Abstract nº: 28398

SICOT 2011 XXV Triennial World Congress

Prague, September 2011

Efficacy and safety of a single intraarticular injection of 2% sodium hyaluronate + mannitol in knee osteoarthritis over a 6 month period

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Introduction

Current management and treatment for knee osteoarthritis (OA) include:

- NSAIDS oral intake
- Oral chondroprotectors
- Repeteated intraarticular (i.a.) infiltrations of chondroprotectors
- Surgery (arthroscopy)

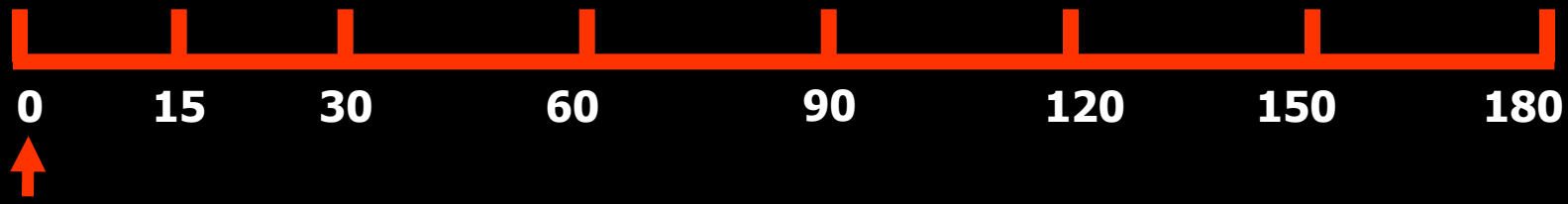
Thus, our **objective** was:

To evaluate the efficacy and safety of a single i.a. injection of 2ml of a solution containing 2% hyaluronic acid (HA) + 0,5% mannitol in knee OA.

Material and Methods
Study design and Treatment

Pilot, multicentre, open and non-comparative, phase IV study

- 80 patients suffering from knee OA Class III according to ACR.
- A **single i.a. injection** of 2 ml of 2% sodium hyaluronate + 0,5% mannitol (Ostenil® plus) was administered at first visit.
- The intake of **paracetamol 800 mg** and/or **ibuprofen 400mg** tablets (maximum 3 tablets per day) was allowed if pain was not tolerated (≥7 using the VAS).
- Pain and joint function were measured by VAS, WOMAC Index, rescue medication, and the investigator and patient's opinion.
- Evaluations on days:



Material and Methods

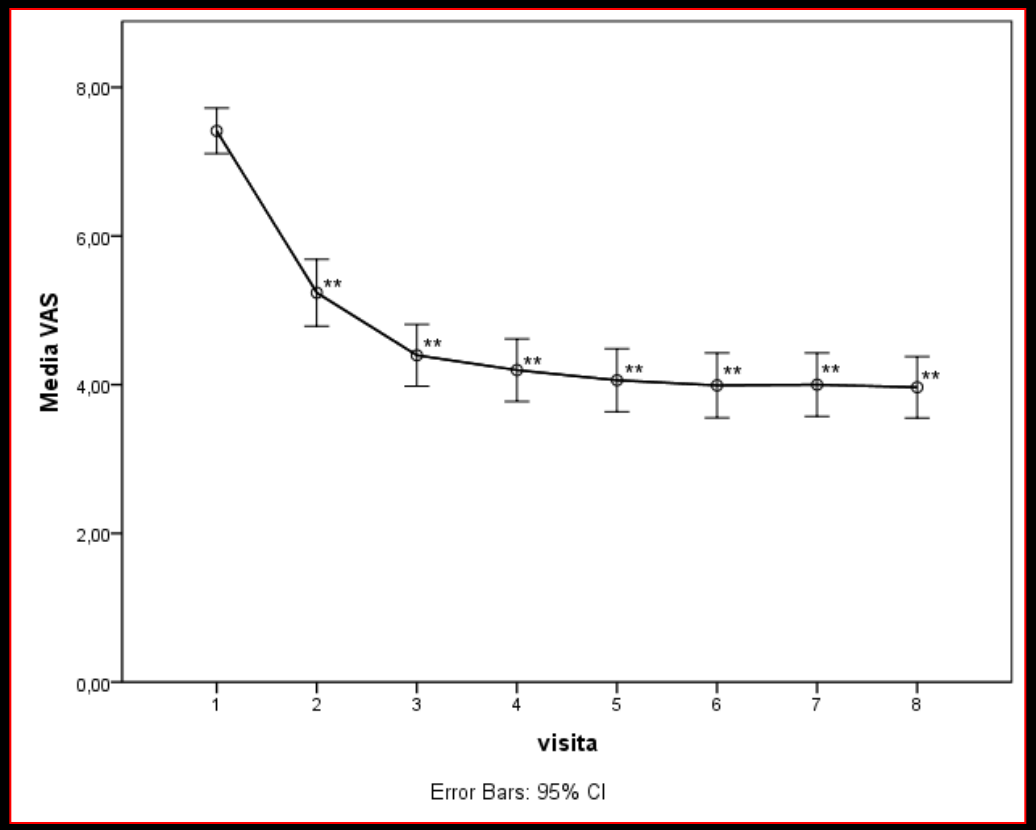
Inclusion criteria

- Patients of both sexes aged 40 or older.
- Class III articular function at least in the knee to be treated (according to ACR criteria).
- Pain and discomfort in the knee during the last 3 months.
- Patients who agree to sign the Informed Consent (IC).

Exclusion criteria

- Existence of other diseases that may interfere.
- Have suffered an arthroscopic lavage over the past year.
- Have received steroids and/or i.a. hyaluronic acid over the past 180 days.
- Be taking low-dose aspirin.
- Be taking glucosamine, chondroitin sulfate or hydrolyzed collagen for 2 months prior to baseline.
- Have participated in another clinical trial during the past 30 days.
- Pregnant women.

Results VAS



Evolution of mean value of pain (VAS)

**p<0,001, pairwise comparisons refered to the first visit values (Bonferroni method).

- Statistically significant reduction (p<0,001) of **joint pain** (VAS) from the second follow-up visit (15 days) compared to baseline, keeping this reduction until the last visit.
- Joint pain improved by 40,7% on Day 30, reaching 46,5% on Day 180.

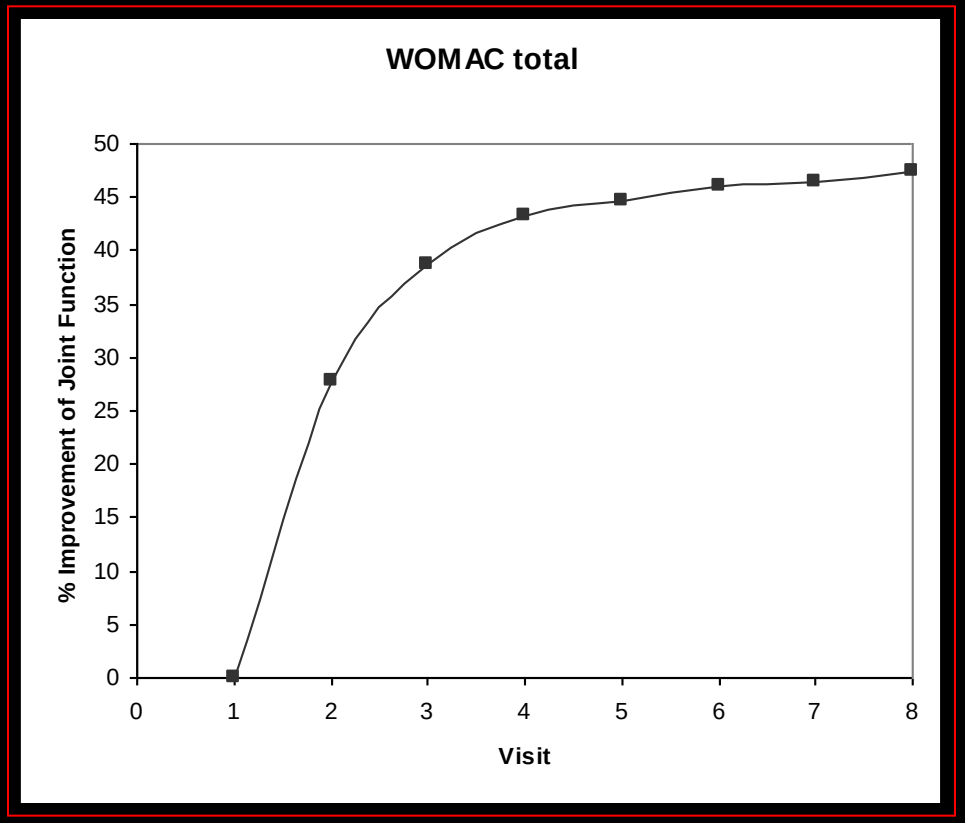
Results WOMAC

Visit	WOMAC Total	WOMAC Pain	WOMAC Stiffness	WOMAC Functional disability
1	2,302 ± 0,597	2,308 ± 0,660	2,227 ± 1,027	2,309 ± 0,599
2	1,664 ± 0,773**	1,625 ± 0,758**	1,487 ± 1,043**	1,696 ± 0,781**
3	1,411 ± 0,788**	1,357± 0,756**	1,196 ± 0,871**	1,453 ± 0,813**
4	1,308 ± 0,817**	1,253 ± 0,784**	1,113 ± 0,891**	1,347 ± 0,847**
5	1,276 ± 0,826**	1,227 ± 0,776**	1,107 ± 0,911**	1,310 ± 0,861**
6	1,240 ± 0,807**	1,212 ± 0,763**	1,044 ± 0,855**	1,271 ± 0,840**
7	1,233 ± 0,781**	1,192 ± 0,733**	1,075 ± 0,877**	1,264 ± 0,813**
8	1,209 ± 0,703**	1,146 ± 0,659**	1,031 ± 0,805**	1,248 ± 0,739**

Mean value ± SD of WOMAC Index

- Statistically significant decrease (**p<0,001) from the 2nd visit compared to the 1st visit (in total WOMAC value and its components of pain, stiffness and functional disability) (Bonferroni method).

Results WOMAC and Efficacy

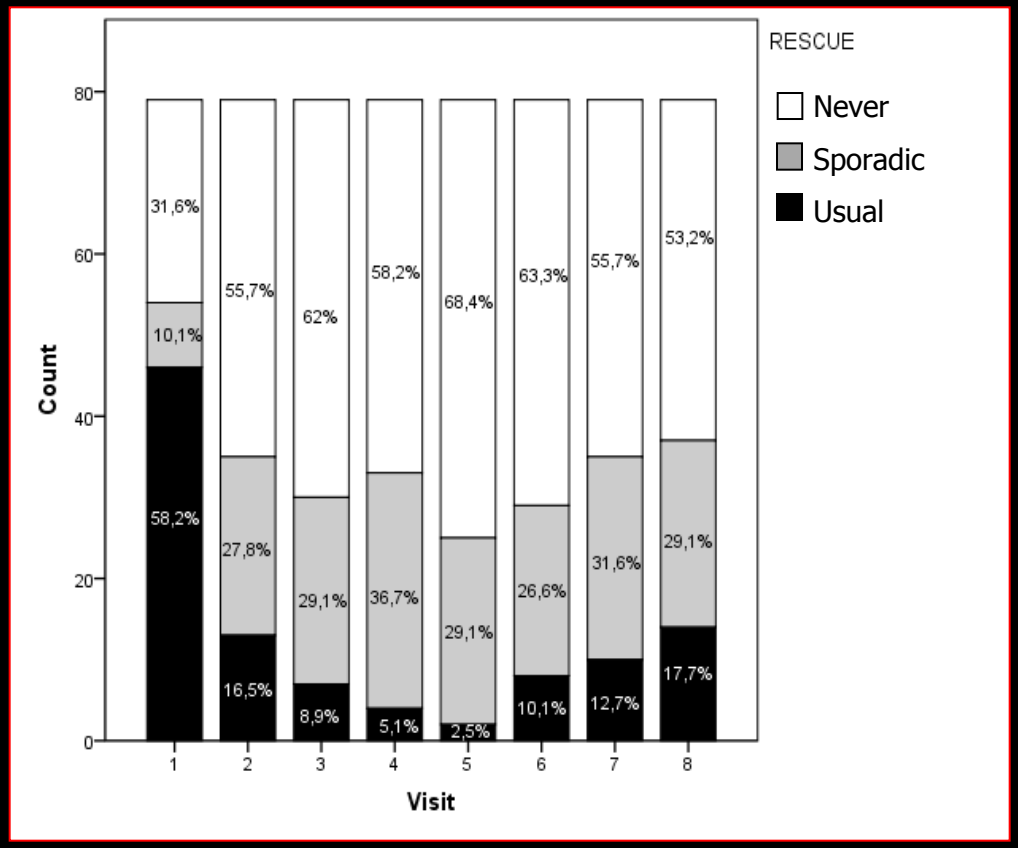


% Improvement in Joint Function

**p<0,001, pairwise comparisons refered to the first visit values (Bonferroni method).

- **Joint function** improved by 38,7% (WOMAC) on Day 30, reaching 47,5% on Day 180.
- **Efficacy evaluation** by the investigator and the patient was good or very good throughout the study (statistically significant), with the exception of the last visit, in which the patient evaluation suggests a slight decrease in efficacy not statistically significant.

Tolerability and Rescue medication



Evolution of rescue medication

- **Tolerability** has been considered as very good by the investigator and patient since the beginning of treatment (infiltration visit).
- No serious adverse events were observed in the study. **Mild side effects** were reported at the second visit (Day 15) in 4 patients (local pain and swelling in the area of infiltration). They disappeared on subsequent visits.

- 58,2% of patients had usual intake of **rescue medication** (RM) in the 1st visit, decreasing in subsequent visits, reaching 2,5% on day 90. At the end of the study, usual RM intake increased until 17,7%.

Discussion

- Clinical studies have shown that repetead i.a. injections of HA improve symptoms, especially pain, in knee OA (Tikiz *et al.* 2005; Sun *et al.* 2006; Altman *et al.* 2009).
- Efficacy and safety of a single injection of HA have been studied with mixed results in knee and hip OA (Chevalier *et al.* 2010; Altman *et al.* 2004; Krocker *et al*. 2006; Conrozier *et al.* 2009; Richette *et al.* 2009).
- Studies with single injections of crosslinked HA, show efficacy and safety, but with more mild local adverse effects than formulations of no-crosslinked AH (Chevalier *et al.* 2010; Conrozier *et al.* 2009).
- **Why one single i.a. injection of HA?**
  - Repeated injections can lead to an increased risk of local adverse events.
  - Reduced number of injections and visits is comfortable for the patient, economic and logistical advantage for the hospital.
  - There are no recent studies with a single i.a. injection of no-crosslinked HA with good results of safety and long-term efficacy.

Conclusions

1. One **single intraarticular injection** of 2 ml of 2% HA plus 0,5% Mannitol (Ostenil® plus) is effective in **reducing pain** and **improving joint function** in patients with knee osteoarthritis.
2. The evolution throughout the different visits of the mean value of all evaluations of efficacy (VAS, WOMAC Index, rescue medication intake, opinion of the investigator and patient) shows a **clear improvement** from the first 15 days of treatment.
3. The **duration** of the effect of a single i.a. injection of HA remain over a period of time of **at least 6 months**.
4. Treatment was **safe** and **well tolerated**.

A single intraarticular injection of HA may represent an optimal therapeutic alternative to current treatment regime in terms of efficacy, tolerability, convenience and hospital's cost.