Safety and efficacy of a single intra-articular injection of mannitol-modified cross-linked hyaluronic acid (HappyMini®) in patients with hallux rigidus. A prospective open-label multicentre pilot study (REPAR trial).

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***Rheumatology**
×Orthopaedic surgery

Belfort, Auch, Cornebarrieu, Lyon, La Crau, Montélimar, Nevers, Viry-Chatillon, Nancy, ***FRANCE***

Sponsor

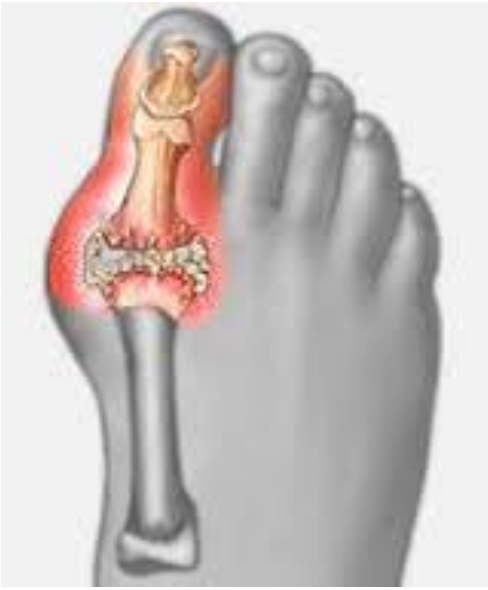
Background

HAnox-M-XL in Hallux Rigidus

✓ Osteoarthritis of the first metatarso-phalangeal (FMP) joint – **Hallux Rigidus-** is a frequent and painful condition that has a significant impact on quality of life.

✓ The conservative treatment usually consists in analgesics, NSAIDs intraarticular injections of corticosteroids or hyaluronic acid (HA) preparations, and the use of semi-rigid insolses.

✓ In case of non-response to medical therapy, surgical procedure should be contemplated.



HAnox-M-XL in Hallux Rigidus

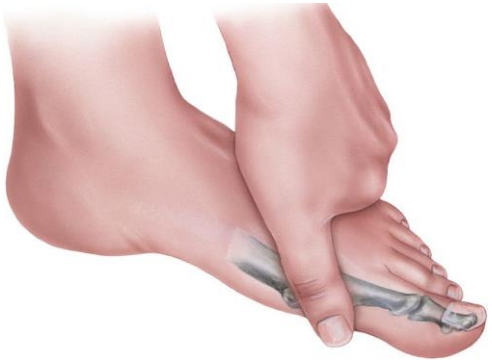
Objectives

✓ To assess the **safety and the efficacy** on pain relief of a **single intra-articular injection of a new mannitol-modified cross-linked hyaluronic acid (HANOX-M-XL)** viscosupplement, in patients suffering from hallux rigidus

✓ To study the **predictive factors of response** to viscosupplementation, with a particular focus on the radiological stage.

Patients and methods

HAnox-M-XL in Hallux Rigidus



✓Patients with **symptomatic FMP OA** were included in a 3-month prospective multicentre open-label trial.

✓Investigators were **rheumatologists or orthopedic surgeons**, specialized in foot OA

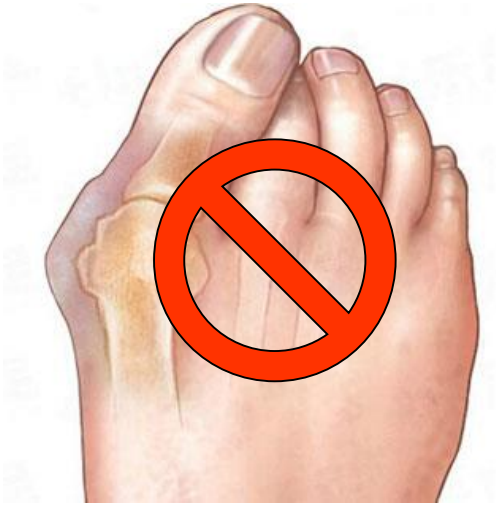
✓The study received the French health authorities approval and was conducted in accordance with the Ethical standards of the Declaration of Helsinki.

Patients and methods

HAnox-M-XL in Hallux Rigidus

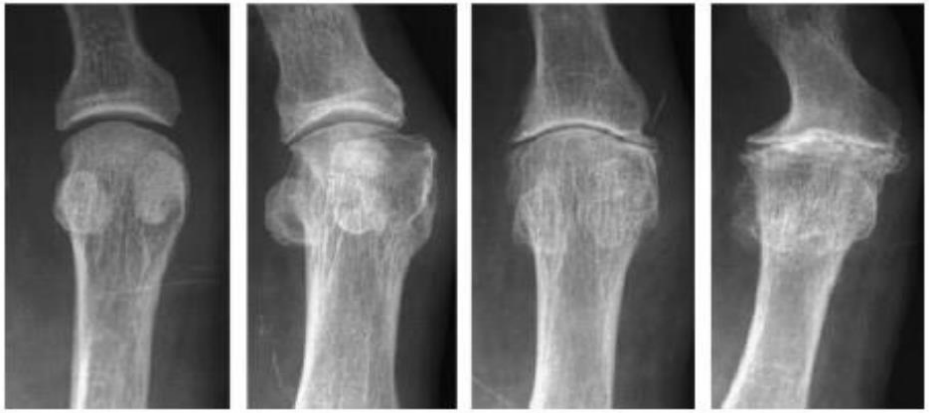
- To be included in the study patients must have **symptomatic Hallux Rigidus, not adequately relieved** by analgesics/ NSAIDs therapy and/or by the use of a plantar orthotic.

- Patients with history of inflammatory (i.e. psoriasis arthritis) or crystal deposition disease (i.e. gout), hallux valgus and those who previously received intra-articular injections with corticosteroids into the target toe were excluded.



HAnox-M-XL in Hallux Rigidus

All patients must have standard radiographs, for the assessment of the radiological grade (0-3).



Menz et al. Osteoarthritis Cartilage 2007 15, 1333-38

X-Ray grade	Joint space narrowing	Ostéophyte
Grade 0	Absence	Absence
Grade 1	Mild	Mild
Grade 2	Moderate	Moderate
Grade 3	Severe	Large

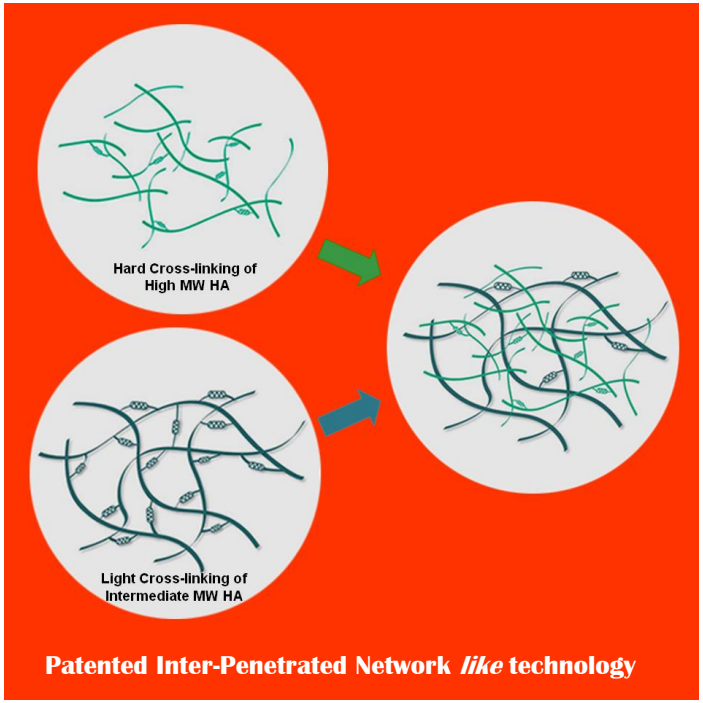
Patients and methods

HAnox-M-XL in Hallux Rigidus

Treatment consisted in a single injection of 1 ml of HANOX-M-XL in the TMC joint under fluoroscopic or ultra-sound guidance.

HANOX-M-XL (**Happymini®,** LABRHA SAS, Lyon, France) is a viscosupplement, that combines:

- ✓ **IPN technology cross-linked HA** of non-animal origin (16 mg/ml)
- ✓ **High concentration** (35 mg/ml) of **MANNITOL**, a polyol known for its **antioxidant** properties by scavenging radical oxygen species (ROS)
- ✓ **Very long IA residence time** > 30 days



HAnox-M-XL in Hallux Rigidus

Patients and methods

- ✓ **Primary endpoints** were the variation between injection (D0) and D90 of the toe pain on 11 point-Likert scale (0-10) and the patient's self-assessment of efficacy (0-3).
- ✓ **Predictive factors of response** including clinical, demographic and radiographic data were also studied
- ✓ **Statistical tests were carried out on the ITT population** . The statistical analysis was performed using Statview© software version 5.0 (SAS institute Inc).

HAnox-M-XL in Hallux Rigidus

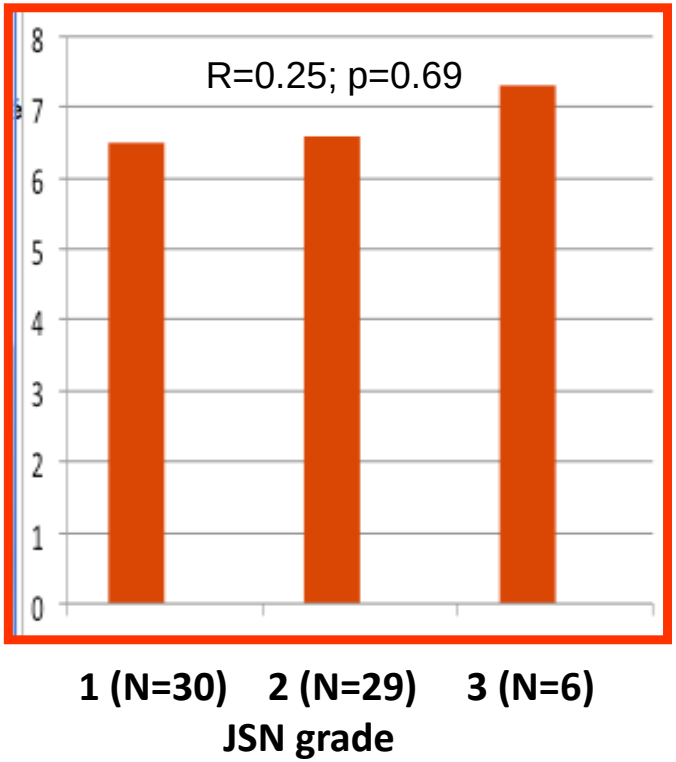
Results: population

- ✓ 65 patients (72.3% women, mean age: 60, mean symptom duration: 24.9 months, BMI 25) were included in the trial. 9 patients (13.5%) were lost to follow-up.
- ✓ Treatments at inclusion:
  - ✓ Analgesics 63%,
  - ✓ NSAIDS 41%,
  - ✓ SYSADOA13%,
  - ✓ Insoles 17%,
- ✓ Guidance:
  - ✓ Radio 59%,
  - ✓ US 41%
- ✓ There was no statistically significant correlation between the radiological stage and the pain score at baseline (p = 0.69).

Mean Pain (SD) at D0

6.5/10 (1.6)

No significant difference according to the radiological grade



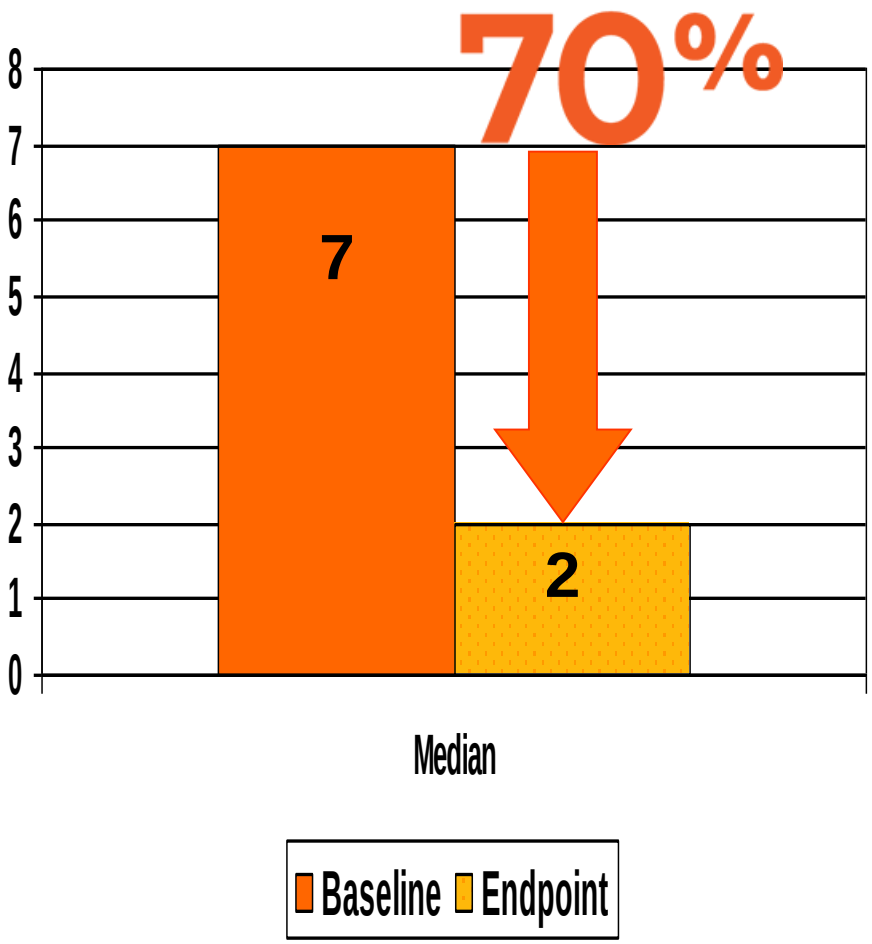
HAnox-M-XL in Hallux Rigidus

Results: Pain

✓**At baseline and end-point, the median pain score was respectively 7** (range 3-10) **and 2** (range 0-9).

✓**The difference in the pain score between baseline and endpoint was highly significant (p < 0.0001).**

✓**At D90, 59% of patients reduced their analgesic or NSAID consumption**

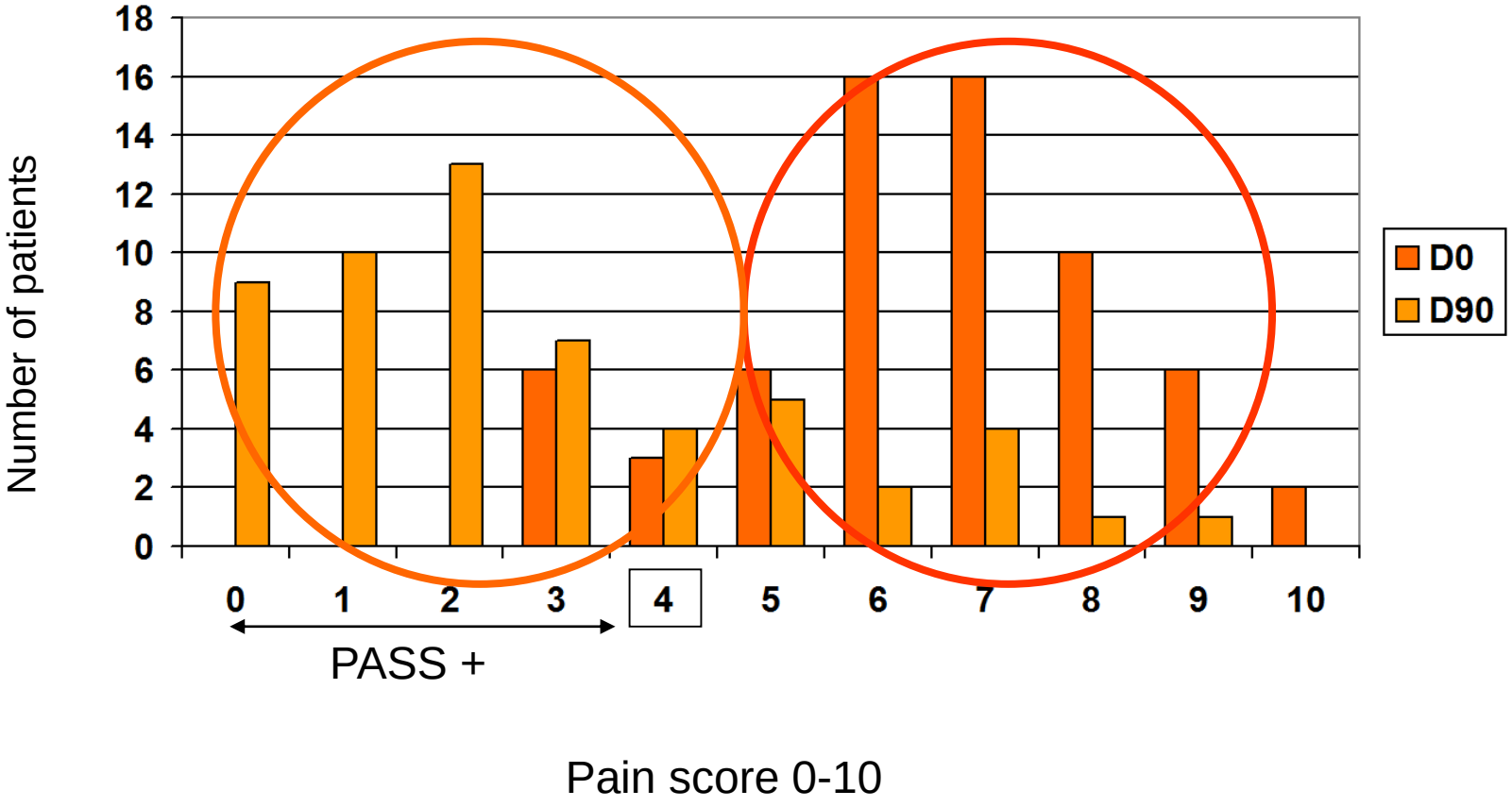


HAnox-M-XL in Hallux Rigidus

Results: Pain

Pain score: Individual data at D0 and D90

Number of patients according to pain score categories (numerical rating scale 0-10) at baseline (N=65) and 3 months after viscosupplementation (N=59).
Patients with pain score ≤4 fulfilled the Patient Acceptable Symptom State (PASS) criterion.



Results: Predictive factors

HAnox-M-XL in Hallux Rigidus

<u>In univariate analysis</u> response to viscosupplementation was:

- ✓ **Unrelated to:**
  - ✓ Age
  - ✓ Gender
  - ✓ BMI
  - ✓ Disease duration
  - ✓ Level of pain on VAS at baseline
  - ✓ Type of guidance (US versus X-rays)
- ✓ **Related with:**
  - ✓ Joint space narrowing grade (p=0.001)

<u>In multivariate analysis</u> Joint space narrowing grade remained the only predictive factor of response to viscosupplementation (p=0.02).

Results: Predictive factors

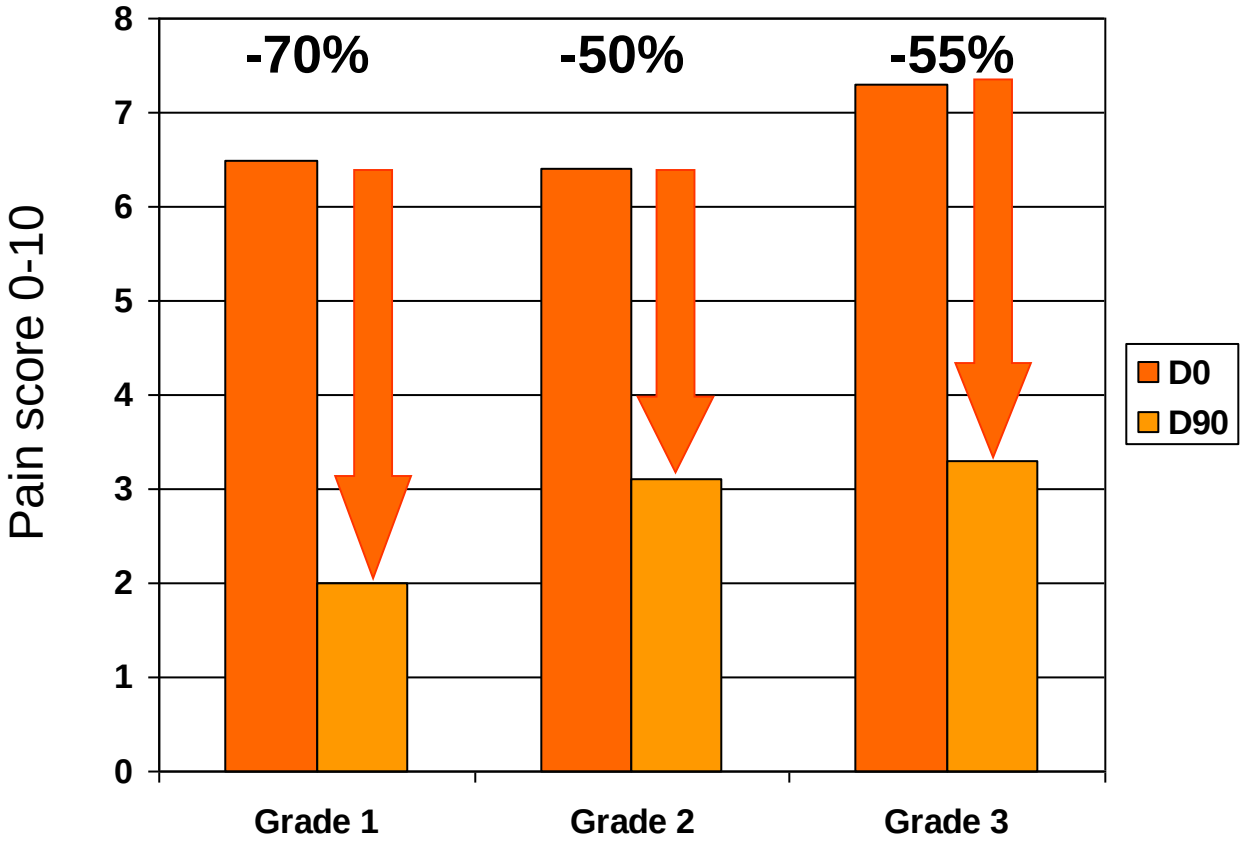
HAnox-M-XL in Hallux Rigidus

Walking pain score (0-10) at time of injection and month 3,

in 65 patients with hallux rigidus treated with 1 intra-articular injection of HANOX-M-XL (N=65),

according to the radiological joint space narrowing (JSN) score

Between-group difference: Grade 1 versus Grade 2-3; p=0.001,
Intra-group differences all p<0.0001.



HAnox-M-XL in Hallux Rigidus

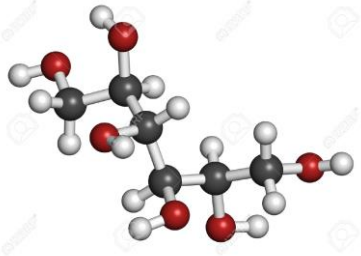
Results: Safety

There was no safety issue.

- ✓ 15 treatment/injection procedure-related adverse events (22.7%) occurred.
- ✓ All AEs were local pain during or following HA administration and resolved without sequel within 1 to 7 days.
- ✓ No severe or systemic AEs

Discussion

Mannitol $C_6H_{14}O_6$



Thanks to its powerful anti-oxidant properties, Mannitol decreases reactive oxygen species (ROS) related-degradation of hyaluronic acid, compared to cross-linked viscosupplements not containing mannitol.

Polymers **2014**, *6*, 1948-1957; doi:10.3390/polym6071948

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Article

Effect of Mannitol on Hyaluronic Acid Stability in Two *in Vitro* Models of Oxidative Stress

Marguerite Rinaudo [1], Bernard Lardy [2], Laurent Grange [3] and Thierry Conrozier [4,*]

Rheumatol Ther (2014) 1:45–54

DOI 10.1007/s40744-014-0001-8

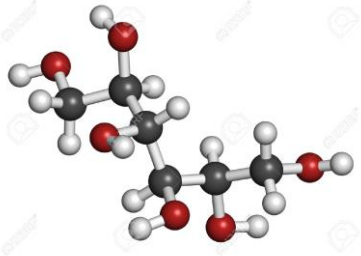
ORIGINAL RESEARCH

Mannitol Preserves the Viscoelastic Properties of Hyaluronic Acid in an In Vitro Model of Oxidative Stress

Thierry Conrozier · Pierre Mathieu · Marguerite Rinaudo

Discussion

Mannitol $C_6H_{14}O_6$



Topical Mannitol exhibits anti-inflammatory and anti-oedematous effects similar to that of diclofenac and ketoprofen.

Pharmacology

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Topical Mannitol Reduces Inflammatory Edema in a Rat Model of Arthritis

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These two properties of mannitol may explain the present results that contrast with those of Munteanu et al (ARD 2011) showing no statistical difference between hylan GF-20 and saline.

Conclusion

HAnox-M-XL in Hallux Rigidus

✓**A single injection of 1 ml of HANOX-M-XL, performed under imaging guidance in FMP joint, reduces significantly pain at walking, for at least 3 months, especially in patients with mild to moderate joint space narrowing.**

✓However the majority of patients with more advanced OA were also significantly improved.

✓Although the overall tolerability was good, a careful information of the patient is necessary, regarding the risk of pain increase the few days following injection.

✓Further controlled studies, with longer follow-ups, are needed to confirm these promising results.

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