Addition of Mannitol to Hyaluronic Acid may Shorten Viscosupplementation Onset of Action in Patients with Knee Osteoarthritis: Post-Hoc Analysis of A Double-blind, Controlled Trial

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Abstract

Objectives: To compare the speed of action of three weekly intra-articular injections of a combination of hyaluronic acid and mannitol (HAnox-M) with that of hyaluronic acid alone (BioHA), in patients with knee osteoarthritis (OA).

Methods: Post-hoc analysis of a randomized, double blind, controlled trial demonstrating the non-inferiority of an association HAnox-M compared to BioHA at month 6 after injections. Data from 205 patients with symptomatic knee OA (Intent-to-Treat population) were retrospectively analyzed. The primary outcome was 1 and 2 week change in the WOMAC pain subscale (0-20). The number and percentage of improved patients at week 1 and 2 were also studied, as well as the level of improvement.

Results: HAnox-M and BioHA groups were not statistically different at baseline and month 6. The median WOMAC pain score at baseline was 9 in both groups. It was 6.0 and 5.0 in the HAnox-M group at Week 1 and Week 2 respectively. It was 7.0 and 6.0 in the BioHA group, namely a decrease of 1 more point in favor of HAnox, obtained from as soon as the 1st injection. At month 3 and 6 the results were identical (5.0 and 4.0 respectively) for both groups. In subjects with grade 3 joint space narrowing (N=84) the decrease of pain (SD) was significantly greater at week 3 in patients treated with HAnox-M than in those treated with Bio-HA: -4.2 (3.2) versus -2.8 (2.6) respectively (p=0.048).

Conclusion: In patients with symptomatic knee osteoarthritis, addition of mannitol to HA may shorten the onset of action of viscosupplementation, chiefly in patients with advanced stage of the disease.

Keywords: Knee osteoarthritis; Viscosupplementation; Mannitol; Hyaluronic acid; Intra-articular

Introduction

The medical management of knee osteoarthritis (OA) includes a combination of non-pharmacological and pharmacological modalities [1-4]. Among them, intra-articular (IA) injection(s) of hyaluronic acid (HA) [5] is widely used worldwide to reduce joint pain and improve function in patients not adequately relieved with conventional therapy. The mechanisms of action of viscosupplementation are complex and not yet fully understood. The more probable hypothesis is a transient restoration of the physiological joint homeostasis [6]. Moreover there are increasing in vitro and in vivo evidences that HA could have chondroprotective properties [7-12] whereas metaanalyses continue to show controversial results regarding the efficacy and safety of viscosupplementation [13-17].

One point on which everyone agrees is that that corticosteroids are more effective than HA in the short term (up to 4 weeks), whereas HA becomes more effective from 4 weeks and in the long term (up to 26-52 weeks) [18]. The delayed onset of action of HA leads many physicians to use coadministration of the 2 agents assuming a synergistic effect, useful in clinical practice to alleviate pain quickly. Hasten the onset of action of HA would be a significant therapeutic advance, the delayed action (up to 8 weeks) of IA HA, being one of the main concern with this treatment. One hypothesis for this delayed effectiveness of viscosupplementation is the limited...
time of residence into the joint of the injected HA. In rabbits the half-life of HA does not exceed one day and the clearance rates are considerably higher in OA than in normal rabbits. [19]. When injected inside the joint, HA is rapidly degraded, chiefly through various reactions with oxygen free radicals [20,21]. One can speculate that the short residence time of the drug into the joint may limit its diffusion within the target tissues. Decreasing the in situ HA degradation for optimizing clinical efficacy of viscosupplementation is a challenging research approach.

HAnox-M is a HA derivative, that combines a high concentration (35 g/l) of mannitol, with a non-cross-linked biofermentative HA. Mannitol is a polyol with radical oxygen species (ROS) scavenging properties [21]. Several in vitro studies have evidenced the effectiveness of mannitol to protect HA against ROS-mediated degradation [21-23]. The combination of mannitol to HA might extend the time of contact between HA and the target tissues and consequently might allow a more rapid onset of action than HA alone. However, the IA half-life of mannitol is likely too short (<4 h) to protect HA from degradation for several weeks and consequently to increase its duration of efficacy beyond the HA usual efficiency (6 to 12 months).

The HAV-2012 trial [24], a prospective, multicentre, randomized, non-inferiority study comparing HAnox-M to BioHA in patients with knee OA, has provided us the possibility to evaluate, through post-hoc analyses, whether the addition of mannitol is able to shorten the onset of action of viscosupplementation.

Patients and Methods

HAV-2012 study [24] was a prospective, double-blind, randomized, multicentre, parallel-group trial, conducted in in France between October 2012 and April 2014 (registration No. 2012-A00570-43). The aim of the trial was to compare both efficacy and safety of a 3 weekly injection regimen of HANOX-M (HAppyVisc®, LABRHA SAS, Lyon, France), combining sodium hyaluronate (1−1.5 Mda, 31 mg/2 ml) with mannitol 3.5%, to BioHA (Euflexxa®, Ferring Pharmaceuticals, Parsippany, USA, 2.4-3.6 Mda, 20 mg/2 ml), in patients with symptomatic knee OA. The study was performed in compliance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki concerning medical research in humans and the country-specific regulations. It was approved by the Ethics Committee of Lyon Sud-Est IV. Before enrolment, patients were required to sign an informed consent form which complied with the requirements of the International Conference on Harmonisation (ICH).

All details of the study design and inclusion criteria were published previously [24]. Briefly, the study included males and females, aged 40−85 years, fulfilling the ACR criteria for knee OA who failed to respond or were intolerant to analgesics and/or non-steroidal anti-inflammatory drugs (NSAIDs) or weak opioids and who had self-assessed their walking pain from 3 to 8 on a 11-point Likert scale (0-10) at baseline. Bilateral knee X-rays were performed within the 3 previous months and included the following incidences: standing posteroanterior view, Lyon-schuss view, lateral view and skyline incidence of the patella. The OARSI score [25] for fibro-femoral (TF) joint space narrowing (JSN) was assessed on the radiological view highlighting the most severe lesions. The main exclusion criteria were OA flare, tibial plateau or femoral condyle bony attrition, excessive varus or valgus knee misalignment, viscosupplementation in the target knee within the previous 9 months, and IA corticosteroids use within the previous 3 months. Analgesics and ibuprofen (daily dose ≤ 800 mg) and naproxen (daily dose <500 mg) were allowed. Symptomatic slow-acting drugs for OA were also allowed only if started at least 2 months before screening and not substantially altered during the study. NSAIDs at anti-inflammatory doses, strong opioids, systemic corticosteroids, IA corticosteroids and viscosupplements into the target knee were prohibited throughout the follow-up. Patients were asked to discontinue analgesic therapy 48 hours before each evaluation visit. Patients were randomized to one of the following treatment groups: HAnox-M or Bio-HA in a 1:1 ratio by blocks of 4 treatments, balanced 2:2.

Both viscosupplements were supplied in 2 ml syringes containing 2 ml of HA solution and were administered, one week apart, 3 consecutive weeks, into the target knee by an experienced physician who was unblinded to treatment and different from the clinical evaluator. The patient and the clinical evaluator were both blinded to treatment throughout the follow-up. The primary efficacy outcome was the variation, between baseline and the last follow-up visit at week (W)26, in the WOMAC A pain sub-score [26] measured on a 5 point Likert scale (5 pt-LS: 0=none, 1=mild, 2=moderate, 3=severe, 4=extreme; total score ranging 0-20). Secondary efficacy outcomes were the change throughout the follow-up of the following criteria: walking pain, patient global assessment, and WOMAC total score. Clinical assessment was performed by the clinical evaluator, blinded to treatment, at baseline, at the time of each injection on W 1, W2, then at the follow-up visits at W12 and W26. WOMAC A was assessed at weeks 1, 2, 3, 12 and 26. Other scores were obtained only at baseline, W12 and W26. The number and percentage of improved patients at week 1 and 2 were also studied, as well as the level of improvement. Patients had to grade their improvement from 0 (none) to 3 (high). Improved patients (who responded 2 or 3) had to quantify the level of improvement (<25%, 25-50%, 50-75% and >75%). Analgesic consumption and adverse events were recorded at each visit.

Statistical analyses were performed, from the Intent-to-treat (ITT) population, using XLStat 2015 Addinsoft software. The homogeneity of the two treatment groups was evaluated using non-parametric tests. The normality of variables was assessed using Shapiro-Wilk test. If normality, they were evaluated by analysis of variance. If matched data, the analysis was complemented by an appropriate t-test. In case of non-normality, a generalized nonlinear model was performed in addition to or replacement of non-parametric tests. For quantitative data analysis, a model of logistic regression was performed and was supplemented if necessary by the McNemar test or by Fisher’s exact test for confirmation of the effect significance. P values <0.05 were considered as statistically significant.
Results

Two-hundred-five patients constituted the ITT population including 103 patients in the HAnox-M group and 102 in the BioHA group. Characteristics of the patients at baseline were consistent with those expected. The 2 treatment groups were statistically comparable for all the studied items. Variations and absolute values of all the outcomes were similar for both group at baseline, month 3 and end-point [24].

The median (range) of the WOMAC pain sub-score was 9.0 (4-19), 6.0 (0-19) and 5.0 (0-15) in the HAnox-M group at baseline, W2 and W3 respectively. It was 9.0 (2-18), 7.0 (0-16) and 6.0 (0-14) in the BioHA group, namely a decrease of 1 more point in favor of HAnox-M, obtained from as soon as one week after the 1st injection. At month 3 and 6 the results were identical for both groups (Median=5.0 and 4.0 respectively). Despite this trend to a quicker efficacy of HAnox-M, the difference did not reach the statistical significance (P=0.2). At W3, 76 patients (74.5%) of the HAnox-M group and 65 (65%) of the BioHA group, answered "good" or "very good" to the question "Have you experienced improvement since the first injection"? The patient's self-assessed percentage of improvement was >50% in 30 and 23 patients, and >75% in 8 and 3 patients for HAnox-M and BioHA patients respectively.

In subjects with the more severe joint space narrowing (OARSI grade 3; n=84) the average decrease of pain (SD) was greater in patients treated with HAnox-M than in those treated with BioHA at both W2: -3.0 (3.6) versus -1.9 (3.1), P=0.10 and W3: -4.2 (3.2) versus -2.8 (2.6), P=0.048 (Table 1).

Table 1: Variations of WOMAC A in patients with OARSI joint space narrowing grade 3.

<table>
<thead>
<tr>
<th>WOMAC A variation between D1 and D8</th>
<th>ITT Population</th>
<th>Hanox-M</th>
<th>BioHA</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>84</td>
<td>45</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Missing (N)</td>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
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<td>-3.0 (3.6)</td>
<td>-1.9 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>-2.0 (12.5)</td>
<td>-3.0 (-12.5)</td>
<td>-2.0 (-12.4)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Discussion

This post-hoc analysis of a controlled, randomized trial, showed a trend to an earlier reduction of pain with HAnox-M, compared to BioHA. Despite the present data cannot allow to conclude conclusively on that fact, one can draw hypotheses to explain our results.

Two recent in vitro studies, using powerful models of oxidative stress, showed that the addition of high concentration of mannitol to HA allowed to protect HA from degradation due to oxidant stress [22,23]. Mannitol (C6H14O6) is a polyol of molar mass=182.17 g/mol, that demonstrated properties of reactive oxygen species scavenger. The beneficial effect of mannitol, due to its anti-oxidant power towards the rich reactive hydroxyl function, has been evidenced in several diseases [27-30]. During viscosupplementation, the interest to add mannitol to HA is obvious. Indeed, as soon as the viscosupplement is injected intra articularly, the HA macromolecular network, which contains many OH groups, reacts with ROS resulting in the rupture of the HA chains and accelerated degradation of the gel [20]. This rapid depolymerisation of HA is likely the primary cause for the short IA half-life of non-cross-linked HA. Another advantage of mannitol is its resistance to heat which permits sterilization by autoclaving, unlike other antioxidants such as polyphenols, vitamin C, vitamin E which are thermo labile and is hydro-soluble unlike antioxidants such as vitamin E or betacaroten. Furthermore mannitol does not significantly alter the rheological behaviour of HA [23]. Polyols may also have direct effects on the osteoarthritic process, via their antioxidant activities. Cavone et al. [31] reported that topical mannitol applications on the hind paws of rats with adjuvant-induced arthritis reduced paw thickness and tissue oedema but not the inflammatory infiltrates. This anti-oedema effect of mannitol application occurred earlier than those prompted by a similar treatment with diclofenac or ketoprofen. In vitro a combination HA/sorbitol, isomer of mannitol, prevented IL-1β-induced oxidative stress, stifled IL-1β-induced metalloproteinase-13, nitric oxide (NO) and prostaglandin E2 release and NO synthase expression, attenuated cell death, capsaicin-3 activation and DNA fragmentation, in human chondrocytes [32]. Interestingly, the antioxidant as well as the anti-inflammatory and anti-catabolic effects of HA/sorbitol were attributed to sorbitol and HA, respectively. Clinically, five open label studies assessing viscosupplements containing mannitol or sorbitol in patients suffering from knee [33-35] and hip [36,37] OA have been recently published. All showed a good ratio efficacy/safety. In a prospective randomized controlled trial the association cross-linked HA/mannitol was even shown to significantly reduce collagen II degradation compared to IA saline injection [38].

The present study suffers from some limitations mainly due to the fact that the trial was not designed for assessing accurately
the early response to treatment. So, only WOMAC pain subscore and patient’s self-assessment of efficacy were obtained at W1 and W2 and patients were not assessed between W2, date of the third injection, and month 3. Despite it has been possible, only one week after the second injection, to highlight an improvement 25% greater in the HAox-M group (-4 points versus -3 points), which allowed to reach the same level of relief to that obtained in the visit of the third months.

In summary, despite limitations which justify that further trials specifically designed for this purpose should be performed, our results suggest that mannitol might have beneficial effect on HA performances, by reducing pain more rapidly than HA alone, especially in patients with severe knee OA. The mechanisms by which mannitol could shorten the onset of action of viscosupplementation remain to be investigated.

Acknowledgements


Competing Interest:

Thierry Conrozier: received fees from LABRHA SAS for scientific consultant services and study coordination. Naji Aff, Roger Lecurieux, Bernard Maillet, Jean-Charles Balblanc received honoraria from LABRHA SAS as clinical investigators of the study.

Author’s Contribution:

TC: participated in the design of the study, was the national coordinator of the trial and wrote the manuscript.

FE: Wrote the manuscript and performed the statistical analysis.

NA, BM, RL and MB: participated in the study and collected data as principal investigators of the trial.

XC participated in the design of the study and validated the final results as the president of the scientific committee.

All authors read, commented, made changes and then approved the final manuscript.

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for knee osteoarthritis: a systematic review and network meta-


