in data from participants administered with repeat single or three-weekly injections of IA-HA. Evidence from real world longitudinal cohort data suggests repeat injections of IA-HA are significantly superior to that seen with control therapies. |
| Raynauld (2005) [16] | WOMAC (pain) | WOMAC pain improved in the repeated treatment subgroup by 35% from baseline measurements. |
| Strand Lim and Takamura (2016) [18] | WOMAC (pain)<br>VAS (pain) | Statistically significant reduction in pain from baseline over 26 weeks. Mean scores and changes from baseline were significantly different in the between-group analysis ($p < 0.001$). |
| Waddell et al. (2005) [19] | WOMAC (walking pain)<br>VAS (pain patient and investigator) | All pain efficacy parameters significantly improved from baseline at week 26 and week 52. |
| *≥Two repeated injection courses of IA-HA* | | |
| Abate et al. (2015) [21] | VAS (pain)<br>Lesquene Index<br>Knee Injury and Osteoarthritis Outcome Score (KOOS) | Participants received three weekly injections of IA-HA initially, and one single injection at 4, 8, and 12 months. Participants observed a significant reduction in knee pain in all efficacy parameters and maintained this efficacy after 1 month and up to 14 months. |
| Jubb (2003) [10] | VAS (walking pain)<br>Pain (6-point categorical scale) | IA-HA was significantly superior to placebo in treating VAS pain (on walking) at weeks 11, 35 and 52. |
| Navarro-Sarabia (2011) [12] | OARSI Responders of pain (decrease in pain of at least 20% or at least 10 mm on the VAS) | At the 40-month visit, significantly more patients responded to HA compared with placebo. The number of responders to IA-HA increased throughout the study, whereas those to placebo did not change. |
| Pham (2004) [15] | VAS (pain)<br>Lequesne's index (pain) | Significant improvement in pain (VAS) and pain measured by Lequesne's index was observed for all treatment groups; however, there was no between-group differences observed. |
| Scali (1995) [17] | Huskisson 100 mm VAS (pain)<br>Pain at rest, night pain, pain on touch, pain on movement (4-point scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe) | Spontaneous pain measured by Huskisson 100 mm VAS and secondary pain measurements significantly improved after first course and continued to decrease up to the end of the study. |

6 months and 12 months from baseline for participants that received a second course of IA-HA.

Pal et al. [14] conducted an open label multicentre prospective study. Participants received a single injection of IA-HA (Synvisc). At 26, 39, or 52 weeks, eligible participants could participate in a repeat treatment phase (repeat eligibility criteria were the same as those for study entry plus no major safety concerns during the first course of treatment). Eleven participants (2.8%) had repeated injections at week 26 or week 52. After repeat injection (week 0 to week 4), statistically significant decreases were observed in WOMAC A1 pain ($p \leq 0.03$). Raynauld et al. conducted a prospective, randomized, pragmatic, health outcomes trial. Participants were randomized to appropriate care with or without IA-HA (hylan G-F 20) [16]. The IA-HA group was then partitioned into

two subgroups: group 1: participants who received a single course of IA-HA, and group 2: participants who received two or more courses of IA-HA. Participants received three intra-articular injections at intervals of 1 week with a minimum of 4 weeks between repeat courses of injection if persistent pain recurred. Pain, as measured by the WOMAC pain score, decreased in the repeat-course subgroup by 35% from baseline (vs. appropriate care group by 14%).

Lastly, Petrella and Wakeford [25] conducted a real-world longitudinal prospective study identifying participants who received two consecutive series of IA-HA injections (Hyalgan) compared to matched participants that had not been treated with IA-HA. Courses of IA-HA consisted of single injection and three weekly injections regimens with repeat courses administered within 6 months of initial treatment. Significant reductions in VAS pain were observed compared to baseline measurements for both treatment regimens ($P < 0.012$).

### ≥ 2 Repeated courses of IA-HA

Jubb et al. [10] conducted a double-blinded RCT where participants received a three-course injection regimen of either IA-HA (Hyalgan) or IA-saline over 3 weeks. This course was repeated twice more at 4-month intervals. At weeks 11, 35 and 52, the patients who received IA-HA had significantly less pain on walking compared to patients who received the placebo. Pham and colleagues also conducted a double-blinded RCT and randomly allocated participants to three groups: (1) three courses of three IA-HA injections and oral placebo; (2) IA-saline injections and diacerein 100 mg/day; and (3) IA-saline injections and oral placebo [15]. Significant reductions in pain VAS were observed within all three treatment groups; however, there were no significant differences between the three treatment groups in reductions in pain.

Abate and colleagues investigated participants who received three weekly injections of IA-HA initially, and one subsequent single injection at 4, 8 and 12 months. Participants observed a significant reduction in knee pain in all efficacy parameters (VAS pain during activities and at rest) and maintained this efficacy after 1 month and up to 14 months ($P < 0.001$) [21].

Navarro-Sarabia and colleagues conducted a patient and evaluator-blinded RCT [17]. Participants received four cycles of five IA-HA (Adant) injections or placebo injections and were followed for 1 year after their fourth course of injections. Significantly more patients who received IA-HA versus placebo had a reduction in pain over the course of their follow-ups.

Scali conducted a prospective study in which patients received a five weekly injection course of IA-HA (Hyalart), which was repeated every 6 months over a period of 25 months [17]. Participants received 25 injections. Spontaneous pain decreased after the first course and continued to decrease up to the end of the study, an approximate 55% reduction in pain compared to baseline assessments.

### Safety of repeat IA-HA treatment

Table 4 summarizes the number of participants who experienced treatment-related AEs or treatment-related SAEs after receiving multiple courses of IA-HA. Altman et al. [20], Pal et al. [14], Raynauld et al. [16] and Strand et al. [18] were the only studies that reported treatment-related AEs or SAEs in study populations receiving multiple courses of IA-HA treatment. Strand et al. [18] observed the highest incidence rate of treatment-related AEs (14.4%), reporting arthralgia (7.2%) and joint swelling (5.6%) as the most common events.

**Table 4**
Treatment-related adverse events in study populations receiving multiple courses of intra-articular hyaluronic acid treatment

| Trial | Participants experiencing a treatment related AE (*N* (%)) | Type of treatment related AEs—*N* (%)[a] |
|---|---|---|
| *One repeated course of IA-HA* | | |
| Altman et al. (2011) [8] | 21 (4.8%) | Arthralgia—12 (2.8%)<br>Joint swelling—5 (1.2%),<br>Peripheral edema—3 (0.7%)<br>Injection site pain—2 (0.5%) |
| Pal et al. (2014) [14] | 0 (0%) | 0 (0%) |
| Raynauld et al. (2005) (1st repeat course) [16] | 2 (4.2%) | Not reported |
| Strand et al. (2016) [18] | 18 (14.4%) | Arthralgia—9 (7.2%)<br>Joint swelling—7 (5.6%) |
| *≥Two repeated courses of IA-HA* | | |
| Raynauld et al. (2005) (2nd repeat course) [16] | 3 (6.3%) | Not reported |

[a] Not all treatment-related AEs were reported by authors.

## Discussion

The current review summarizes the limited published evidence on repeated courses of IA-HA treatment for knee OA and found that repeated injections of IA-HA reduced pain and were a safe therapeutic option. These results were demonstrated within investigations of a single repeat course and courses of two or more reinjection cycles. Significant improvement in pain from baseline to the final follow-up was reported in all studies. In RCTs with extension studies, a continued reduction in pain was also observed for participants who received additional courses of treatment.

We found varied results in the between-group comparisons for IA-HA and other treatment options. For example, although a reduction in pain was observed, one single-blinded study did not report a significant between-group difference in pain when comparing IA-HA to physical therapy agents. Additionally, two placebo-controlled studies found conflicting results with one reporting between-group differences and the other not finding between group differences. Specifically, the RCT conducted by Jubb et al. [10] found a significant between-group difference in VAS pain (walking) between IA-HA and IA-saline after each injection course. Conversely, Pham and colleagues [15] observed a clinically relevant improvement in VAS pain but did not observe a significant between-group difference between IA-HA versus placebo. These dissimilar results may be attributable to a large placebo effect, differences in the efficacy of the HA preparations, and/or the continued use of NSAIDs and analgesic medications in the majority of participants (96%) included in the Jubb et al.'s [10] study.

Treatment-related AEs and SAEs were reported, demonstrating that repeated injections of IA-HA are a safe treatment option. Altman et al. [8], Pal et al. [14] and Strand et al. [18] were the only studies to report treatment-related AEs in study populations receiving multiple courses of IA-HA. Pal et al. [14] did not observe any treatment-related AEs for participants in the 4-week retreatment phase of the trial. The most commonly reported treatment-related AEs in the studies by Altman et al. [8] and Strand et al. [18] were arthralgia and joint swelling. In the EUFLEXXA trial by Altman et al. [8], the number of treatment-related AEs in the extension study ($n = 21$; 4.8%) was similar to the number of AEs in the initial RCT ($n = 29$; 10%) [20]. Strand et al. [18] reported similar results. Although Strand et al. [18] reported the highest percentage

of treatment-related AEs ($n$ = 18; 14%) in the IA-HA group, the number of events was not significantly different compared to the phosphate buffer solution group ($n$ = 8; 10.8%). Moreover, the proportion of treatment AEs were lower in the retreated study population compared to participants who did not receive an additional course of treatment. This suggests that the proportion of treatment-related AEs through long-term use of IA-HA is similar to a single course of treatment.

Long-term follow-up data suggests that repeated courses of IA-HA reduce pain and are safe in treating knee OA. Specifically, the double-blind AMELIA study, which followed participants for 40 months, provided evidence that repeated cycles of IA-HA reduced knee pain versus IA-saline during the in-between cycle period and that there was a marked carry-over effect for at least 1 year after the last cycle [12]. No difference in OARSI responder rates was observed between IA-HA and placebo within the first seven months, suggesting a large and immediate placebo effect may have been experienced by participants receiving IA-saline. However this was effectively diminished after one year of follow-up, with participants responding significantly more to multiple cycles of IA-HA treatment until the end of the trial compared to IA-saline [12]. The AMELIA trial was an important contribution to the understanding of the effectiveness and safety of repeated cycles of IA-HA [17]. Conversely, other injections (e.g., NSAIDs and corticosteroid) have been shown to have less effective results after long-term repeated courses, as well as negative adverse effects [26].

This review may be subject to risks of bias; however, the heterogeneity of included study designs precludes the ability to conduct a formal risk of bias assessment. The wide variety of evidence within this review may lead to a potentially large amount of heterogeneity between studies that should be considered when interpreting these results. Despite the lack of a formal risk of bias assessment, we can subjectively speculate that our findings provide robust insights into repeated courses of IA-HA for treating knee OA. There are a number of large blinded trials included in this review indicating the presence of a high level of evidence, while information from open label trials and prospective studies is helpful in providing additional data on the topic.

This review is strengthened by its methodological approach in systematically identifying all published literature on repeated courses of IA-HA. Despite this strength, this review is limited by the methodologies within the included studies. First, non-randomized studies were included, and a few RCTs were conducted. Second, each included study was unique in its design, treatment regimen, length of follow-up, and pain outcome measure. This resulted in large between-study heterogeneity, and we were therefore unable to pool data across the studies. Third, some included studies failed to provide explanations for treatment discontinuation. This may be due to a lack of treatment efficacy or serious treatment-related side effects. Conversely, participants may have experienced significant reductions in pain during the first course of therapy and investigators suggested additional courses of IA-HA were not required. Distinct reasons for treatment discontinuation should be provided to properly assess long-term use of IA-HA. Fourth, most studies did not report treatment-related AEs and SAEs. Fifth, there was a lack of studies that compared long-term use of IA-HA to a control group.

## Conclusion

This review found that multiple courses of IA-HA injections reduced pain and were safe for the management of knee OA. Future research is needed to confirm these findings as there were multiple methodological limitations within each of the included studies. Future clinical practice guidelines should consider the product characteristics, long-term use and repeated courses of IA-HA treatment for the management of knee OA.

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## Appendix 1

See Table A1.

**Table A1**
Literature search strategy

| MEDLINE and EMBASE | PubMed |
|---|---|
| 1. Hyaluronic acid[title] | 1. Hyaluronic acid |
| 2. Hylan[title] | 2. Hylan |
| 3. Hyaluronan[title] | 3. Hyaluronan |
| 4. Viscosupplementation[title] | 4. Viscosupplementation |
| 5. Osteoarthrit$.mp | 5. Osteoarthritis |
| 6. Knee.mp | 6. Knee |
| 7. 1 or 2 or 3 or 4 | 7. 1 or 2 or 3 or 4 |
| 8. 5 and 6 | 8. 5 and 6 |
| 9. 7 and 8 | 9. 7 and 8 |
| 10. Euflexxa.mp | 10. Euflexxa |
| 11. Synvisc$.mp | 11. Synvisc |
| 12. Supartz.mp | 12. Supartz |
| 13. Orthovisc.mp | 13. Orthovisc |
| 14. Durolane.mp | 14. Durolane |
| 15. Hyalgan.mp | 15. Hyalgan |
| 16. Artzal.mp | 16. Artzal |
| 17. Adant.mp | 17. Adant |
| 18. NRD101.mp | 18. NRD101 |
| 19. BioHY.mp | 19. BioHY |
| 20. Fermathron.mp | 20. Fermathron |
| 21. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 | 21. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 |
| 22. 9 or 21 | 22. 9 or 21 |

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