REVIEW

Ann R Coll Surg Engl 2013; **95**: 545–551
doi 10.1308/003588413X13629960049432

The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain

D Trigkilidas, A Anand

University of Warwick, UK

ABSTRACT

INTRODUCTION Knee osteoarthritis (OA) is a common and progressive joint disease. Treatment options for knee OA vary from simple analgesia in mild cases to knee replacement for advanced disease. Knee pain due to moderate OA can be targeted with intra-articular injections. Steroid injections have been used widely in managing acute flare-ups of the disease. In recent years, viscosupplementation has been used as a therapeutic modality for the management of knee OA. The principle of viscosupplementation is based on the physiological properties of the hyaluronic acid (HA) in the synovial joint. Despite a sound principle and promising in vitro studies, clinical studies have been less conclusive on the effectiveness of HA in managing osteoarthritic knee pain. The aim of this systematic review was to assess the effectiveness of HA intra-articular injections in the management of osteoarthritic knee pain.

METHODS A systematic review of the literature was performed using MEDLINE®, Embase™ and CINAHL® (Cumulative Index to Nursing and Allied Health Literature). The databases were searched for randomised controlled trials available on the effectiveness of HA intra-articular injections in managing osteoarthritic knee pain.

RESULTS The search yielded 188 studies. Of these, 14 met the eligibility criteria and were reviewed in chronological order.

CONCLUSIONS HA intra-articular injections have a modest effect on early to moderate knee OA. The effect peaks at around 6–8 weeks following administration, with a doubtful effect at 6 months.

KEYWORDS

Hyaluronic acid – Knee – Osteoarthritis

Accepted 7 May 2013

CORRESPONDENCE TO

Dionysios Trigkilidas, 103 Linden Gardens, Enfield EN1 4DY, UK
E: diotrigkilidas@hotmail.com

Knee osteoarthritis (OA) is a common and progressive joint disease. In the US, it is believed that 240 per 100,000 people are affected each year.[1] It has a major effect on the quality of the individual's life and knee OA is one of the five leading causes of disability among non-institutionalised adults. Forty per cent of adults with knee OA report their health as poor or fair. It also has a major socioeconomic impact as it results in absences from work and early retirement. It is estimated that job related losses due to OA in general are between $3.4 and $13.2 billion per year.

Treatment options for knee OA vary according to the severity of the disease. For the mild cases, simple analgesia and lifestyle modifications may be enough to control the symptoms. In advanced stages of the disease, knee replacement is a safe and cost effective treatment for alleviating pain as well as restoring physical function.[2] Knee pain due to moderate OA can be targeted with intra-articular injections. Steroid-based injections in combination with local anaesthetic have been used widely in managing acute flare-ups of the disease. Their action is based on the powerful anti-inflammatory effect they provide in the joint, thereby alleviating pain due to synovitis, which commonly occurs in OA.

In recent years, viscosupplementation has been used as a therapeutic modality for the management of knee OA. The principle of viscosupplementation[3] is based on the physiological properties of the hyaluronic acid (HA) in the synovial joint.

Background

Also known as hyaluronate or hyalunoran, HA is a large viscoelastic glycosaminoglycan molecule that is found naturally in synovial fluid and cartilage.[4] Its properties include shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface and lubrication.[5] In vitro, it is shown to have anti-inflammatory effects on cells,[5,6] and it may slow chondrocyte apoptosis in OA by binding CD44 and ICAM-1 receptors, and regulating in this way the process of cartilage matrix degradation.[4]

The concentration and the molecular weight of HA in the synovial fluid of patients with knee OA are shown to be

reduced.[7,8] As the viscoelasticity of synovial fluid is proportional to HA concentration and integrity, it is believed that intra-articular HA injections would restore the viscoelasticity of synovial HA and therefore also its natural protective functions in the joint.

Despite a sound principle and promising in vitro studies,[5,6] clinical studies have been less conclusive on the effectiveness of HA in managing osteoarthritic knee pain. Some studies suggest that there is an effect when compared with a placebo[9] while other studies suggest that there is no clear benefit.[10,11] Furthermore, compared with the much cheaper alternative of corticosteroid injections, some studies conclude that HA is of no additional benefit[12] whereas others suggest that it has a more prolonged effect than corticosteroids.[9,13]

The aim of this review was to assess the efficacy of HA intra-articular injections in managing osteoarthritic knee pain.

Methods

A systematic review of the literature was performed. MEDLINE®, Embase™ and CINAHL® (Cumulative Index to Nursing and Allied Health Literature) were searched on 30 November 2011 for randomised controlled trials available on the effectiveness of HA intra-articular injections in managing osteoarthritic knee pain. Studies were eligible for inclusion in the review if: the study population consisted of human patients with knee OA; the intervention was the use of intra-articular HA; the comparators were either a placebo or corticosteroid intra-articular injections; outcome measures were improvement in pain or function scores; they were randomised controlled trials (RCTs); and they were available as full free text from the Warwick university library or Google™ Scholar. Non-randomised studies, pilot studies, studies on cost effectiveness and studies not published in the English language were excluded.

PubMed was used as the search engine for MEDLINE®. The search was performed using both free text and MeSH (Medical Subject Headings) terms for studies published on any date up to the search date. The free text inserted in the search engine was 'hyaluronic acid injections knee pain'. The MeSH terms used were 'hyaluronic acid', 'knee joint' and 'injections, intra-articular'. The Embase™ search was performed using the keywords 'hyaluronic acid', 'injections' and 'knee', including all subheadings, for studies from 1947 up to 30 November 2011. The CINAHL® database was searched using the free text 'hyaluronic acid knee injections' for studies published on any date up to the search date. All the eligible studies were reviewed using the appraisal checklist from the Critical Appraisal Skills Programme.[14–16]

Results

The search yielded 188 studies in total. Of these, 61 were duplicate studies, bringing the total to 127. After review of the title and/or abstract, a further 67 studies were excluded as irrelevant, reducing the number to 60. Of these studies, 22 were available as free full text from the Warwick university library or Google™ Scholar. A further eight studies were excluded after review of the full text as they did not meet the eligibility criteria. The 14 studies left were reviewed in chronological order (Fig 1).[4,12,17–28]

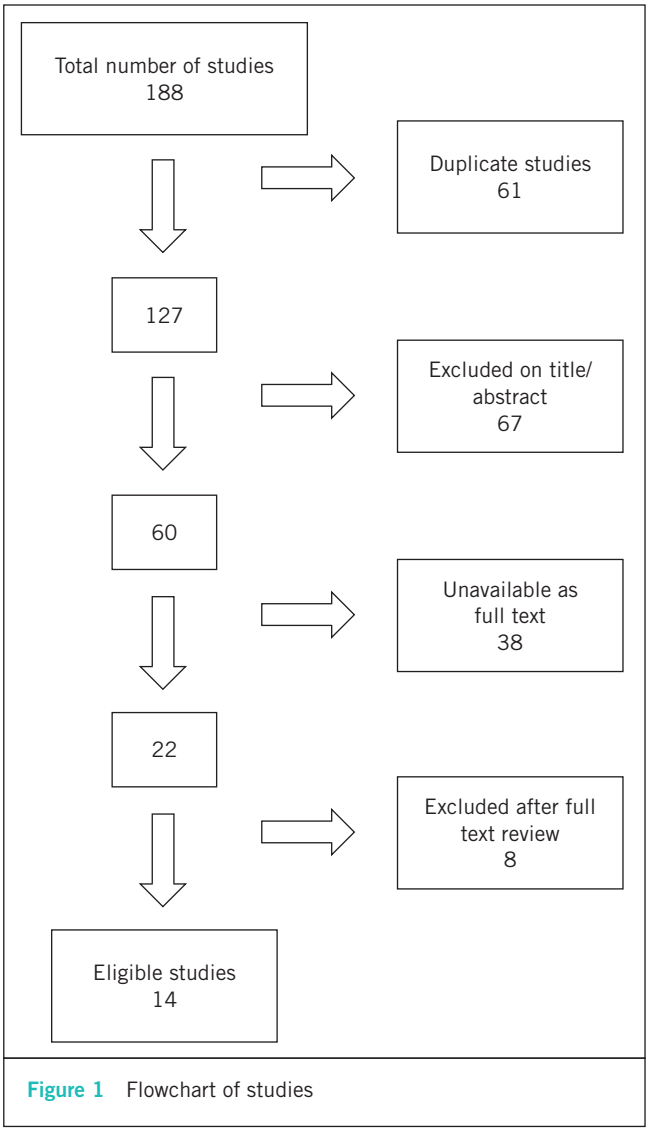

Figure 1 Flowchart of studies

Study 1

Dougados *et al* performed a prospective, randomised, placebo controlled, multicentre trial to evaluate the efficacy of hyalectin over one year.[17] This was one of the earliest studies aiming to assess the effectiveness of HA over a long time. They randomised 110 patients to either receive the active treatment or a placebo. The patients were selected against clearly stated inclusion and exclusion criteria. The sample size was based on population calculations aiming for a power of 80%. The patient randomisation process was not described. This raises concerns about the study as at baseline, the two groups were uneven with regard to pain after exercise and volume of synovial fluid effusion. The intervention group received three weekly injections of HA while

the controls received three weekly injections of a placebo. There was no single primary outcome measure defined.

Instead, the authors assessed pain on a visual analogue scale (VAS) at rest and after exercise, degree of knee effusion, and functional impairment using the Lequesne index at weeks 7 and 52 of the trial.[17] The results showed a significant improvement in favour of HA at week 7 in terms of synovial fluid volume, pain at exercise and functional impairment but not for pain at rest. At one year, there was no difference at pain assessment, effusion was not assessed and there was only a weak difference (p=0.046) in favour of HA with regard to the Lequesne index.

The study by Dougados *et al* was one of the first aiming to assess the effect at one year.[17] The main criticisms, however, were that it was not blinded, the groups were uneven at baseline and they allowed the use of intra-articular steroid injections to be performed, thereby introducing a new variable that could influence their results. The authors concluded that HA has a long-term effect in patients with knee OA but this statement is not justified according to their results.

Study 2

Henderson *et al* performed a randomised, double blind, placebo controlled, single centre trial comparing low molecular weight HA with a placebo in the treatment of knee OA.[18] Although provisional population size calculations suggested 50 participants in each arm for a power of 90%, 91 patients entered the study and were randomised into the two groups. Seven patients withdrew during the treatment period, reducing the overall number to eighty-four. The treatment group received five weekly injections of 20mg Hyalgan® (Fidia Farmaceutici, Abano Terme, Italy) while the placebo group received the same volume of the vehicle alone. It is not clear what the primary outcome measure of the study was.

Sixteen outcome parameters were evaluated up to five months after completion of the treatment phase.[18] Henderson *et al* did not find any statistically significant differences between the two groups at any end point, concluding that low molecular weight HA (750kDa Hyalgan®) was no better than the placebo and therefore lacked efficacy as a treatment for knee OA. Nevertheless, at the five-month end point, the drop out rate had reduced the overall cohort from 84 to 56. This raises concerns about a potentially high type 2 error and lack of study power to detect any clinically significant differences between the two groups.

Study 3

In a randomised, double blind, comparative trial, Jones *et al* compared HA with steroid (triamcinolone) for patients with inflammatory knee OA.[19] They randomised 63 patients into the two groups at a 1:1 ratio. One of the inclusion criteria was that the patient had bilateral knee OA. The worst knee received the active treatment while the other received a placebo. In this way, although there was no true control group, each patient acted as his or her own control. The HA group received five weekly injections while the steroid group received one dose of 20mg triamcinolone followed by four placebo injections. The primary outcome measure was reduction of pain on a self-selected activity assessed by a VAS score at monthly intervals up to six months.

The population was selected based on population size calculations for a power of 80% but no allowances were made for drop out rates.[19] There was a massive drop out rate in both groups at the six-month point. Only 12 patients out of the initial 32 in the HA group and 8 out of the 31 in the steroid group remained in the study, compromising its power. Jones *et al* suggested a trend in favour of HA, especially at six months, but owing to the high drop out rate, no statistically significant difference was detected between the two groups.

Study 4

Lohmander *et al* conducted a randomised, double blind, placebo controlled, multicentre trial to measure the efficacy of intra-articular HA injections in the treatment of knee OA.[20] They randomised 240 patients based on sample size calculations to receive either weekly injections of Artzal® (Seikagaku, Tokyo, Japan) for 5 weeks or a placebo (5 injections of the vehicle only). The study was patient and observer blinded. There was no description of the randomisation process. The primary outcome measures were a reduction in the Lequesne index and a VAS score at 20 weeks.

The study did not show any statistically significant difference between the two groups. When Lohmander *et al* stratified their population according to age and severity on the Lequesne index, patients over 60 years with a severity score of 10 or above seemed to respond better to the HA treatment.[20] It was concluded that these patients were likely to benefit more from HA injections. However, the study was not designed to detect this difference initially. Furthermore, there was no mention of the number of patients in that subgroup or whether there was enough study power to detect a clinically significant difference. Consequently, their conclusion may not be justified.

Study 5

In a randomised, double blind, placebo controlled trial, Wu *et al* assessed the efficacy of HA (Artz®; Seikagaku) in knee OA.[21] They recruited 90 patients (116 knees) who fulfilled their eligibility criteria. The patients were randomised to receive either the active treatment (HA) or its vehicle (placebo). The follow-up duration was up to six months, and the patients were evaluated on subjective and objective symptoms. This was a poor quality study. The population was selected based on eligibility criteria but compared with other studies, these were not described in detail, making reproducibility of the study very difficult. There were no sample size calculations, the randomisation process was not described and there was no clear primary outcome measure. More importantly, the authors did not use any validated or widely accepted outcome scores to assess efficacy, making their results very difficult to compare with other similar studies. The authors concluded that HA is superior to placebo in managing knee pain.

Study 6

Wobig *et al* performed a randomised, double blind, multicentre trial on the efficacy and safety of hylan G-F 20.[22] They

randomised 117 patients with chronic idiopathic knee OA into two groups: one receiving hylan G-F 20 and the other saline. They used a VAS to evaluate pain during weight bearing, pain at rest, reduction of pain during the most painful movement of the knee and treatment success up to 26 weeks. The study showed dramatic early improvement in all variables in the hylan G-F 20 group.

The main criticism of this study is that the two groups were uneven with regard to baseline disease characteristics. Statistically more patients who had pain for one year or less and lower Larsen grades of OA were included in the hylan G-F 20 group than in the comparator group. Although the authors claim that these differences were inconsequential in terms of the efficacy results, the imbalance of the two groups raises concerns about the study's randomisation process.

Study 7

In a randomised, double blind, placebo controlled study by Huskisson and Donnelly, the efficacy of HA was assessed against that of a placebo.[25] The patients were selected according to clearly defined eligibility criteria. A total of 100 patients were randomised into the two study arms, 50 in each group. There were no details on the randomisation process, which is important as at baseline, the two groups were significantly uneven with regard to sex distribution. The sample size was based on calculations aiming for a power of 90% to detect a 15% difference on the VAS score for pain on walking, one of the primary outcome measures. These calculations do not allow for patients dropping out or loss to follow-up.

The intervention group received five weekly Hyalgan® injections while the comparator group received five weekly injections of normal saline of the same volume.[25] The two primary outcome measures were pain on walking measured on a VAS scale out of 100mm, and knee function as assessed by the Lequesne index at 5 weeks and 6 months.

Huskisson and Donnelly's results showed a significant difference for pain at five weeks in favour of HA.[25] This was maintained at six months. For knee function, there was a significant improvement at five weeks and at two months in favour of HA but this was not maintained at six months. There was a drop out rate of nearly 20% from the study. As in many of the previous studies, there was a significant improvement from the baseline for the control group at five weeks following the injections, once again suggesting a powerful placebo effect. The authors concluded that HA is effective in the management of patients with knee OA, which is justified according to their results.

Study 8

Leopold *et al* performed a prospective, randomised, clinical trial comparing intra-articular steroid injections and HA injections with regard to pain relief or function in patients with knee OA.[12] They recruited 100 consecutive patients who fulfilled their study eligibility criteria over a period of 1 year. The inclusion and exclusion criteria for the study were clearly stated. The selected population was randomised into two groups: to either receive HA injections or steroid injections. The randomisation process was clearly described. Although they employed a computerised random number algorithm for the randomisation process, this was used to create 100 study cards that were placed in sealed envelopes. The envelopes were opened when the patients were eligible for study inclusion. The use of sealed envelopes in randomisation is not as robust and could have introduced bias to the study.

The study population was based on power calculations that showed that at least 36 patients per group were required to obtain a power of at least 80%.[12] The intervention group received a course of three weekly intra-articular injections with hylan G-F 20 according to the manufacturer's recommendations. Following this, no additional injections were allowed. The comparison group was injected with betamethasone. This was a single injection mixed with lignocaine and bupivacaine that could be repeated at any time during the study according to patient demand. The injection procedure was clearly stated, making the study reproducible.

There was no single primary outcome for this study.[12] Instead, there were three outcomes, all treated as primary. These were the modified 100-point Knee Society clinical rating system score, the WOMAC® (Western Ontario and McMaster Universities) score and a 100mm VAS pain score. All the outcome measures were appropriate for this study. They were recorded at baseline, at three months and at six months. All the data were collected by a study nurse who was blinded to the treatment.

The results were presented clearly in tabulated form, making them easy to follow.[12] Both groups had a statistically significant improvement from the baseline for the WOMAC® scores. With regard to the Knee Society system, there was no significant improvement in either of the groups. The VAS scores improved for the HA group but not for the steroid group. More importantly, there was no significant difference between the two groups. Interestingly, it was found that women had a significantly lower response to treatment in both groups and in all outcome scores than men. Leopold *et al* could not explain this difference. It may have been due to the population selected. The investigation was performed in an army hospital caring for soldiers, veterans and their families. It could therefore be that the male population in the study was not representative of the normal population.

Overall, this was a well designed study with high power and a small loss to follow-up.[12] Despite this, one of its negative points that could have affected the results was in the method of injection administration. For the HA group, the knee effusions were aspirated first, the needle was left in place and then the injection was administered through the same needle. This procedure was not followed with the steroid injections and the authors did not explain why. This could mean that many steroid injections were given extra-articularly, compromising the results.

The authors concluded that the use of HA over steroid injections is not justified as a first-line treatment in patients with OA, especially as it requires more injections and is not cost effective.[12] This conclusion is justified based on their results.

Study 9

Altman *et al* evaluated the efficacy of a single injection of a non-animal stabilised HA preparation in patients with

knee OA.[4] They performed a randomised, controlled, double blind, multicentre trial and selected their population according to clearly defined eligibility criteria based on sample size calculations. They randomised 347 patients into two groups in a 1:1 ratio: the intervention group, in which patients received the HA injection, and the comparator group, in which patients received the same volume of placebo (saline). The primary outcome measure was a reduction of more than 40% from the baseline on the WOMAC® pain score at 26 weeks.

The results did not show any statistically significant difference between the two groups.[4] Altman *et al* attributed this to the possible confounder that patients with OA at multiple sites were allowed to participate. The difficulty in identifying the exact cause of pain may have masked the effect of the treatment. When they stratified the patients to select those with OA of the knee only, they found a statistically significant difference in favour of HA. Nevertheless, this result needs to be interpreted with caution. By that point, the numbers were too small and the study was not designed to answer this question.

Study 10

Day *et al* conducted a randomised, double blind, multicentre study comparing a course of five injections of HA, given at one-week intervals, with a placebo.[24] Following assessment for eligibility, 240 patients were randomised into the two groups. This was a high quality study, with high power and low loss to follow-up. The protocol of administration of the injections was presented very clearly, making the study reproducible. The primary outcome measure was the WOMAC® score at 6, 10, 14 and 18 weeks. The results were presented clearly in tabulated form. Although there was a large reduction in the pain and stiffness in both groups, there was an additional statistically significant difference in favour of the HA group from 6 to 18 weeks. The difference in the function component of the WOMAC® score, however, did not reach statistical significance.

Study 11

Neustadt *et al* examined the effects of high molecular weight HA (Orthovisc®; Anika Therapeutics, Bedford, MA, US) in knee OA.[25] They performed a randomised, controlled, double blind, multicentre trial where 372 patients were assigned to three groups at a 1:1:1 ratio. The intervention groups received either four injections of Orthovisc®, one injection every week, or three injections of Orthovisc® and one arthrocentesis procedure. The comparator group received four arthrocentesis procedures with no injections. The primary outcome measure was the proportion of patients achieving a 20% relative and 50mm absolute improvement from the baseline in the WOMAC® pain score at weeks 8, 12, 16 and 22. All patients were selected against inclusion and exclusion criteria. The sample size was based on calculations from a previous study.

The results showed that there was a significant improvement from the baseline for all three groups, suggesting a strong placebo effect for arthrocentesis, compatible with the results of many previous studies.[25] Nevertheless, they failed to show a statistically significant difference between the intervention groups and the placebo group.

Study 12

In a study by Petrella and Petrella, the authors assessed the efficacy of intra-articular HA injections compared with a placebo and whether there was a difference between receiving three versus six consecutive injections.[26] They performed a randomised, controlled, double blind trial. Overall, 106 patients were selected against clearly stated eligibility criteria. The sample size was based on size calculations but the power of the study was not stated. Using a computer generated randomisation process, the patients were allocated to two groups to receive either three weekly injections of HA or placebo injections. The two groups were comparable at baseline. Following the initial phase of three weeks, both groups received a further cycle of three weekly injections of HA.

The primary outcome measure was improvement on the WOMAC® score for pain at three weeks.[26] One of the secondary outcomes was the difference between 3 versus 6 injections at 6 and 12 weeks. The results showed a significant improvement from baseline at three weeks for both groups but there was also a significant difference between the groups in favour of HA. For the second phase of the trial, both groups improved significantly from the baseline but there was no difference between the groups. A weak point of this study is that it cannot provide data longer than three weeks on the efficacy of HA over placebo. Furthermore, the second phase did not have a placebo comparator group. The authors concluded that HA was superior to placebo in improving knee pain with no difference between three or six consecutive injections.

Study 13

In another RCT, Diracoglu *et al* determined the short-term effects of intra-articular HA on proprioception, isokinetic muscle force, pain and functional conditioning in patients with knee OA.[27] This was a prospective, double blind study. Sixty patients were enrolled for the study after assessment for eligibility against clearly defined criteria. They were randomised to receive either HA injections or a placebo in a 2:1 ratio. The primary outcome was the effect on proprioception immediately after each injection and at one week after the last injection. Secondary outcomes included isokinetic muscle force, VAS pain scores and WOMAC® scores at one week after the last injection. This study did not have sample size or power calculations.

The baseline characteristics of the groups did not show any statistically significant differences and the groups were treated similarly except for the intervention received.[27] There was a statistically significant difference for proprioception as well as pain and function. The authors concluded that intra-articular HA injections can lead to short-term improvement in pain and function in patients with knee OA.

Study 14

Chevalier *et al* conducted a randomised, controlled, multicentre trial to compare efficacy and safety of a single injection of hylan G-F 20, a high molecular weight HA, versus a

placebo.[28] For this study, patients with primary symptomatic knee OA who consented to participate were screened for eligibility against clear inclusion criteria prior to randomisation. The intervention group received a single 6ml injection of hylan G-F 20 while the comparator group received physiological sodium chloride solution (placebo). The primary outcome measure was change from baseline over 26 weeks using the WOMAC® pain score. In total, 253 patients were randomised into the two groups in a 1:1 ratio. The number was based on population size calculations to allow for a power of 80% with a 25% drop out rate. The study was double blinded.

The results were presented clearly and included tables of the baseline characteristics of the two groups as well as a flowchart of the participants.[28] There was a modest superiority of hylan over the placebo for pain at 26 weeks. The WOMAC® function score, however, did not show any difference between the two groups. There was no difference between the two groups with regard to adverse events.

Table 1 summarises the results from the 14 studies reviewed.

Discussion

Out of the 14 studies that were reviewed, 12 compared HA with a placebo. Of these, five studies showed no statistically significant difference between the two groups. Of the remaining seven studies, one suggested an effect in favour of HA for up to a year following injection[17] and another study for up to six months following injection.[21] Nevertheless, these studies were of relatively poor methodology, raising concerns about the validity of their results. Three studies

Table 1 Summary of papers reviewed

Study	Study design	Number of participants	Intervention vs comparator	Outcome measures	Conclusions
Dougados, 1993[17]	Multicentre RCT	110	HA vs placebo	VAS, knee flexion, Lequesne index	HA has long-term effect
Henderson, 1994[18]	RCT	91	HA vs placebo	No primary outcome measure, 16 outcome parameters used	No difference
Jones, 1995[19]	RCT	63	HA vs steroid	VAS	HA better than steroid at 6 months
Lohmander, 1996[20]	Multicentre RCT	240	HA vs placebo	VAS, Lequesne index	No difference overall but patients over 60 with severe disease may do better with HA
Wu, 1997[21]	RCT	90	HA vs placebo		HA better than placebo
Wobig, 1998[22]	Multicentre RCT	117	HA vs placebo	VAS	HA better than placebo
Huskisson, 1999[23]	RCT	100	HA vs placebo	VAS, Lequesne index	HA better than placebo at 6 months
Leopold, 2003[12]	RCT	100	HA vs steroid	VAS, WOMAC®, Knee Society score	No difference
Altman, 2004[4]	Multicentre RCT	347	HA vs placebo	WOMAC®	No difference
Day, 2004[24]	Multicentre RCT	240	HA vs placebo	VAS, WOMAC®	HA better than placebo between 6–18 weeks
Neustadt, 2005[25]	Multicentre RCT	372	4 injections of HMW HA vs 3 injections of HMW HA vs placebo	VAS, WOMAC®	No difference
Petrella, 2006[26]	RCT	106	HA vs placebo, 3 vs 6 injections	WOMAC®	HA better than placebo, no difference between 3 or 6 injections
Dicaroglu, 2009[27]	RCT	60	HA vs placebo	VAS, WOMAC®	HA better for short term
Chevalier, 2010[28]	Multicentre RCT	253	HMW HA vs placebo	VAS, WOMAC®	HA better for pain; no difference for WOMAC®

RCT = randomised controlled trial; HA = hyaluronic acid; VAS = visual analogue scale; WOMAC® = Western Ontario and McMaster Universities score; HMW = high molecular weight

suggested a statistically significant superiority of HA over placebo but for only a short period of time not exceeding 18 weeks.[24,26,27] Finally, two studies showed a modest effect in favour of HA over placebo for pain that was noticeable at six months but not for function.[25,28]

Of the two studies that compared HA with steroid injections, one showed no statistically significant difference between the two groups.[12] The other suggested that HA was better at six months than steroid injections but this study had a very high drop out rate at six months,[19] making the results questionable.

There were many limitations with this review. The main ones were that the search was only performed electronically without any manual search for relevant articles or unpublished data. The search was limited to the English language, human studies and RCTs. Another major limitation was that only papers with full text available from the Warwick university library or Google™ Scholar were analysed. Despite this, a relatively large number of RCTs were identified and studied. Consequently, reasonable conclusions on the efficacy of HA on knee OA can be made.

An important observation that appears to be consistent among many RCTs is that there is a high placebo effect with knee arthrocentesis. In most trials, the placebo group had a significant reduction in pain scores and improvement of function from the baseline.

Conclusions

From this systematic review, it is evident that despite numerous RCTs, there is weak evidence to support the efficacy of HA in managing knee osteoarthritic pain. The evidence that HA is more efficacious than steroid injections is even weaker. At very best, the effect of HA on knee OA can be described as modest.

Overall, there appears to be a small effect with the use of HA over placebo, which peaks around week 8 following the last injection. There is very little evidence to support that the effect is still noticeable at six months. Compared with steroids, steroid injections tend to be superior to HA up to four weeks, with HA becoming superior after that timeframe and up to eight weeks.

References

1. Osteoarthritis. Centres for Disease Control and Prevention. http://www.cdc.gov/arthritis/basics/osteoarthritis.htm (cited August 2013).
2. NIH Consensus Statement on total knee replacement. *NIH Consens State Sci Statements* 2003; **20**: 1–34.
3. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheumatol Suppl* 1993; **39**: 3–9.
4. Altman RD, Akermark C, Beaulieu AD, Schnitzer T. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthritis Cartilage* 2004; **12**: 642–649.
5. Larsen NE, Lombard KM, Parent EG, Balazs EA. Effect of hyalan on cartilage and chondrocyte cultures. *J Orthop Res* 1992; **10**: 23–32.
6. Ghosh P. The role of hyaluronic acid (hyaluronan) in health and disease: interactions with cells, cartilage and components of synovial fluid. *Clin Exp Rheumatol* 1994; **12**: 75–82.
7. Dahl LB, Dhal IM, Engström-Laurent A, Granath K. Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. *Ann Rheum Dis* 1985; **44**: 817–822.
8. Belcher C, Yaqup R, Fawtrop F *et al*. Synovial fluid chondroitin and keratan sulphate epitopes, glycoaminoglycans, and hyaluronan in arthritic and normal knees. *Ann Rheum Dis* 1997; **56**: 299–307.
9. Bellamy N, Campbell J, Robinson V *et al*. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006; **2**: CD005321.
10. Kul-Panza E, Berker N. Is hyaluronate sodium effective in the management of knee osteoarthritis? A placebo-controlled double-blind study. *Minerva Med* 2010; **101**: 63–72.
11. Jørgensen A, Stengaard-Pedersen K, Simonsen O *et al*. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. *Ann Rheum Dis* 2010; **69**: 1,097–1,102.
12. Leopold SS, Redd BB, Warme WJ *et al*. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. A prospective, randomized trial. *J Bone Joint Surg Am* 2003; **85**: 1,197–1,203.
13. Tasciotaoglu F, Oner C. Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. *Clin Rheumatol* 2003; **22**: 112–117.
14. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? *JAMA* 1993; **270**: 2,598–2,601.
15. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? *JAMA* 1993; **271**: 59–63.
16. Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. *JAMA* 1994; **272**: 1,367–1,371.
17. Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. *Osteoarthritis Cartilage* 1993; **1**: 97–103.
18. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. *Ann Rheum Dis* 1994; **53**: 529–534.
19. Jones AC, Pattrick M, Doherty S, Doherty M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. *Osteoarthritis Cartilage* 1995; **3**: 269–273.
20. Lohmander LS, Dalén N, Englund G *et al*. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. *Ann Rheum Dis* 1996; **55**: 424–431.
21. Wu JJ, Shih LY, Hsu HC, Chen TH. The double-blind test of sodium hyaluronate (ARTZ) on osteoarthritis knee. *Zhonghua Yi Xue Za Zhi* 1997; **59**: 99–106.
22. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther* 1998; **20**: 410–423.
23. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology* 1999; **38**: 602–607.
24. Day R, Brooks P, Conaghan PG, Petersen M. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. *J Rheumatol* 2004; **31**: 775–782.
25. Neustadt D, Caldwell J, Bell M *et al*. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. *J Rheumatol* 2005; **32**: 1,928–1,936.
26. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *J Rheumatol* 2006; **33**: 951–956.
27. Diracoglu D, Vural M, Baskent A *et al*. The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis. *J Back Musculoskelet Rehabil* 2009; **22**: 1–9.
28. Chevalier X, Jerosch J, Goupille P *et al*. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis* 2010; **69**: 113–119.