Imaging Guidance Improves the Results of Viscosupplementation with HANOX-M-XL in Patients with Ankle Osteoarthritis: Results of a Clinical Survey in 50 Patients Treated in Daily Practice

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ABSTRACT

BACKGROUND: The objective of this survey was to assess retrospectively the interest of performing viscosupplementation using imaging guidance in patients suffering from ankle osteoarthritis (OA).

PATIENTS AND METHODS: This is a multicenter retrospective survey using a standardized questionnaire. Fifty patients suffering from ankle OA and treated, in daily clinical practice, with a single intra-articular injection of a novel viscosupplement made of a combination of a non-animal cross-linked hyaluronan and mannitol, HANOX M-XL, were included in the survey. The injection procedure (imaging or landmark guidance), demographic data, patient's self-evaluation of pain, satisfaction, treatment efficacy, and tolerability were collected. Predictive factors of both efficacy and patient's satisfaction were investigated.

RESULTS: The percentages of patients very satisfied/satisfied and not really satisfied/dissatisfied with the treatment were 68% and 32%, respectively. Efficacy was rated as very good, good, moderate, and poor by 38%, 30%, 12%, and 20% of the cases, respectively. Efficacy was unrelated to gender and age and was highly correlated with pain score ($P < 0.0001$). In satisfied patients, the decrease in consumption of analgesics/non-steroidal anti-inflammatory drugs was >75% in 64% of the cases. Efficacy was significantly different with regard to imaging guidance. There was a statistically significant difference in efficacy and satisfaction between landmark-guided and imaging-guided injections ($P = 0.02$). The success rate was 2.3 times higher in the imaging-guided group than in the landmark-guided group. No significant difference was found between patients injected under fluoroscopy or ultrasound guidance, despite a trend favoring ultrasound ($P = 0.09$). Tolerability was rated as very good/good in 47 patients, moderate in two, and poor in one and was unrelated to the type of guidance.

CONCLUSION: This preliminary study suggests that the use of imaging guidance significantly optimizes the success rate of ankle viscosupplementation. No safety concern was observed.

LEVEL OF EVIDENCE: III.

KEYWORDS: hyaluronic acid, viscosupplementation, ankle, osteoarthritis, fluoroscopy, ultrasonography, guidance

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Introduction

Current treatment for lower limb osteoarthritis (OA) is made of a combination of non-pharmacological and pharmacological modalities,[1–4] including viscosupplementation. Viscosupplementation consists of intra-articular (IA) injections of solutions of hyaluronan (hyaluronic acid (HA)),[5] aimed to alleviate pain and improve joint function, likely by restoring the physiological and rheological homeostases of OA joints.[6] Recently, viscosupplementation has been suggested to be the most effective treatment for symptomatic knee OA, as attested by an effect size of 0.63.[7] *In vitro* and *in vivo* studies have shown that HA might also have structure-modifying properties in reducing type II collagen degradation.[8–12] Furthermore, several studies have suggested that HA IA injections could be a useful adjuvant treatment for OA of other joints, such as ankle, shoulder, and hip, in patients not adequately relieved with conventional therapy (analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy).[13,14]

However, clinical trials showed controversial results regarding the effectiveness of viscosupplementation in ankle OA.[15] A number of open-label trials have reported promising results,[16,17] though no definitive conclusions can be

drawn from these studies, either because of the absence of a placebo group or the weakness of statistical power due to small sample size. Furthermore, very few predictive factors of response have been clearly identified, except in some studies in which a lower anatomical grade and shorter pain duration were demonstrated to be independent predictors of the patients' satisfaction.[18]

The objective of this retrospective survey, whose data are issued from the daily clinical practice, was to assess whether performing HA injections with the use of an imaging guidance helps to optimize the success rate of viscosupplementation in patients suffering from ankle OA.

Patients and Methods

Patients. Fifty consecutive patients referred for symptomatic ankle OA to 11 physicians (six rheumatologists, four orthopedic surgeons, and one specialist of sport medicine) and who received a single injection of HANOX-M-XL into the tibiotalar joint within the previous 12 months were included in the survey.

Intervention. HANOX-M-XL (marketed as Happy-Cross®, Laboratoire LABRHA, Lyon, France) is a viscosupplement, specifically designed to treat medium-sized joint OA, which combines a high molecular weight (MW) cross-linked sodium (16 mg/g) of non-animal origin with a high concentration of mannitol (35 g/g), conferring to the solution a very high viscosity (ie, 2560 Pa·seconds at 0.01 seconds^{-1}). HANOX-M-XL was supplied in a pre-filled syringe containing 2.2 mL of solution. Mannitol is a polyol known for its antioxidant properties by scavenging radical oxygen species (ROS). The *in vitro* effectiveness of mannitol to protect HA against ROS-mediated depolymerization has been demonstrated,[19–21] suggesting that addition of mannitol to HA might increase the IA residence time of the latter and consequently might allow a single injection regimen.

Methods. The patients were contacted by phone. A 10-item standardized questionnaire was administered by a research nurse blinded to patients' and physicians' identity. Before the interview, the patients were required to give their agreement on the scientific and anonymous usage of the data collected in the questionnaire. The survey was achieved in compliance with the reference methodology of the French "Commission Nationale Informatique et Libertés" (CNIL No 1583599V0) and the Scientific Committee of the Nord Franche-Comté Hospital. Demographic data (gender, age), consumption of analgesics or NSAIDs, pain at walking on a 10-point Likert scale (LS), patient's self-evaluation of efficacy, satisfaction with the treatment and tolerability on a 4-point LS, and assessment of the functional impairment (as severe enough to require surgery: yes/no) were collected. The patients were classified according to the following types of injection guidance: fluoroscopy, ultrasonography, or landmark guidance. The choice of the guidance was mainly based on access to imaging equipment and the physician's habits.

Statistics. A descriptive analysis was performed on the collected data. Qualitative variables were described using frequencies and percentages. Quantitative variables were described using mean, standard deviation (SD), and characteristics of their distribution (minimum, maximum, and median). Univariate analysis was performed using chi-square test or Fischer's exact test or Mann–Whitney test as appropriate. For between-group comparisons (image-guided versus landmark-guided injections), in view of the small sample size, the items were classified into two groups (yes/no) for efficacy, satisfaction, and tolerability (ie, "very satisfied/satisfied" were pooled into "satisfied" and "not really satisfied/not satisfied at all" were pooled into " dissatisfied"). Again, patients were classified into two or three groups for guidance: "guidance/no guidance" and "Fluo/US/landmarks". A chi-square test was then applied. A multivariate analysis was also performed, including satisfaction, guidance, gender, severity at baseline, and age. All statistical tests were carried out two tailed at the 5% level of significance. The statistical analysis was carried out using StatView© software version 5.0 (SAS Institute Inc).

Results

The main data are summarized in Table 1. All the contacted patients agreed to answer the questionnaire so that all the patients, treated by the physicians participating in the survey, were analyzed. Among the 50 patients, 35 were men and 15 women. The patients' mean age (range) was 59.8 years (26–85 years), and the average follow-up since the injection was 19 weeks (12–41 weeks). Nine patients (18%) assessed the functional impairment as severe enough to require surgery. Forty-two percent of the subjects were regular users of analgesics and/or NSAIDs. IA injection was performed under fluoroscopy guidance in 29 cases, ultrasonography in nine cases, and using anatomical landmarks in 12 cases.

Tolerability was rated as very good/good in 47 patients (94%), moderate in two (4%), and poor in one (2%) and was unrelated to imaging guidance. The only reported side effect was a transient increase in ankle pain, which lasted from one to five days after injection, unrelated to the imaging guidance ($P = 0.39$) and resolved without sequel in all three cases.

The percentages of patients who answered "very satisfied/satisfied" and "not really satisfied/not satisfied at all" with the treatment were 68% and 32%, respectively. Efficacy was considered as very good and good by 37% and 31% of patients, respectively; moderate by 12% of patients, and poor by 20% of patients.

Efficacy was unrelated to gender ($P = 0.29$), age ($P = 0.81$), and time since injection ($P = 0.35$). There was a trend for a poorer efficacy in patients with severe impairment before injection ($P = 0.09$). Among the nine patients who rated their disability "severe", only four (44.4%) were satisfied with the treatment. Of the 41 remaining subjects, 30 (73.2%) answered that viscosupplementation was effective. Efficacy was highly correlated with pain score ($P < 0.0001$) at the time of the

Table 1. Characteristics of 50 patients with ankle OA treated with a single injection of HANOX-M-XL.

ITEMS	ALL PATIENTS N = 50	FLUOROSCOPY GUIDANCE N = 29	ULTRASOUND GUIDANCE N = 9	NO GUIDANCE N = 12	*P* VALUES GUIDANCE VS NO GUIDANCE
Age (range)	59.8 (26–85)	60.4 (26–85)	60.8 (34–76)	56.5 (28–81)	0.49
Gender (M/F)	35/15	21/8	6/3	8/4	0.95
Pain score 0–10* (SD)	4.7 (3.2)	4.9 (3.5)	2.9 (2.1)	5.4 (2.9)	0.26
Time since injection (weeks)	19 (10.7)	20.5 (11.8)	15.5 (8.9)	17.1 (8.9)	0.40
Severe impairment** (Yes/No)	9/41	5/24	2/7	2/10	0.98
Satisfied (Yes/No)	34/16	21/8	9/0	4/8	0.02*
Efficacy *** (++/+/±)	19/15/6/10	11/10/2/6	6/3/0/0	2/2/4/4	0.05*
NSAIDs****/analgesics (Yes/No)	21/29	13/16	2/7	6/6	0.54
Tolerability (good/moderate/poor)	47/2/1	28/1/0	9/0/0	10/1/1	0.33

Notes: *At time of interview. **At time of injection.***Efficacy: ++, very good; +, good, ±, moderate; –, bad. ****NSAIDs = non steroidal anti-inflammatory drugs.

interview. In satisfied patients, the average pain score (SD) was 2.9 (2.1), while it was 8.4 (1.6) in dissatisfied subjects.

Satisfaction and efficacy were significantly better in patients injected under imaging guidance than in those injected using anatomical landmarks ($P = 0.03$). The result was confirmed in the multivariate analysis (Fisher's test, $P = 0.026$). In patients injected using anatomical landmarks, only four out of 12 rated efficacy as "very good or good" versus 29 out of the 38 subjects who were injected using fluoroscopy ($n = 20/29$) or under ultrasonography ($n = 9/9$). However, the difference between ultrasound and fluoroscopy did not reach the level of significance ($P = 0.09$).

All satisfied patients, who were taking analgesics or NSAIDs before injection, managed to reduce their drug consumption. Among them, 64% reduced it by >75%.

Discussion

Despite several limitations that are discussed later, this retrospective survey provides interesting data.

First of all, the data obtained from daily practice conditions showed the very good safety of HANOX-M-XL, confirming the good tolerability of the combination HA + mannitol, as it has been previously reported in knee[22–24] and hip OA.[25] No systemic adverse event (AE) was reported, and the local tolerability was excellent and similar to that expected. Only 6% of the patients experienced pain the very first days after injection, which is therefore much less than the 31% of mild or moderate local treatment-related AEs reported after hylan IA injection.[26]

Owing to the lack of a control group and the retrospective nature of this study, efficacy of HANOX-M-XL cannot be conclusively proven. Anyway, the survey was not designed for this purpose but only to obtain pilot data from the "real" life. Interestingly, it suggests that more than two patients out of three suffering from ankle OA are still satisfied with the treatment five months after a single injection of HANOX-M-XL. The percentage of responders are better than that published by Witteveen et al.[26] who reported the results of a multicenter open-label study in 55 patients with talocrural OA who received 2 mL IA injection of hylan G-F 20 plus an optional second injection if pain remained at baseline levels during the following three months. Thirty-one patients improved with one injection (56.4%), while 24 patients needed a second one. Other authors have shown that three to five injections of linear HA of intermediate MW were effective to decrease pain.[27–29] In contrast, DeGroot et al.[30] showed no significant difference between one injection of low-MW HA and saline serum. Nevertheless, Chang et al.[17] indicated that the MW was not associated with the magnitude of pain relief, but that increases in total doses and active ingredients administered might result in a better outcome. Conversely, the same authors concluded that increases in injection volumes might cause a reduction in effect size.[17] In HANOX-M-XL, being twice as concentrated as hylan GF-20, the total amount of injected HA is 35.2 mg in a 2.2-mL volume, which might explain the effectiveness perceived by a wide majority of patients. It is also possible that mannitol has its own anti-inflammatory effect, as it has been shown in an animal model of inflammation.[31]

Much more interesting is the significant difference of efficacy and patient's satisfaction according to the use or lack of imaging guidance. As a result of a higher level of success with ultrasound- and fluoroscopy-guided compared to landmark-guided injections, irrespective of the joint treated,[32–35] the use of imaging guidance is advised as often as possible, according to the technical capabilities of the physician. This opinion is strengthened by the results of a cadaveric study showing that the accuracy rate for ultrasound-guided injections was 100% versus 85% for non-guided injections.[36] Similar results were obtained on cadavers using non-guided anterolateral or anteromedial routes.[37] Other authors showed that unguided ankle injections lead to a failure rate of 24%.[38] Although the present data do not allow to advise on a specific type of guidance to be used, they suggest that ultrasonography might be

preferred to fluoroscopy. Of course, the difference in response rate between the two techniques might be due to chance, especially because the sample size of the patients injected under ultrasound was small. We can also propose the hypothesis that patients injected under ultrasound had a less severe disease. Indeed, as our data come from daily clinical practice, it is possible that some physicians had reserved ultrasound guidance to ankles easy to inject and consequently had referred the more advanced stages of ankle OA to radiologists for X-ray-guided injections. Nevertheless, the percentages of patients with severe impairment at the time of injection were similar in both groups (22.2% and 20%, respectively). One of the reasons of the higher rate of success in patients injected under fluoroscopy might be that ultrasound avoids the use of iodinated contrast agent. Indeed, a rheological study has demonstrated a dose-dependent deleterious effect of meglumine ioxaglate on HA viscoelasticity, as a ratio of 1:1.[39] Consequently, in case of fluoroscopy-guided injection, we suggest to use the lowest possible volume of contrast agent. Furthermore, contrary to fluoroscopic techniques, ultrasound can be used in patients intolerant to iodine. Moreover, the "European Community Directive 97/43/Euratom", about the general principles for protection from the radiation exposure, mentions that if available alternative techniques having the same objective but involving no or less exposure to ionizing radiation exist, they should be preferred. In addition, ultrasound guidance is cheaper in comparison to the fluoroscopic guidance.[40]

The main limitation of this study is, obviously, its retrospective nature and the fact that the results are based exclusively on patients' self-assessment. Furthermore, for the same reason, it has not been possible to obtain the imaging examinations and thus to adjust the results to the anatomical severity of the disease. However, this does not change the main finding of this study: the necessity to perform the injections under imaging control.

Conclusion

In summary, the present survey showed that imaging guidance is useful to optimize the results of viscosupplementation in ankle OA. Five months after a single injection of HANOX M-XL in the target ankle of patients with talocrural OA, three patients out of four remained satisfied with the treatment provided the viscosupplement was injected under imaging control to ensure the accurate IA injection. The proportion of satisfied patients was only one out of three in landmark-guided injection patients. Larger scale prospective trials, specifically designed for this purpose, are still needed to confirm with certainty these preliminary data.

Ethical Statement

The patients gave their informed consent prior to being included in the survey. The study was performed in accordance with the ethical standards of the Declaration of Helsinki and in agreement with the reference methodology of the French Commission Nationale Informatique et Libertés. Because this study comprised a retrospective review of records and a patient survey, ethics committee approval was not required.

Author Contributions

Conceived and designed the experiments: TC, MB. Analyzed the data: TC, MB. Wrote the first draft of the manuscript: MB. Contributed to the writing of the manuscript: TC, MB, AMB. Agree with manuscript results and conclusions: TC, MB, DB, ER, JMP, AMB. Jointly developed the structure and arguments for the paper: TC, MB. Made critical revisions and approved final version: DB, ER, JMP, AMB. All authors reviewed and approved of the final manuscript.

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