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Review Article

Viscosupplementation for treating knee osteoarthrosis: review of the literature☆

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ABSTRACT

The aim here was to evaluate the evidence that might support or refute the use of intra-articular viscosupplementation in treating patients with symptomatic knee osteoarthrosis. A review of the literature was conducted using the Medline, PubMed and Cochrane Controlled Trial Register databases and Cochrane database systematic reviews (Cochrane Library). Only studies presenting a high level of evidence were taken into consideration. This study included analysis on randomized clinical trials that included at least 100 patients in each intervention group, meta-analyses and systematic reviews. Two meta-analyses, five systematic reviews and six randomized clinical trials fulfilled the inclusion criteria for this review. In the light of the best evidence available so far, there is no consensus for indicating or even for contraindicating the use of intra-articular viscosupplementation among patients with symptomatic knee osteoarthrosis (level of evidence I and degree of recommendation A). Further studies with appropriate methodology are needed to elucidate this matter.

Viscossuplementação no tratamento da osteoartrose do joelho: uma revisão da literatura

Palavras-chave:
Joelho
Osteoartrite
Ácido hialurônico
Viscossuplementação

RESUMO

Avaliar evidências que apoiem ou refutem o uso de viscossuplementação intra-articular no tratamento de pacientes com osteoartrose sintomática de joelho. Foi feita uma revisão da literatura com o uso dos bancos de dados Medline, Pubmed e Cochrane Controlled Trial Register e Cochrane Databases Systematic Reviews (Cochrane Library). Foram considerados apenas estudos com elevado nível de evidências. O estudo incluiu a análise de ensaios clínicos randomizados que incluíram pelo menos 100 pacientes em cada grupo de intervenção, metanálises e revisões sistemáticas. Duas metanálises, cinco revisões sistemáticas e seis ensaios clínicos randomizados preencheram os critérios de inclusão desta revisão. Frente às

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melhores evidências existentes até o momento, não existe consenso para indicação e até mesmo contraindicação do uso da viscossuplementação intra-articular em pacientes com osteoartrose sintomática do joelho (nível de evidência I e grau de recomendação A). Futuros estudos com metodologia adequada são necessários para elucidação dessa questão.

Introduction

Osteoarthrosis is characterized by pain and progressive joint dysfunction resulting from destruction of the cartilage and subchondral bone, with occurrences of reduction of the joint space, inflammation/synovitis and formation of periarticular osteophytes.[1–4] Among the major joints, the knees are the ones most affected, such that knee osteoarthrosis gives rise to functional deficits in 10% of individuals over the age of 55 years and in 25% in cases of advanced disease.[5] Currently, there are no epidemiological studies in Brazil that have precisely elucidated the prevalence of osteoarthrosis or the public expenditure related to this disease. In view of the significant increase in life expectancy that has occurred in the Brazilian population and the increasing proportion of elderly people, osteoarthrosis needs to be considered to be a matter of public health interest.[6]

Several options for conservative treatment of osteoarthrosis exist. These include weight reduction, physiotherapy, physical exercise and extra-articular devices for functional assistance. The options for pharmacological therapy (ordinary analgesics, opioids, non-steroidal anti-inflammatory drugs and corticoids) are aimed towards pain relief. Glucosamines, diacerein and hyaluronic acid are drugs known to be modifiers of the natural history of the disease, and these promote improvement of functional and pain levels over the short term. Nonetheless, further studies are needed in order to elucidate the efficiency of drugs for avoiding disease progression. There is still no effective medication for changing the course of this disease.[7,8]

Synovial fluid is composed of polysaccharides, among other elements. These contain glucosamine, glucuronic acid and hyaluronic acid, and this last substance is considered to be a key molecule in joint biomechanics. Hyaluronic acid is a biopolymer formed by glucuronic acid and N-acetylglucosamine. It has a viscous texture and is found in the synovial fluid, vitreous humour and collagenous connective tissue of numerous organisms and is an important glycosaminoglycan (GAG) in constituting the joint. This molecule is the only non-sulfated GAG. It has the capacity to become associated with proteins in order to form molecular aggregates, but it does not form proteoglycans. In joints affected by osteoarthrosis, the concentration and molecular weight of hyaluronic acid in the synovial fluid become reduced, which alters its properties through diminishing its viscosity and reducing its capacity to absorb shock and provide lubrication, and leads to damage to cartilage and increased symptoms.[9–13]

It is believed that the mechanism of action of hyaluronic acid in joints is related to inhibition of inflammatory mediators and cartilage degeneration enzymes. This reduces cartilage degradation and increases the production of cartilaginous matrix.[7,14] Hyaluronic acid preparations for intra-articular use can be further divided between those of low and high molecular weight. According to some studies, there are advantages in using the high molecular weight presentation.[7,8] Despite the possible benefits of viscosupplementation, its use remains controversial.

The present review had the objective of assessing the current evidence supporting or contraindicating the use of intra-articular viscosupplementation with hyaluronic acid for treating knee osteoarthrosis.

Materials and methods

A review of the literature was conducted using the Medline, PubMed, Cochrane Controlled Trial Register and Cochrane Systematic Review (Cochrane Library) databases. This investigation used the keywords *viscosupplementation*, *hyaluronic acid*, *osteoarthritis*, *randomized*, *review* and *meta-analysis*. Only studies defined as presenting high-quality evidence (level A, according to the Oxford Centre for Evidence-Based Medicine),[15] such as systematic reviews, meta-analyses and randomized clinical trials (RCTs), were included. The population of interest included patients with symptomatic osteoarthrosis of the knee who were undergoing non-surgical treatment for painful osteoarthrosis.

The inclusion criteria for articles were as follows:

- Systematic reviews or meta-analyses on randomized clinical trials that assessed the use of intra-articular viscosupplementation for treating osteoarthrosis of the knee in humans;
- Randomized controlled clinical trials (RCTs) that compared the use of viscosupplementation with placebo or other medication, were adequately designed and included at least 100 patients in each intervention (viscosupplementation or viscosupplementation and placebo).

The criteria for excluding articles were as follows:

- Studies on animals;
- Studies with fewer than 100 patients in each arm of the intervention.

Results

Out of the 239 potentially eligible studies that were investigated through Medline and PubMed (keywords: *viscosupplementation AND hyaluronic acid*), only 13 fulfilled the inclusion criteria. Of these, six were randomized clinical trials,

Table 1 – Summaries of the randomized clinical trials (RCTs) evaluated.

Study (ref#)	Level of evidence	Type of study	Parameters evaluated	Results and conclusions
[16]	1 A	RCT, controlled, DB N = 253 Hylan G-F 20 versus placebo	WOMAC with pain Evaluations after 4, 8, 12, 18 and 26 weeks	Hylan G-F 20 is safe and effective for pain relief.
[17]	1 A	RCT, controlled, DB N = 306 Hyaluronic acid versus placebo	Pain and functional capacity Follow-up of 40 months	Repetition of cycles of IAHA improves the symptoms of knee osteoarthrosis between the cycles and also has a good effect for at least 1 year after the last infiltration.
[18]	1 A	RCT, controlled, DB N = 117 Hylan G-F 20 versus physiological saline solution	WOMAC with pain	Hylan G-F was effective and better tolerated for treating idiopathic chronic osteoarthritis
[19]	1 A	RCT, multicenter, open N = 255	WOMAC with pain, adverse effects	Hylan G-F results in benefits for the knee and for general health, thus reducing the levels of associated therapies (NSAIDS) and systemic adverse reactions
[20]	1 A	RCT, simple randomization N = 392 Intra-articular Hylan G-F 20, sodium hyaluronate	WOMAC with pain and patient satisfaction Evaluated after 6 weeks and 3, 6 and 12 months	Both treatments provided pain reduction. The clinical effectiveness and patient satisfaction are better after using Hylan G-F 20
[21]	1 A	RCT, controlled, SB N = 660 Hylan, hyaluronic acid	WOMAC with pain	No evidence of differences between Hylan and hyaluronic acid. No reason for using Hylan in patients with osteoarthrosis, given the cost and local adverse effects.

RCT, randomized clinical trial; DB, double blinding; HA, hyaluronic acid; IAHA, intra-articular hyaluronic acid; SB, single-blinding.

five were systematic reviews and two were meta-analyses. Summaries and comments relating to the studies evaluated are presented in Tables 1 and 2.[16–28]

Discussion

Osteoarthrosis is the commonest form of arthritis in patients over the age of 50 years and the knees are among the joints most commonly affected. Because the knees are load-bearing joints, alterations to their biomechanics lead to significant morbidity and functional limitation.[6] With the increase in life expectancy of the Brazilian population, osteoarthrosis is tending to become a public health problem. No studies directed towards evaluating the prevalence of osteoarthrosis or the public expenditure involved in treating it have been conducted in Brazil.[6] In the United States, sates of medications for treating this disease had a turnover of US$ 760 million in 2004.[29]

The pharmacological therapeutic options for knee arthrosis currently available have the aim of promoting pain relief and functional improvement. There are still no medications available on the market with proven influence on the progression of the disease.[7,8]

In individuals with osteoarthrosis, hyaluronic acid in the synovial fluid undergoes reductions in concentration and molecular weight, which lead to loss of viscosity and, consequently, loss of the functions of lubrication and shock absorption. This process contributes towards progression of joint degeneration and activation of inflammatory pathways.[13,30] Viscosupplementation with hyaluronic acid was developed in order to promote longer-lasting pain relief and functional recovery, and to delay disease progression.[17] Different mechanisms have been proposed for explaining its effect, such as stimulation of production of endogenous hyaluronic acid, suppression of degradation of the cartilaginous matrix and suppression of the inflammatory response to interleukin-1. To further increase the viscosity of hyaluronic acid and diminish joint clearance, chemically modified hyaluronic acid compounds were created such that they would have higher molecular weights (around 23×10^7 Da) and also a longer half-life, which would theoretically increase the potential and duration of its effect.[31–35]

In a multicenter randomized controlled clinical trial with 40 months of follow-up, named the Amelia Project, Navarro-Sarabia et al.[17] evaluated 306 patients over the age of 45 years who presented knee osteoarthrosis (Kellgren–Lawrence grades II and III, with a minimum joint space of 2 mm). Four cycles of intra-articular injection of hyaluronic acid or placebo were performed. The patients were evaluated with regard to clinical and functional improvement and side effects. These authors concluded that the treatment was safe and that there were significant improvements in functional capacity and symptoms, in relation to the control group, with an effect that was maintained even 1 year after the last application.[17]

Chevalier et al.[16] evaluated 253 patients over the age of 40 years who presented symptomatic primary osteoarthrosis of the knee, in a multicenter double-blind randomized study with 26 weeks of follow-up. The patients received a single application of a high molecular weight compound (Hylan G-F 20) or placebo. The safety of the treatment and the clinical

Table 2 – Summary of the meta-analysis and systematic review studies evaluated.

Study (ref#)	Level of evidence	Type of study	Parameters evaluated	Results and conclusions
[22]	1 A	Systematic review 5 case series and 13 RCTs High molecular weight HA	Pain	High molecular weight HA is effective for treating continuous pain in patients with knee osteoarthrosis. Its action has a slower start but longer effects than those of intra-articular steroids.
[23]	1 A	Systematic review 14 studies HA, placebo, sodium hyaluronate	WOMAC with pain and functional capacity	Use of HA is not recommended in patients with symptomatic knee osteoarthritis
[24]	1 A	Systematic review 9 RCTs Intra-articular HA versus placebo	Pain Evaluated 1, 5–7, 8–12 and 15–22 weeks after HA injection	HA has a modest effect on pain in patients with knee osteoarthritis, 5–7 and 8–10 weeks after the injection, but has no effect after 15–22 weeks.
[25]	1 A	Systematic review 7 RCTs, 6 case series and 1 cross-sectional study Hylan G-F 20, placebo, NSAIDS, sodium hyaluronate	Pain and functional capacity of the knee	Hylan G-F improves pain and functional capacity of knees over the short term.
[26]	1 A	Systematic review 67 RCTs Several classes of HA versus placebo	Pain and functional capacity of the knee	Viscosupplementation is effective in treating knee osteoarthritis; it reduces the pain and improves functional capacity.
[27]	1 A	Meta-analysis 29 RCTs IAHA approved in the United States	Pain and functional capacity 4–13 and 14–26 weeks after infiltration	IAHA is safe and effective in patients with symptomatic knee osteoarthritis
[28]	1 A	Meta-analysis 89 studies HA or derivative, placebo	Pain and functional capacity	The benefit of viscosupplementation for improving pain and functional capacity in the knee is minimal or non-existent. Its use should be discouraged given the greater local adverse effects.

RCT, randomized clinical trial; DB, double blinding; HA, hyaluronic acid; IAHA, intra-articular hyaluronic acid.

repercussion (WOMAC index) were evaluated and the authors concluded that the treatment was safe and that there was a significant clinical improvement among the patients who underwent viscosupplementation.

Like in the abovementioned study, in a multicenter randomized study conducted by Raynauld et al.,[19] 255 patients who received high molecular weight hyaluronic acid or placebo were evaluated over a 1-year period. These authors found a significant difference (greater than 20% in the WOMAC score) between their groups, which demonstrates that there were benefits from viscosupplementation. In other randomized controlled trials that used high molecular weight hyaluronic acid (which are listed in Table 1), it was also concluded that there were significant clinical improvements.[18]

With regard to the molecular weight of the hyaluronic acid to be used, two studies compared the use of high and low molecular weight hyaluronic acid for treating osteoarthrosis. According to Raman et al.,[20] use of high-weight hyaluronic acid (Hylan G-F 20) has the advantage of a more long-lasting effect, but with clinical efficacy and tolerability similar to other presentations. In a clinical trial that compared three presentations of hyaluronic acid for treating osteoarthrosis of the knee, Jüni et al.[21] concluded that the different molecular weights of hyaluronic acid did not give rise to any significant differences.

In a systematic review of 76 studies of medium quality, Bellamy et al.[26] came to the conclusion that viscosupplementation was safe and led to significant clinical and functional improvements, in comparison with placebo. They also reported that the effect of this treatment was longer-lasting than that of intra-articular corticosteroids. Many of the studies included in their review presented design inadequacies.

Aggarwal and Sempowski[22] reviewed five case series and 13 randomized controlled trials and concluded that use of viscosupplementation for treating mild to moderate osteoarthrosis of the knee, with high molecular weight hyaluronic acid, showed significant benefits in relation to clinical improvement and durability of effect. They also demonstrated that the patients had good tolerability towards the treatment and, in comparison with use of intra-articular corticoids, the peak action occurred later and the effect was longer-lasting. Miller et al.[27] analyzed the effect and safety of viscosupplementation in patients with osteoarthrosis of the knee and gathered together a sample of 4866 individuals in 29 randomized clinical trials. Studies with design inadequacies or insufficient

sample size were excluded. These authors concluded that viscosupplementation was effective for achieving clinical and functional improvements, as well as being safe.

In a meta-analysis, Rutjes et al.[28] evaluated 89 studies and 12,667 participants with knee osteoarthrosis. Their conclusion was that, because of lack of evidence of any significant clinical and functional improvement, along with the potential risk of severe adverse effects viscosupplementation should be discouraged for treating knee arthrosis.

According to the 2013 guidelines for treating osteoarthrosis of the knee,[23] published by the American Academy of Orthopaedic Surgeons (AAOS) after a meta-analysis that involved 14 randomized controlled trials, there is strong evidence for not recommending the use of intra-articular hyaluronic acid, because all the studies that made comparisons with a control group showed uncertainty regarding practical clinical application of the treatment. Five of the seven studies evaluated that related to molecular weight presented patients who perhaps would not represent the general condition of the population with knee osteoarthrosis. This meta-analysis was criticized in the study by Miller et al.[27] because of confusion in the data analysis and use of compounds that had not been approved in the United States.

Final remarks

The pattern of osteoarthrosis treatment using hyaluronic acid is extremely variable between studies. There are differences in the preparations used, number of applications, dose injected per application and number of cycles used, in addition to time differences between them. The profile of the patients analyzed in each study also varied, such that some presented young patients with mild arthrosis and others, elderly patients with severe arthrosis. The parameters for analyzing clinical and functional improvements also changed between the studies. Many of them did not have a control group and there is also a lack of studies comparing viscosupplementation with other treatments. Most of the studies are of poor quality with inadequate designs.

Conclusion

In the light of the evidence that currently exists, there is still no solid basis for indicating or even for contraindicating the use of intra-articular viscosupplementation with hyaluronic acid or its derivatives for treating symptomatic knee osteoarthrosis.

Conflicts of interest

The authors declare no conflicts of interest.

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