Annals Of Orthopaedics, Trauma And Rehabilitation
ISSN# 2833-2431

Short Communication

Impact of the Needle Size on the Dynamic Viscosity of Hanox-M-Xl, A Cross-Linked Hyaluronic Acid Viscosupplement

Elise Murat[1,2] and Thierry Conrozier[3*]

[1]Laboratoire de rhumatologie appliquée, 19 place Tolozan, Lyon, France

[2]Laboratoire d'exploration et morphométrie articulaire (LEMA), Bd Deruelle, Lyon, France

[3]Service de Rhumatologie, Hôpital Nord Franche-Comté, Belfort, France

ARTICLE INFO

Received Date: July 27, 2023
Accepted Date: September 19, 2023
Published Date: September 20, 2023

KEYWORDS

Osteoarthritis; Hyaluronic acid; Viscosity; Rheology; Viscosupplementation; Needle

Citation for this article: Elise Murat and Thierry Conrozier. Impact of the Needle Size on the Dynamic Viscosity of Hanox-M-Xl, A Cross-Linked Hyaluronic Acid Viscosupplement. Annals of Orthopaedics, Trauma And Rehabilitation. 2023; 6(1):145

Corresponding author:
Thierry Conrozier, Service de Rhumatologie, Hôpital Nord Franche-Comté, 100 route de Moval CS10499 Trevenans 90015 Belfort, France
Email: Thierry.conrozier@hnfc.fr

ABSTRACT

Rationale: Viscosupplementation (VS) by intra-articular (IA) injections of hyaluronic acid (HA) is widely used for treating osteoarthritis (OA) of the knee, hip, ankle, shoulder and trapezio-metacarpal joints. Thus, the needle size (diameter and length) has to be adapted to the joint in which HA is injected. HA being a fragile macromolecule, it might be structurally altered according to the needle size during IA injection.

Aim: The objective of this study was to compare the dynamic viscosity of a highly cross-linked HA viscosupplement (HANOX-M-XL), according to three different types of needles, usually used for viscosupplementation.

Methods: The dynamic viscosity of HANOX-M-XL was assessed using a cone-plate rheometer after injection with 3 needles differing in diameter and length: 21Gauge (G) x 40 mm; 22G x 90 mm and 25G x 25 mm. A measure without needle was performed as control. The dynamic viscosity η (Pa.s) was determined in triplicates according to the shear rate γ from 0.1 to 100 s^{-1}.

Results: The mean dynamic viscosity η (Pa.s) was 107.7 $\pm$5.8 Pa.s at a shear rate of 0.5 s^{-1} and 5.0 $\pm$0.2 Pa.s at a shear rate of 50 s^{-1}. The dynamic viscosity did not vary significantly according to the needle used (p values= 0.79 and 0.84 respectively).

Conclusion: The needle length and diameter do not modify the rheological behaviour of the cross-linked HA viscosupplement. These findings prove that HANOX-M-XL is not depolymerized during the injection procedure regardless of the needle size.

Keywords: Osteoarthritis; Hyaluronic acid; Viscosity; Rheology; Viscosupplementation; Needle

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder, affecting millions of people [1], characterized by a progressive alteration of the different tissues constituting the joints (articular cartilage, subchondral bone, synovium). Among the many structural changes in the OA joint, responsible for pain, alterations in hyaluronic acid (HA), a major component of both the cartilage extracellular matrix and the synovial fluid, play an important role [2]. HA is non-sulfated glycosaminoglycan that is characterized by a high polymerization and a macromolecular structure, consisting in repeated units of β-(1,4)-glucuronic acid and β-(1,3)-N-acetylglucosamine linked together by alternating

β-1,3 and β-1,4 glycosidic bonds. In the human body, HA can consist mainly of up to 10,000 or more repeating units, resulting in a molecular weight of 4 to 6 million Da (MDa). HA can bind a large amount of water molecules and become viscous through the establishment of intramolecular and intermolecular hydrogen bonds [3]. Hence, HA plays an important role in lubrication, shock absorption, and viscoelastic behaviour of the synovial fluid in the joints. It has been well established that the decline in viscoelastic performance of osteoarthritic synovial fluid was directly related to a qualitative and quantitative deficit in HA [4,5]. Balazs and Denlinger [6] developed the concept of viscosupplementation (VS). Viscosupplementation by intra-articular (IA) injections of high molecular weight HA (>1MDa) is a symptomatic treatment, intended to reduce pain and improve joint mobility by restoring the rheological properties of the osteoarthritic synovial fluid. Intraarticular injection of hyaluronan-based formulations currently represents the most employed, not invasive, symptomatic treatment of knee OA [7] and is used to a lesser extent for treating OA of the hip, ankle, shoulder and trapezio-metacarpal joints [8]. Thus, the multiplicity of indications makes the needle size (diameter and length) must be adapted to the joint in which HA is injected. It is obvious that a small superficial joint, such as the trapezio-metacarpal joint, cannot be injected with the same needle as the coxofemoral joint, which is a large and very deep joint [9].

The native linear HA molecule having a very short half-life [10], manufacturers have developed sustained-release derivatives thanks to the cross-linking process which consists of linking the HA molecules with cross-linking agents. Beyond a much longer half-life, crosslinked HAs exhibit higher viscosity and elasticity than linear HA [11]. Every rose has its thorn, its high viscosity makes the cross-linked HAs susceptible to being structurally altered during the injection process, particularly if a long and/or very fine needle must be used. In fact, cross-linked HAs are supposed to have better cohesion once injected into the joint. However, this rigidity could be a concern during the injection process by exposing the gel to phenomena of mechanical rupture of the three-dimensional network created by crosslinking. Although the viscosupplementation is widely used and has a long history in treating limb OA, very little is known about the deformability of the HA macromolecules and their possible degradation during the injection process.

The aim of the study was to assess whether le length and calibre of needles have a significant impact on the dynamic viscosity of a crosslinked HA viscosupplement, and and therefore could impact the efficiency of the viscosupplementation.

MATERIAL AND METHOD

Studied viscosupplement:

HANOX-M-XL (HappyCross®, LABRHA SAS, Lyon, France) is a viscosupplement made of a crosslinked HA, at a concentration of 16 mg/ml, combined with mannitol (35 mg/ml) [12]. HANOX-M-XL is highly crosslinked and exhibits a complex modulus G* o 157 ± 9.1 Pa, and a phase tangent tan δ of 0.175 ± 0.003, in the linear viscoelastic domain (LVED) (unpublished data). The clinical effectiveness of HANOX-M-XL has been studied in knee OA of the knee [13,14], hip [15], ankle [16], temporo-mandibular [17], trapezio-metacarpal [18] and metatarso-phalangeal joints [19].

Studied needles:

Three types of needles were compared: 21Gauge (G) x 1.5", length (L) 40 mm; 22G x 3.5", L90 mm and 25G x 1" L25 mm. A measure without needle has been performed as control.

Dynamic viscosity measurement:

Rheological measurements were performed using a cone-plate rheometer (RheoWin HAAKE Viscotester iQ Air, Thermo Electron SAS) at 20°C. The sample of HANOX-M-XL was deposited on the lower plane, then the upper plane was lowered to a deburring air gap (trim gap) of 1050 µm. Any excess product was removed with a spatula. The air gap was set to 1000 µm. The dynamic viscosity η (Pa.s) was determined in triplicates according to the shear rate γ from 0.1 to 100 s^{-1}. The dynamic viscosity was measured before (control) and after being injected through the needles with different characteristics of length and diameter, described above.

Statistical analysis

An analysis of variance was used to compare the results of the dynamic viscosity η obtained during the various measurements of the experiment.

RESULTS

The mean dynamic viscosity η (Pa.s) from all combined experimental conditions was 107.7 ± 5.8 Pa.s at a shear rate of 0.5s^{-1} and was 5.0 ± 0.2 Pa.s at a shear rate of 50 s^{-1}. The dynamic viscosity for each type of needle at a shear rate of 0.5 and 50s^{-1} is given in table 1. Statistical analysis did not show any statistical difference between the needles used.

The rheological profile of the HANOX-M-XL according to the needle type is presented in figure 1, that clearly shows that neither the gauge, nor the length of the needles modify the dynamic viscosity at all share rates.

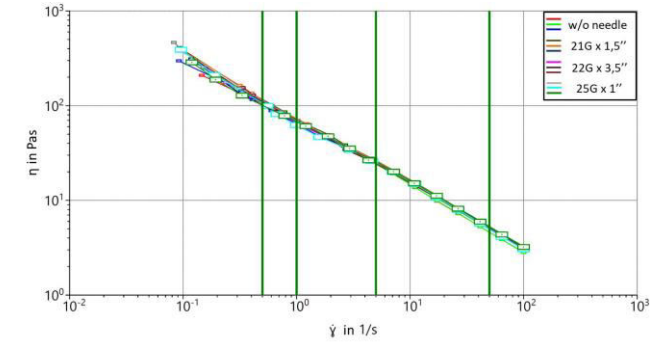

Figure 1: Dynamic viscosity of HANOX-M-XL according to different types of needles at a shear rate of 0.5 and 50 s^{-1}.

Table 1: Dynamic viscosity η (Pa.s) of HANOX-M-XL according to different types of needles at a shear rate of 0.5 and 50 s^{-1}.

		No needle	21G x 1.5"	22G x 3.5"	25G x 1"	P value
η (Pa.s) γ = 0.5 s^{-1}	1	105.7	115.9	105.3	114.3	0.79
	2	107.5	116.2	108.8	107.0	
	3	100.2	100.2	110.6	100.2	
Mean η (SD) Pa.s γ = 0.5 s^{-1}		*104.5 (3.8)*	*110.8 (9.2)*	*108.2 (2.7)*	*107.2 (7.1)*	
η (Pa.s) γ = 50 s^{-1}	1	4.59	5.18	5.02	5.10	0.84
	2	4.52	5.10	5.18	4.94	
	3	5.10	5.18	4.86	5.18	
Mean η (Pa.s) γ = 50 s^{-1}		*4.7 (0.3)*	*5.2 (0.1)*	*5.0 (0.2)*	*5.1 (0.1)*	

DISCUSSION

Although viscosupplementation has been widely used to treat symptomatic OA for more than 3 decades, there is, at our knowledge, no published study assessing the deformability of the HA macromolecule and its possible degradation during the injection process. However, differences among HA products may be considered. To date, two categories of HA viscosupplements may be identified, namely: linear HAs and chemically modified HAs. Linear HAs are made of a solution of linear native chains of HA differing themselves in concentration, molecular weight and source. Their rheological behaviour is that of a non-Newtonian fluid. The second category consists of hydrogels in which HA molecules have been chemically linked, using crosslinking agents (mainly butanediol-diglycidyl ether, vinylsulfone and formaldehyde) [20] or by stabilizing linear polymers by hydrophobic and hydrophilic interactions, with the help of hexadecylamide [21]. Their rheological behaviour is that of a gel, with an elastic modulus G' higher than the viscous modulus G" at all frequency ranges. These chemical modifications give them greater elastoviscosity and longer intra-articular persistence than linear HA. On the other hand, their high viscoelasticity makes them more difficult to inject.

In this study, we compared the rheological behaviour of HANOX-M-XL, a cross-linked HA viscosupplement, after injection through three different types of needles, the most frequently used by physicians for viscosupplementation. The 21G x 40 mm needle is the most frequently used needle used for knee and shoulder viscosupplementation. The knee and shoulder are large joints, relatively superficial for whom a standard needle (30 to 50 mm in length) is most often used. However, in obese subjects, it may be necessary to use a longer needle. In hip injection, which is a deep joint, a long needle of 90 mm length is usually necessary. Inversely, small and thin needles of 25G x 20 to 25 mm are mandatory for injecting small and superficial joints as trapezio-metacarpal, metatarsophalangeal and temporomandibular joints.

Our results show that neither the length of the needle nor its diameter modify the rheological behaviour of HANOX-M-X. As clearly shown in Figure 1, the viscosity curves are perfectly similar regardless of the needle used. It is known that the viscoelastic properties of HA are related to both HA MW and HA concentration [20]. Therefore, at a constant HA concentration, any decrease in viscosity is the result of a decrease in the molecular mass of the HA, and consequently of a degradation of the three-dimensional structure of the HA macromolecule. Since the dynamic viscosity was not modified, our results demonstrate that the HA molecular weight did not

decrease during the injection process, regardless of the needle used, therefore that the crosslinking was not altered when the gel passed through the needle.

Until now, no clinical study has suggested a reduction in the effectiveness of HANOX-M-XL depending on the size of the joints, and therefore the needles used [13-19]. The present rheological study supports this clinical feeling by demonstrating that the elastic properties of HANOX-M-XL are not modified depending on the needle chosen.

CONCLUSION

In conclusion, despite high elastoviscous behaviour due to crosslinking, HANOX-M-XL can be injected through long and thin needles without risk of being mechanically degraded during injection. However, since the crosslinking characteristics are very different between HA products, these results should be extrapolated with caution to other crosslinked viscosupplements.

CONFLICT OF INTEREST STATEMENT

TC received fees from LABRHA for expert and consultant services.

Elise Murat is an employed of LABRHA

AUTHOR CONTRIBUTIONS

TC designed the protocol, analyzed the data and wrote the manuscript

EM carried out the measurements and reviewed the manuscript

FUNDING

The study was funded by LABRHA SAS, 19 place Tolozan, 69001 Lyon, France

DATA AVAILABILITY STATEMENT

The datasets for this study can be found in LABRHA SAS, 19 place Tolozan, 69001 Lyon, France

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