

The evidence of surgery delay after viscosupplementation is increasing

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Abstract

Osteoarthritis (OA) is a widespread disease throughout the world and prosthetic replacement is considered an effective and definitive treatment. However, some patients do not want or cannot undergo this type of invasive procedure due to the risk of complications. Besides, this kind of surgery is a very expensive treatment for the healthcare system.

Real life studies have shown, with growing evidence, that repeated cycles of intra-articular injections of hyaluronic acid (HA)

resulted in a significant reduction in pain symptoms as well as an improvement in joint function. Moreover, an important reduction in analgesics consumption was observed. Some studies have shown a delay of total knee replacement (TKR) for up to 2 years. There is minimal data available about the impact of HA injections on the delay of total hip replacement (THR).

This review has also evaluated, in addition to clinical research studies, several papers with data from administrative databases suggesting that viscosupplementation possesses the potential to delay or obviate the need for surgery in patients with knee or hip OA.

Further studies are necessary to understand the predictors of response, the diversity of response to different HA products, the appropriate dosage and cyclicity in relation to the radiological and clinical stage of the disease.

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Introduction

Osteoarthritis (OA) has emerged as one of the leading causes of disability worldwide. Although no currently known cure of OA can reverse the progression of the disease, total knee or hip replacement is an effective and definitive treatment for the late stage of the disease. However, this kind of surgery is an invasive procedure with potential risks for serious complications and it is a very expensive treatment for the healthcare system. The number of joint replacements is increasing worldwide and especially in western countries.

There are several international recommendations for the management of knee OA, published by the American Medical Society for Sport Medicine (AMSSM),¹ and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)² and EUROVISCO GROUP³ recommending non-pharmacologic and pharmacologic interventions. The majority of these reports show evidence indicating that intra-articular hyaluronic acid (IAHA) offers a good benefit/risk balance among the proposed pharmacologic treatments, even if there is a lack of complete agreement among national and international guidelines.

Hyaluronate is a natural component of the synovial fluid that is reduced in OA patients. The Intra-articular injection of HA restores viscoelasticity of the synovial fluid providing lubrication, increasing shock absorption, and joint protection.⁴ Moreover HA interacts with the receptors of chondrocytes, synoviocytes, osteocytes and immune cells, regulating cell proliferation, differentiation and migration. The main biological activity of HA leads to an en-

hanced synthesis of endogenous HA, proteoglycan and chondroitin sulphate as well as a decrease of cartilage breakdown. Additional biological effects include the reduction of lymphocytes and macrophages motility as well as of inflammatory mediators.⁴

There is uncertainty if the available HA based-agents should be considered as a group or whether they have significant clinical differences related to the intrinsic properties of viscosity, origin, molecular weight (MW), concentration *etc.* of each available HA product. In a meta-analysis Altman⁵ investigated 68 studies showing that products with an average MW ≥ 3000 kDa provided favourable efficacy results when compared with products of an average MW < 3000 kDa. Products with a molecular weight ≥ 3000 kDa demonstrated significantly fewer discontinuations due to treatment-related adverse events compared to ≤ 1500 kDa products. Trial discontinuation rates were similar between biological fermentation-derived HA products and avian-derived HA. Biological fermentation-derived HA demonstrated fewer acute flare-ups at the injection site than did avian-derived HA products, while high-molecular-weight products demonstrated the highest rate of injection site flare-up. The authors conclude that despite similarities, IA-HA products should not be treated as a group, as there are differences in IA-HA products that influence both efficacy and safety; IA-HA products with a MW ≥ 3000 kDa and those produced through microbial fermentation seem to show a certain superiority in terms of efficacy and safety.

According to the majority of recommendations,¹⁻³ the patients more susceptible to viscosupplementation are those with symptomatic, mild to moderate knee OA, radiologically characterized by joint space narrowing (JSN) grade 0-2 or Kellgren-Lawrence degree I-III), with normal weight or moderate overweight (BMI < 30), not sufficiently improved by nonpharmacological interventions and analgesics/NSAIDs or with contraindication to analgesics/NSAIDs.

The safety profile of IAHA is excellent since the incidence of AEs reported by clinical trials in knee OA is very low, without achieving significance when compared to the incidence of AEs in the placebo group. Reported AEs are local, mild and transient. The AEs can be distinguished between *self-limited*, such as post-injection pain and swelling that are the most frequently reported AEs, and *not self-limited* AEs that are rare and requiring medication. Mild differences between types of IA HA products have been inconsistently reported.⁴

Moreover, repeated courses of IA-HA injections for knee OA were demonstrated to be an effective and safe treatment, maintaining pain control over a long time without introducing increased safety risk.⁶

Delay in arthroplasty after viscosupplementation

Real life studies⁷ demonstrate with increasing evidence that repeated cycles of intra-articular injections of hyaluronic acid (HA) lead to a noticeable improvement in pain symptoms and joint function; moreover, there is an important reduction in analgesics consumption that lasts up to 12 months after the last infiltrative cycle. Intra-articular (IA) treatments are more effective than oral pain treatments for OA, with HA injections showing the greatest pain reduction.^{8,9}

Waddell evaluated TKR delay in two different studies in a population of patients treated with HA. In the first study,¹⁰ patients who were candidates for TKR, were treated with 1 or more courses of intra-articular HA injections (3 weekly injections per course). The incidence of TKR treated with HA (1187 knees, 863 patients) was 19% (n = 225 knees) and the median TKR time in these patients

was 638 days (1.8 years). For patients in whom TKR was not recommended at the time of observation, the median time of HA treatment and patient follow-up was 810 days (2.2 years). A total of 1978 cycles of HA were performed in 1187 knees. Survival analysis showed that 75% of the knees had not undergone TKR for a period of 1370 days (3.8 years). Survival analysis and logistic regression indicated that between age, gender, ethnicity, BMI and presence of joint effusion, only age significantly affected TKR time.

A recent study¹¹ conducted in the USA and based on the Optum Clinformatics data, a clinical-administrative registry, collected from 2006 until the end of the second quarter of 2016, evaluated, on a cohort of over 4,000,000 patients, the effectiveness of viscosupplementation not only on the reduction of symptoms but also on the delay of TKR. The average time between the diagnosis of knee OA and surgery was 1.2 years. Patients treated with HA injections had a significantly longer time from diagnosis to TKR, by at least 7 months. This study also highlights that viscosupplementation is a cyclic treatment that must be repeated periodically. And it is precisely the patients who perform a greater number of infiltration cycles who have a greater delay in prosthetics. The majority of patients received at least one course of HA injections but there was a trend in which patients who received more courses of HA had a longer time towards surgery. Specifically, patients who underwent 1 to more than 5 HA treatment courses had an average time to surgery that increased from 21 months (1.8 years) to 59 months (4.9 years).

Another recent study¹² evaluated the TKR delay effects of IA HA injections compared with a control group without indications for IA HA injections using real-world US administrative data. The selection period lasted from July 1, 2007 to June 30, 2010. The results showed that repeated courses of treatment with HA are safe and are associated with the delay of TKR for up to 3 years. The TKR delaying effect of HA injection was more important in cohorts with repeated courses of HA treatment: 19 out of 20 patients in the cohort of ≥ 5 HA courses were free from TKR 3 years later.

In 2009 Turajane¹³ published data from a prospective clinical study conducted on 183 patients affected by knee OA who had received at least one cycle of weekly intra-articular infiltrations of HA. Patients who responded positively to treatment were asked to repeat the infiltration cycle every 6-12 months based on their symptoms. Then patients were classified into three groups according to the Ahlback radiological classification system: 46 patients were in group 1 (Ahlback grade I-II), 70 patients in group 2 (Ahlback grade III-IV) and 67 patients in group 3 (Ahlback grade V). The incidence of knee replacement surgery was 28.4% with an average time of TKR of 15.4 months (0.7-51.7 months). For patients who had not undergone prosthetic replacement during the study period (80.4%, 64.3% and 73.1% for group 1, 2 and 3 respectively), the average follow-up was 45.6 months. The average survival time was 42.1 months.

In 2016, Waddell further examined, in a second study,¹⁴ the prospective data on the incidence and time of prosthetic knee replacement in patients with OA grade IV, again treated with HA from 1997 to 2010 (for a total of 1863 knees) and a subgroup of patients treated from 1997 to 2003 (1187 knees), to determine the influence of HA injection on prosthetic delay. In both cohorts, 25-28% of the knees underwent prosthetic replacement, with an average of between 2.8 and 3.1 years' interval between viscosupplementation and surgery. Survival analysis showed that arthroplasty surgery was delayed by more than 7 years in 75% of 1863 patients with OA grade IV.

In 2015 Altman¹⁵ retrospectively evaluated a database of 79 million patients, to identify patients with knee OA undergoing surgery during a period of 6 years. The database included 182,022 patients with knee OA who underwent TKR; 50349 (27.7%) of these

patients were classified as HA users and underwent at least one cycle prior to surgery, while 131,673 patients (72.3%) had never been treated with viscosupplementation.

The results of this study showed that, at the same age, gender and comorbidity, the risk of TKR decreases according to the number of HA infiltration cycles. Half of the non-HA patients underwent TKR 114 days after the diagnosis of knee OA, while half of the patients treated with HA underwent TKR 484 days after diagnosis. Besides, patients who received more than 5 HA cycles delayed TKR by 3.6 years.

In 2016, the same author evaluated the association between HA injections and arthroplasty in 22,555 patients aged between 18 and 64 who underwent TKR between January 1, 2006 and December 31, 2011, identified by the MarketScan commercial database in USA.¹⁶ All patients had a period of at least 6 years in the registry before surgery. 14,132 were not treated with HA while 8423 were not treated. The median of the time following the intervention was 326 days for the untreated group and 908 days for the group undergoing viscosupplementation; the difference was about 1.6 years.

An observational cohort study by Shewale *et al.*¹⁷ compared the effectiveness of different molecular weight HA in delaying TKR using Lifelink Plus claims (2006-2015). 30,417 HA-user patients with knee OA were analysed, of which 12410 high molecular weight (HMWHA) users, 9127 moderate molecular weight (MMWHA) users and 8526 low molecular weight (LMWHA) users. The authors did not identify any statistically significant difference between the three types of HA in terms of demographic data and the main adverse effects related to the method. The authors showed that the MMWHA and LMWHA users had a lower probability of reaching the endpoint (surgical interventions of the knee) than the LMWHA users. However, when these results were co-variated for possible confounding factors, no statistically significant difference was confirmed between the two groups.

There are few data available about the impact of HA injections on the delay of total hip replacement (THR). Firstly, in 2008, Van den Bekerom compared different HA formulations in 120 patients and evaluated the delay in performing THR. In particular, 51% of patients did not progress to THR in the 3 years after HA treatment, with no difference in the results between the different formulations used.¹⁸

A study conducted by Migliore *et al.*¹⁹ assessed retrospectively the impact of treatment with HA injections on the progression to THR in patients with symptomatic hip OA. Patients presenting at the authors' rheumatology unit between 2004 and 2007 and treated with HA were recorded. Each patient underwent an orthopedic evaluation to determine whether or not they were candidates for surgery. Endpoints were the number of patients progressing to THR and the survival time between the start of treatment and THR, if performed. 84 out of 224 patients included in the study (37.5%) progressed to THR; instead, patients not progressing to THR after treatment were 92%, 76% and 68% at 12, 24 and 36 months respectively. The risk of progressing to THR was 6.6 times higher in patients suitable for surgery than in patients not considered surgical candidates. Another study supporting viscosupplementation as a conservative treatment to perform before considering patients as candidates for THR, was conducted on 176 patients suffering from hip OA.²⁰ Each patient received HA given by ultrasound-guided injection and, at the same time, was evaluated for surgery by six orthopedists. The concordance score among the six orthopedists was defined based on clinical and radiological data. 82% of patients had not undergone THR during HA treatment in the whole cohort after 48 months, whereas in the group considered by orthopedists as suitable for surgery, only 34% underwent THR throughout the whole

follow-up and about 20% in 2 years of follow-up, suggesting viscosupplementation as a valuable technique in the management of patient with hip OA.

Expert opinion

Real-life studies and data from administrative databases suggest that viscosupplementation is an effective treatment in delaying or avoiding the need for prosthetic replacement surgery. In patients affected by initial or intermediate knee OA, cyclic and repeated HA treatments seem to be able to stabilize disease activity and therefore modify the disease course, finally leading to a delay in arthroplasty. We can hypothesize that viscosupplementation could be more effective when performed at an early stage of the disease.

These data resulting from administrative databases can explain how, in clinical practice, many patients after viscosupplementation retain a low degree of symptoms and an acceptable quality of life. Probably without this therapy, they would have undergone early prosthesis with relevant clinical and economic implications.

Conclusions

Several real-life studies suggest a delay of TKR for up to 2-3 years after viscosupplementation. Some of these studies have been conducted with data from administrative databases. Although these studies do not allow us to make clinical correlations on the predicting factors of response, they highlight how patients treated with HA and especially those who have performed cyclic treatments, are those who have the greatest delay in prosthetics.

However further clinical studies are necessary to confirm this trend on delay of joint replacement after viscosupplementation and in particular with the aim of investigating the predictors of response, the diversity of response to different HA products, the appropriate dosage and cyclicality in relation to the radiological and clinical stage of the disease.

Patients, the medical scientific community and public and private insurance decision-makers should be aware of these data suggesting the potentiality of viscosupplementation to delay or obviate the need for prosthetic replacement surgery in view of the economic implications of the increasing surgical costs of the near-epidemic knee and hip OA in Western populations. This intra-articular treatment can be economical and suitable for patients and society in terms of both direct and indirect costs.

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