

# Comparative efficacy of three and five intra-articular injections of sodium hyaluronate in the treatment of knee osteoarthritis – a 12-month study

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## Introduction

The aim of this clinical study was to compare the efficacy and safety of a course of 3 or 5 intra-articular injections of sodium hyaluronate (SH) 1.0% administered once weekly in two groups of patients suffering from knee osteoarthritis, and to assess the long-term efficacy over a 12-month period from the first injection.

## Methods

- Multicentre, randomised, masked-observer study.
- Patients aged 50–70 years with knee osteoarthritis according to ACR criteria.<sup>1</sup>
- Two parallel groups received once-weekly injections of SH 20 mg/2.0 ml (Ostenil®, TRB Chemedica AG, Germany) into the knee:
  - 3 injections (weeks 0, 1, 2), followed by two lidocaine injections (weeks 3, 4), or
  - 5 injections (weeks 0, 1, 2, 3, 4).
- Study duration 12 months with assessments at weeks 5, 12, 24, 36, 48 after the first injection.
- Efficacy parameters:
  - joint pain, stiffness and physical function assessed by WOMAC A, B, C<sup>2,3</sup>
  - global efficacy judgement by the investigator and patient
  - treatment response was defined as ≥20% improvement in WOMAC index.

## Results

A total of 140 patients (70 patients in each group) were randomised and analysed. The results are shown in Tables 1 to 6 and Figures 1 to 4.

Demographics		3-injection group n = 70	5-injection group n = 70
Gender, n (%)	Female	56 (80.0%)	53 (75.7%)
	Male	14 (20.0%)	17 (24.3%)
Age (years)	Mean ± SD	60.1 ± 6.6	60.3 ± 7.7
	Min–max	50–74	49–75
Duration of disease (years)	Mean ± SD	8.2 ± 7.4	8.6 ± 7.8
	Kellgren–Lawrence, n (%)		
	I	11 (15.7%)	6 (8.6%)
	II	42 (60.0%)	37 (52.9%)
	III	17 (24.3%)	27 (38.6%)

SD, standard deviation

Table 1: Demographic data.

## Pain on WOMAC A

WOMAC A values decreased from baseline in a statistically significant manner in both groups ( $p < 0.001$ , ANOVA test) and remained at a stable level until week 48 (Figure 1, Table 2). No statistically significant inter-group difference was found.

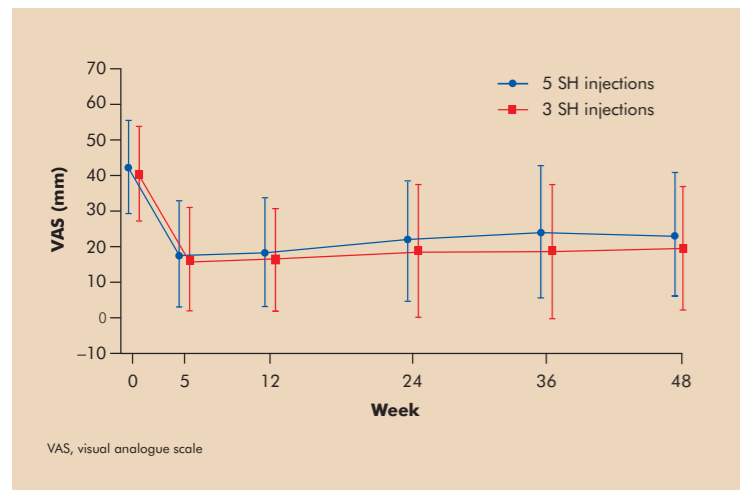


Figure 1: VAS pain on WOMAC A.

WOMAC A (mm VAS) mean ± SD	3-injection group	5-injection group
baseline	40.3 ± 13.0	41.7 ± 12.7
week 5	16.3 ± 14.2	17.5 ± 14.3
week 12	16.1 ± 13.9	17.7 ± 14.7
week 24	18.7 ± 18.1	21.1 ± 16.6
week 36	18.6 ± 17.9	23.3 ± 18.0
week 48	19.5 ± 16.3	22.6 ± 17.2

VAS, visual analogue scale

Table 2: Pain on WOMAC A.

## Joint stiffness on WOMAC B

WOMAC B values decreased from baseline in a statistically significant manner in both groups ( $p < 0.001$ , ANOVA test) and remained at a stable level until week 48 (Figure 2, Table 3). No statistically significant inter-group difference was found.

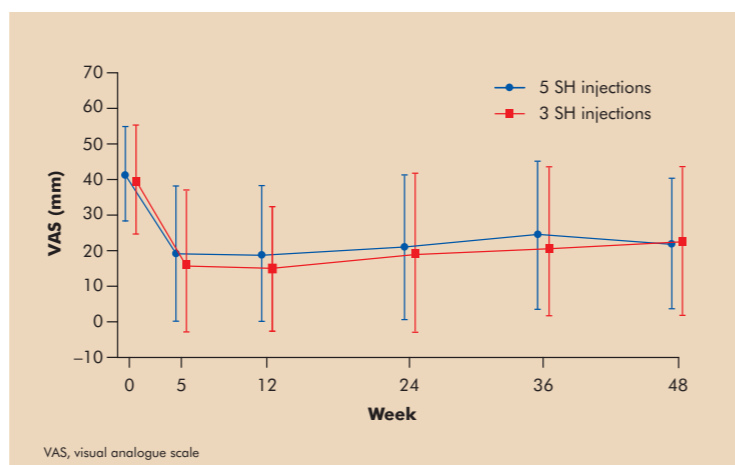


Figure 2: VAS stiffness on WOMAC B.

WOMAC B (mm VAS) mean ± SD	3-injection group	5-injection group
Baseline	39.4 ± 14.6	40.4 ± 12.7
Week 5	17.0 ± 19.2	18.9 ± 18.3
Week 12	15.1 ± 16.6	18.9 ± 18.3
Week 24	19.5 ± 21.6	20.6 ± 19.5
Week 36	20.8 ± 21.2	23.9 ± 20.0
Week 48	22.7 ± 19.9	21.7 ± 17.7

VAS, visual analogue scale

Table 3: Joint stiffness on WOMAC B.

## Physical function on WOMAC C

WOMAC C values decreased from baseline in a statistically significant manner in both groups ( $p < 0.001$ , ANOVA test) and remained at a stable level until week 48 (Table 4, Figure 3). No statistically significant inter-group difference was found.

WOMAC C (mm VAS) mean ± SD	3-injection group	5-injection group
Baseline	42.7 ± 21.8	43.2 ± 20.3
Week 5	17.3 ± 14.6	19.2 ± 14.7
Week 12	16.1 ± 14.0	19.6 ± 15.8
Week 24	19.5 ± 18.3	21.3 ± 16.8
Week 36	19.4 ± 17.9	23.6 ± 17.9
Week 48	21.0 ± 17.2	22.8 ± 15.2

VAS, visual analogue scale

Table 4: Physical function on WOMAC C.

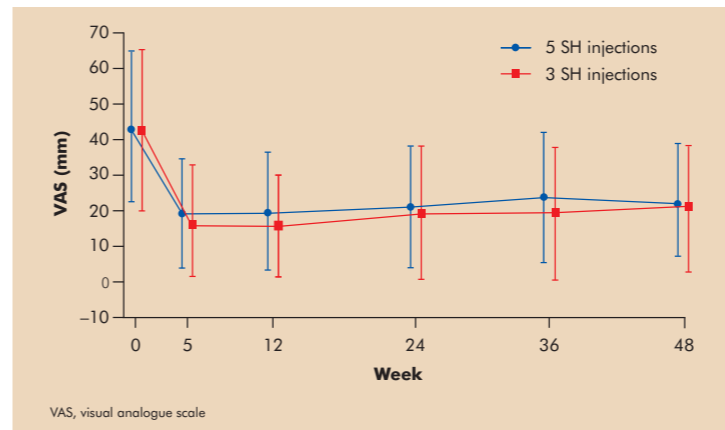


Figure 3: VAS physical function on WOMAC C.

## Global efficacy judgement

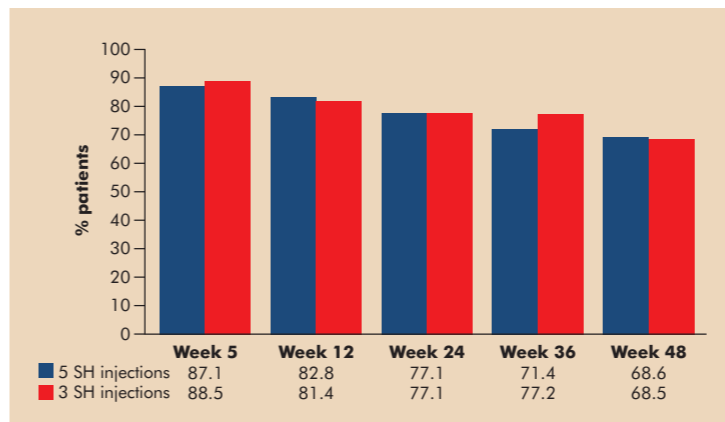


Figure 4: Global judgement of efficacy: % patients assessing the treatment as 'moderately effective' to 'very effective'.

Assessment	Efficacy judgement	3-injection group judgement by the investigator (n = 70) (n[%])	5-injection group judgement by the investigator (n = 70) (n[%])	3-injection group judgement by the patient (n = 70) (n[%])	5-injection group judgement by the patient (n = 70) (n[%])
Week 5	Not effective	2 (2.9%)	0	4 (5.7%)	1 (1.4%)
	Slightly effective	5 (7.1%)	7 (10.0%)	4 (5.7%)	8 (11.4%)
	Moderately effective	29 (41.4%)	34 (48.6%)	32 (45.7%)	33 (47.1%)
	Very effective	34 (48.6%)	29 (41.4%)	30 (42.9%)	28 (40.0%)
	NA	0	0	0	0
Week 12	Not effective	2 (2.9%)	4 (5.7%)	2 (2.9%)	4 (5.7%)
	Slightly effective	7 (10.0%)	5 (7.1%)	11 (15.7%)	8 (11.4%)
	Moderately effective	29 (41.4%)	32 (45.7%)	32 (45.7%)	33 (47.1%)
	Very effective	32 (45.7%)	29 (41.4%)	25 (35.7%)	25 (35.7%)
	NA	0	0	0	0
Week 24	Not effective	3 (4.3%)	7 (10%)	3 (4.3%)	7 (10.0%)
	Slightly effective	11 (15.7%)	6 (8.6%)	13 (18.6%)	7 (10.0%)
	Moderately effective	28 (40.0%)	30 (42.9%)	31 (44.3%)	30 (42.9%)
	Very effective	28 (40.0%)	25 (35.7%)	23 (32.9%)	24 (34.3%)
	NA	0	2 (2.9%)	0	2 (2.9%)
Week 36	Not effective	2 (2.9%)	8 (11.4%)	3 (4.3%)	7 (10.0%)
	Slightly effective	12 (17.1%)	6 (8.6%)	12 (17.1%)	12 (17.1%)
	Moderately effective	31 (44.3%)	35 (50%)	38 (54.3%)	30 (42.9%)
	Very effective	24 (34.3%)	20 (28.6%)	16 (22.9%)	20 (28.6%)
	NA	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
Week 48	Not effective	3 (4.3%)	4 (5.7%)	4 (5.7%)	6 (8.6%)
	Slightly effective	15 (21.4%)	8 (11.4%)	15 (21.4%)	11 (15.7%)
	Moderately effective	25 (35.7%)	35 (50%)	30 (42.9%)	32 (45.7%)
	Very effective	24 (34.3%)	18 (25.7%)	18 (25.7%)	16 (22.9%)
	NA	3 (4.3%)	5 (7.1%)	3 (4.3%)	5 (7.1%)

NA, not applicable

Table 5: Global judgement of efficacy by the investigator and patient.

## Treatment responders

	3-injection group n = 70	5-injection group n = 70
Week 5	49 (70.0%)	46 (65.7%)
Week 48	35 (50.0%)	31 (44.2%)

Table 6: Patients (n[%]) with improvement in WOMAC ≥20% compared with baseline.

## Safety

SH was well tolerated by the patients. Local adverse events (synovitis) were reported in two patients (one in each group). No serious adverse events occurred in this study.

## Conclusions

- The intra-articular administration of SH 1% for 3 or 5 injections was efficient in controlling pain and improving stiffness and physical function in patients with symptomatic knee osteoarthritis.
- The treatment effect persisted 12 months after the first injection in both groups.
- There was no statistically significant difference in the efficacy of a 3-injection course versus a 5-injection course. This could be explained in part by the presence of patients with more severe radiological grade in the 5-injection group.
- Further studies are needed to compare the efficacy of 3 versus 5 injections in patients with more restrictive symptomatic criteria.

## References

1. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis Rheum* 1986; 29(8):1039–49.
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3. Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. *Semin Arthritis Rheum* 1989; 18(4 Suppl 2):14–7.