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Effects of Viscoseal, a synovial fluid substitute, on recovery after arthroscopic partial meniscectomy and joint lavage

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Abstract This was a pilot, single blind, randomised, controlled study in patients requiring partial meniscectomy. The aim was to assess whether replacing the synovial fluid lost during arthroscopy with a hyaluronic acid-containing synovial fluid substitute (Viscoseal) would reduce the severity and duration of post-operative symptoms during the 4 weeks post-surgery, in comparison to the standard arthroscopy procedure alone. Fifty patients were randomly assigned to either undergo arthroscopic partial meniscectomy alone (control group: $n=25$) or to receive 10 ml Viscoseal into the joint at the end of the procedure (Viscoseal group: $n=25$). Forty patients (20 per group) completed the study. Despite the small patient population in this pilot study, some interesting results were obtained. On Day 1 after surgery, the mean values for pain at rest (VAS) increased in both groups but this increase was lower in the Viscoseal group (8.9 ± 23.1 mm) than in the standard therapy group (20.0 ± 25.9 mm) (Mann–Whitney statistic MW-S: $P=0.0525$) and remained in favour of Viscoseal for the first 3 days after surgery. Joint swelling decreased to a greater extent in the Viscoseal group with an observed superiority at Day 7 (MW-S: $P=0.1187$) and a proven superiority at Days 12 (MW-S: $P=0.015$) and 28 (MW-S: $P=0.0072$). Diclofenac intake was lower in the Viscoseal group from Day 3 to Day 28 with a proven superiority (LB-CI > 0.5) in favour of Viscoseal on Days 3 (MW-S: $P= 0.0093$), 4 (MW-S: $P= 0.0075$), and 7 (MW-S: $P = 0.0195$) indicating that the product had an NSAID-sparing effect. Viscoseal was safe and well-tolerated and no adverse reactions occurred during the study. These findings indicate that Viscoseal may be useful as a synovial fluid substitute after arthroscopy.

Keywords Arthroscopy · Synovial fluid substitute · Hyaluronic acid · Efficacy · Safety

Introduction

While the long-term benefits of arthroscopic partial meniscectomy have been established, the immediate post-operative period up to about 4 weeks after the intervention is characterised by symptoms including pain, impaired joint function and joint effusion [1]. Post-operative pain is usually greater in the first 24 h after surgery [1]. This pain could be due to several events including soft tissue injury during surgery and due to the liberation of free radicals, cytokines and other hyperalgesic substances that form an integral part of the inflammatory process. Although various analgesic techniques including systemic drugs, central and peripheral blocking agents, oral NSAIDs and intra-articular drug administration have been used to prevent or treat pain due to arthroscopic knee surgery, the analgesic effect is short lived [2]. In addition, the pres-

ence of post-operative joint effusion hampers rehabilitation and increases the time to recovery [3].

We hypothesised that the post-operative pain may also be due to the lack of synovial fluid in the joint because in a normal joint the synovial fluid acts as a lubricant and shock absorber and masks nociceptors thus allowing pain-free and fluid joint movement [4]. This is due to its content of hyaluronic acid (HA) which gives the synovial fluid its characteristic viscoelastic properties. A layer of HA also covers the cartilage and synovial membrane [5, 6] and protects the underlying tissues from damage due to free radicals and other destructive elements [7]. During arthroscopy, joint irrigation results in the removal of the synovial fluid and this protective HA layer. On completion of the arthroscopic procedure, most of the remaining lavage solution is removed by joint manipulation. However, some may remain and both saline and Ringer lactate have been shown to be detrimental to chondrocytes if left in contact with the cartilage [8]. In addition, cartilage metabolism appears to be damaged for up to 2 weeks after experimental irrigation in rabbit osteoarthritic knees [9].

We therefore carried out this study to determine whether the use of a hyaluronic acid-containing synovial fluid substitute (Viscoseal, TRB Chemedica AG, Munich, Germany) after arthroscopic partial meniscectomy would reduce the incidence and severity of the above-mentioned post-surgical symptoms and result in an earlier return of joint function, compared to patients undergoing standard arthroscopic partial meniscectomy alone.

Patients and methods

This was an investigator-initiated, pilot, single blind, randomised, controlled, feasibility study. Male and female patients, between 18 years and 60 years of age, with meniscal pathology requiring arthroscopic intervention and having provided signed informed consent to participate in this study were recruited. The main exclusion criteria are presented in Table 1.

Eligible patients were asked not to take any analgesics or anti-inflammatory medication during the 2 days pre-surgery. Baseline data for the assessment parameters were collected just prior to surgery on Day 0. All patients received spinal anaesthesia (Bupivacaine 4.5% hyperbar, 7–10 mg) prior to arthroscopy and were randomised to the treatment groups during arthroscopy once the inclusion and exclusion criteria were confirmed. Joint irrigation was performed with the assistance of an arthroscopic pump-system (FMS) using 0.9% NaCl (Baxter Laboratories) solution at 30°C. At the end of the arthroscopic procedure and final joint lavage all patients had a Redon drain put into the operated knee for one day in order to evacuate eventual post-operative fluid and haemarthrosis. Patients assigned to the control group received no further treatment after final lavage (standard therapy group) while those in the other group received 10 ml Viscoseal into the joint through the outflow cannula after final joint lavage. In this group of patients, the Redon drain was blocked after the administration of Viscoseal and the joint manipulated. The Redon drain was unblocked after approximately 15–20 min. No post-operative intra-articular anaesthesia was used in either group to avoid bias in data interpretation. However, patients had access to diclofenac 50 mg tablets in case of unbearable pain. All other medications (anti-depressants, tranquillisers, etc.) that could interfere with the assessment of pain were not permitted during the study. Prior to discharge on the day after surgery, patients were given a diary and an explanation in the self-use of a 100 mm visual analogue scale (VAS) for pain assessment. They were asked to record their level of pain at rest (VAS) at about the same time each day and to record the number of diclofenac tablets taken daily from the day of discharge up to the first follow-up visit on day 7 after surgery. After removal of the drain, all patients followed a rehabilitation protocol for meniscectomy and were asked to return for assessments on days 7, 12 and 28. At each visit they were questioned on any adverse events they might have experienced since their last visit. Their diclofenac intake since the previous visit was also recorded.

A total of 50 patients with meniscal pathology requiring arthroscopic intervention were recruited. Two patients in each group cancelled their arthroscopy for unknown reasons, while three patients in each group presented exclusion criteria during arthroscopy and were not randomised. Hence, 40 eligible patients were randomly assigned to two groups during arthroscopy using a computer-generated randomisation table.

Table 1 Main exclusion criteria

Traumatic meniscal pathology associated with ligament-injury;
Previous surgery on affected knee;
Progressive joint disease (osteoarthritis of the affected knee);
Accompanying hip osteoarthritis of sufficient severity to interfere with the functional assessment of the knee;
Known or suspected infection of the affected joint;
Painful knee conditions other than osteoarthritis, such as rheumatoid diseases (RA, gout);
Other joint diseases or previous management of the operated knee that might interfere with the assessment of the meniscectomy.

Test product

The test product, Viscoseal, is registered as a medical device in the European Union and other countries including Switzerland for use as a synovial fluid substitute after arthroscopy. It contains 0.5% sodium hyaluronate in an isotonic buffered solution. This concentration of sodium hyaluronate is similar to the concentration of hyaluronic acid present in normal synovial fluid [10]. The hyaluronic acid in Viscoseal is a specific, highly purified fraction obtained by bacterial fermentation (*S. zooepidemicus*) and is devoid of animal proteins. The solution is sufficiently viscous (intrinsic viscosity 15 dl/g) to act as a synovial fluid substitute after arthroscopy. Viscoseal from batch number 011004 was used in this study.

Evaluation parameters

The following parameters were assessed at screening, just before surgery on day 0 and then on days 7, 12 and 28.

- Pain at rest, using a 100-mm VAS (0 mm = no pain, 100 mm = extreme pain).
- Pain on squatting, using a 100-mm VAS (0 mm = no pain, 100 mm = extreme pain).
- Joint swelling, evaluated according to a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).
- Joint function using the Lysholm Score [11].
- Daily activities using a modified Musculoskeletal Outcomes Data Evaluation and Management System (MODEMS) score [12]. Only parts 20 (a–j) were used.
- Analgesic consumption (number of diclofenac 50 mg tablets taken per day).
- Efficacy judgement expressed by the patients and the investigator using a 5-point scale (0 = nil; 1 = poor; 2 = moderate; 3 = good; 4 = very good).

For the evaluation of safety, patients were questioned on any adverse events they might have experienced since their last visit.

Statistical methods

As this was a pilot study no sample-size calculation was necessary. We felt that 40 patients (20 per group) completing the study would be sufficient to evaluate the performance profile of the test product in terms of efficacy and safety. Demographic data were analysed using the Mann–Whitney *U* test for homogeneity analysis of the two groups (two tailed, alpha = 0.1). For the efficacy parameters, mean and median values and the MW-S statistic and related one-sided 97.5% Confidence Interval (CI) were calculated using the Mann-Whitney *U* test (one sided, alpha = 0.025) for all available time-points. Probability *P*-values are included only as a descriptive interpretation. The statistical software TESTIMATE from IDV (Gauting) was used for the analysis.

Results

All patients completed the study. The two groups were homogeneous for age and sex (Table 2). However, mean body weights were higher in the Viscoseal group and more patients in this group (16/20) presented joint effusion at baseline compared to the control group (12/20).

Pain at rest

At baseline, the mean value for pain at rest was 24.9 ± 14.8 mm (median: 26.0 ± 24.0 mm) in the Viscoseal group and 30.5 ± 19.3 mm (median: 27.0 ± 22.5 mm) in the control group. The Mann–Whitney *U* test showed that there was a slight but non-significant difference between groups at baseline. On day 1 after surgery, pain

Table 2 Demographic characteristics of the patients included into the study

	Viscoseal group	Standard therapy group
Age (mean ± SD) years	47.4 ± 8.9	46.4 ± 8.6
Sex: M/F	16/4	16/4
Weight (mean ± SD) kg	78.5 ± 10.0	72.8 ± 11.6
Operated knee (R/L)	9/11	12/8
Joint effusion present	16	12
Lysholm score	55.3 ± 20.2	54.3 ± 17.3

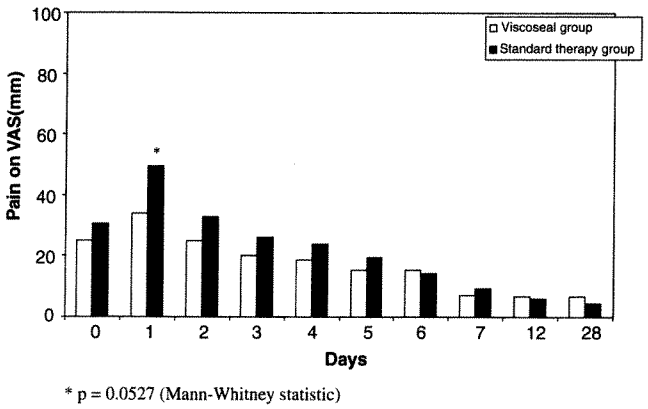

Fig. 1 Pain at rest (mm VAS). *$P = 0.0527$ (Mann–Whitney statistic)

increased by 20.0 ± 25.9 mm in the standard therapy group and by only 8.9 ± 23.1 mm in the Viscoseal group compared to baseline values. Viscoseal was superior to standard therapy at this time point (MW-S: $P = 0.0525$). The trend remained in favour of the Viscoseal group up to day 5 but there were no significant differences between groups from day 2 onwards (Fig. 1).

Joint swelling

The values obtained for joint swelling during the study are presented in Table 3. The two groups were not homogeneous for this parameter at baseline as more patients in the Viscoseal group (16/20) had joint effusion compared to the control group (12/20). In addition, more patients in the Viscoseal group (55%) had moderate to severe knee swelling compared to the control group (25%). In the Viscoseal group this value decreased to 27% at day 7 and 10% at day 12 and, by day 28, no patient presented moderate to severe swelling. In contrast, 25% of the patients in the control group had moderate to severe joint swelling at day 7 and 20% on day 12 and day 28, respectively. At the end of the study, 12/20 (60%) patients in the Viscoseal group had no joint swelling compared to 7/20 (35%) in the control group. An observed superiority in favour of the Viscoseal group was found at day 7 (MW-S: $P = 0.1187$) while a proven superiority (Lower Bound of the Confidence Interval: LB-CI > 0.5) was found at days 12 (MW-S: $P = 0.015$) and 28 (MW-S: $P = 0.0072$). The Mann–Whitney statistic and confidence interval (97.5% - one-sided) are presented in Fig. 2.

Diclofenac consumption

Diclofenac consumption was slightly higher in the Viscoseal group on days 1 and 2 after surgery (Table 4). However, from day 3 until the end of the study period (day 28), intake was lower in the Viscoseal group compared to the control group. A proven superiority (LB-CI > 0.5) was observed in favour of the Viscoseal group at days 3 (MW-S: $P = 0.0093$), 4 (MW-S: $P = 0.0075$) and 7 (MW-S: $P = 0.0195$) while an observed superiority was found at days 5 (MW-S: $P = 0.0767$), 6 (MW-S: $P = 0.2217$), 12 (MW-S: $P = 0.0906$) and 28 (MW-S: $P = 0.2283$; Fig. 3). This indicates that instilling Viscoseal into the joint after final lavage resulted in an NSAID-sparing effect.

Pain on squatting

The values for pain on squatting obtained at the selection visit were taken as the baseline as most patients found it too painful to perform this assessment just before arthroscopy on day 0. At day 7, pain on

Table 3 Severity of joint swelling according to a 4-point score (0 = none, 3 = severe) (number of patients and percent patients)

	Day 0 (prior to surgery)		Day 7		Day 12		Day 28	
	Viscoseal, *n* (%)	Control (%)	Viscoseal (%)	Control (%)	Viscoseal (%)	Control (%)	Viscoseal (%)	Control (%)
None	4 (20)	8 (40)	5 (26)	5 (25)	9 (45)	4 (20)	12 (60)	7 (35)
Mild	5 (25)	7 (35)	9 (47)	10 (50)	9 (45)	12 (60)	8 (40)	9 (45)
Moderate	10 (50)	3 (15)	4 (21)	3 (15)	2 (10)	2 (10)	0	3 (15)
Severe	1 (5)	2 (10)	1 (5)	2 (10)	0	2 (10)	0	1 (5)

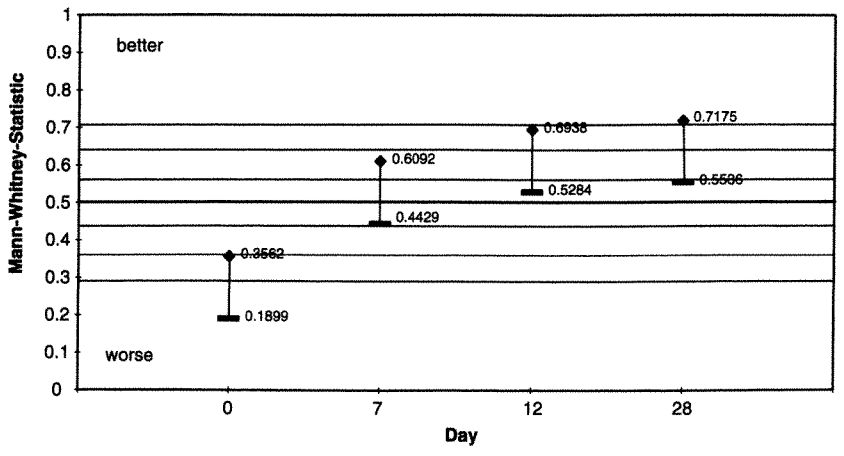

Fig. 2 Joint swelling in the target joint. Mann–Whitney statistic and confidence interval (97.5%-CI, one-sided). Viscoseal treatment was superior to standard therapy at all time points after surgery with a proven superiority on days 12 and 28 (LB-CI > 0.5)

Table 4 Diclofenac intake during the study (mean number/day)

Day	1	2	3	4	5	6	7	12	28
Viscoseal ($n=20$)	2.2 ± 1.66	1.8 ± 1.77	1.1 ± 1.0[a]	1.0 ± 0.94[a]	1.1 ± 1.05	1.1 ± 1.10	1.1 ± 0.72[a]	0.31 ± 0.53	0.1 ± 0.31
Control	1.9 ± 1.05	1.7 ± 1.05	1.8 ± 1.15	1.6 ± 1.12	1.4 ± 1.17	1.3 ± 1.16	1.3 ± 0.97	0.70 ± 0.90	0.2 ± 0.37

[a] Proven superiority in favour of Viscoseal treatment ($P=0.0093$) on day 3, ($P=0.0075$) on day 4 and ($P=0.0195$) on day 7. There was observed superiority in favour of Viscoseal treatment on days 5 ($P=0.0767$), 6 ($P=0.2217$), 12 ($P=0.0906$) and 28 ($P=0.2283$) (Mann–Whitney statistic)

squatting decreased by 28.1 ± 26.8 mm (median: 18.5 ± 20 mm) in the Viscoseal group and by only 10.8 ± 38.2 mm (median: 10.5 ± 72 mm) in the control group (Fig. 4). There was an observed superiority in favour of the Viscoseal group compared to standard therapy at this time point (MW-S:$P=0.2184$). The difference between groups decreased with time but patients in the Viscoseal group had less pain on squatting throughout the study.

Lysholm score

Both groups had similar values for the Lysholm score at baseline (Table 2). Function improved in the Viscoseal group throughout the study. At day 7, there was a proven non-inferiority of the Viscoseal group (LB-CI > 0.36; MW-S: $P = 0.243$). This difference decreased at days 12 and 28 and there were no differences between groups at these time points. The observed MW-S statistic was slightly higher than 0.5 over all time-points.

Daily activities

Both groups showed similar values for daily activities at baseline. However, patients in the Viscoseal group showed a greater improvement in daily activities at day 7 and with an observed superiority compared to standard therapy at this time-point (MW-S: $P=0.2294$). Both groups had similar results on day 12 but an observed superiority was found for Viscoseal on day 28 (MW-S > 0.5 and LB-CI > 0.36; $P=0.3192$).

General evaluation by the patient

The general evaluation of treatment efficacy expressed by the patients showed a greater improvement in the Viscoseal group compared to the control group at the different assessment times. A proven superiority was found in favour of the Viscoseal group on days 7 (MW-S: $P=0.0229$) and 12 (MW-S: $P=0.0022$) and non-inferiority at day 28 (MW-S: $P=0.3862$) post-surgery (Fig. 5). Although this is a subjective assessment, the patients did not know which treatment they had received in this single-blind study. Hence their evaluation of treatment efficacy was undertaken under blinded conditions.

Safety

No serious or unexpected adverse events were reported in either group. Viscoseal was well -tolerated by all patients.

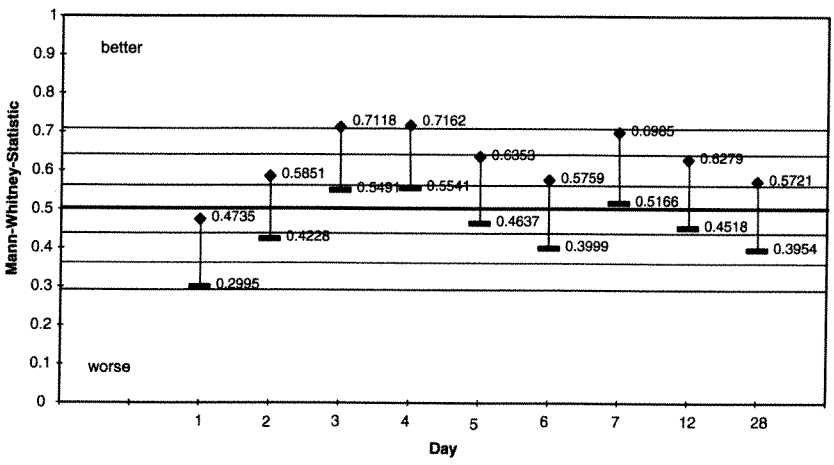

Fig. 3 Diclofenac consumption (tabs/day). Mann–Whitney statistic and confidence interval (97.5%-CI, one-sided)

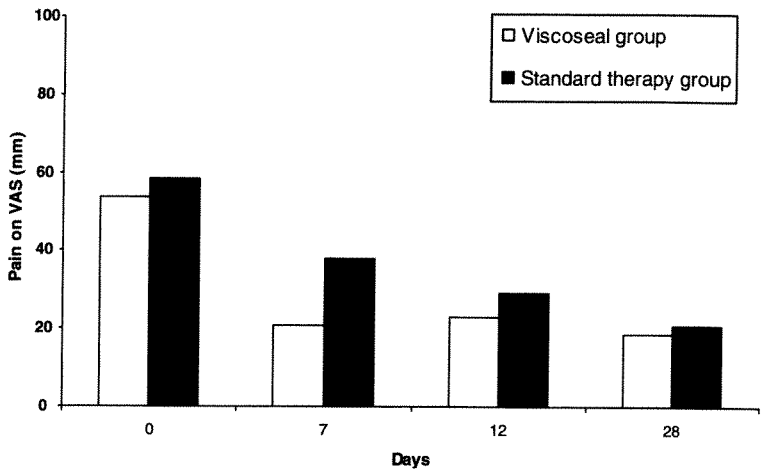

Fig. 4 Pain on squatting (mm VAS). *Observed superiority in favour of the Viscoseal group compared to standard therapy on day 7 (MW-S: $P=0.2184$)

Discussion

Post-operative pain and joint effusion following arthroscopic surgery are often a disabling problem and a major obstacle to rehabilitation and recovery. Arthroscopic meniscectomy may cause enough pain and joint swelling to delay rehabilitation and return to work for up to 2 weeks after surgery [13] while quantitative evaluations have shown that recovery is still incomplete 4–8 weeks post-surgery [14]. Effective pain management and a reduction in joint effusion would therefore not only improve recovery but also contribute to early rehabilitation [2]. Current therapeutic schemes for pain control have shown inconsistent results [15–17] or short-term effects lasting from a few hours to about 2 days post-surgery [18, 19]. NSAIDs have been used effectively to treat joint effusions [20] but the well-known gastric side effects limit their use [21].

In this study we used a sterile, HA-based synovial fluid substitute (Viscoseal) after final irrigation in one group of patients. Viscoseal contains 0.5% HA, which is close to the concentration of HA present in normal synovial fluid (0.2–0.4%) [10]. The rationale for using an HA-containing synovial fluid substitute is due to the fact that HA plays an important role in the joint. HA is secreted continuously into the joint space by the synovial membrane where it comprises the major macro-molecular part of the synovial fluid. It is responsible for the unique viscoelastic properties of the synovial fluid and is highly concentrated at the surface of the articular cartilage and the superficial layers of the synovial membranes [17, 22, 23]. In the synovial fluid, HA acts as a lubricant and a shock absorber. Due to the meshwork it forms in aqueous solutions [24], it acts as a semi-permeable barrier regulating metabolic exchanges between the cartilage and the synovial fluid, as a cell traffic controlling agent and as a viscoelastic shield around synoviocytes and adjacent nerve endings shielding the latter from nociceptive substances [23]. Through its molecular sieve effect, HA hinders the free movement of lytic enzymes, inflamma-

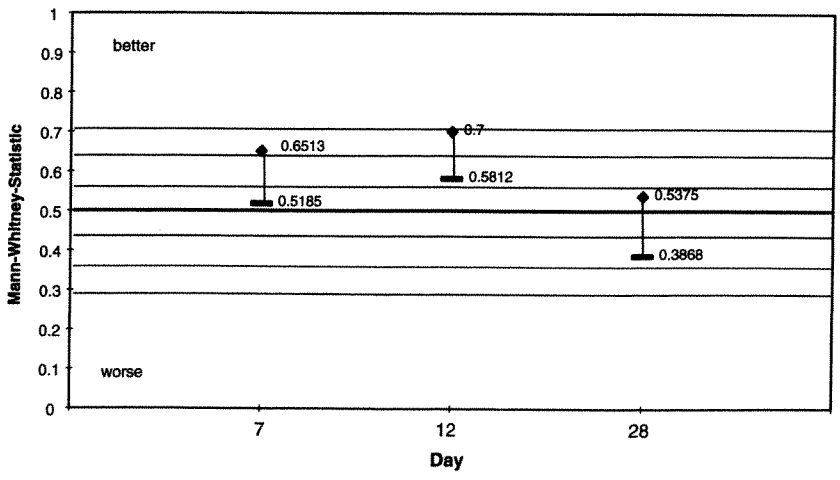

Fig. 5 General evaluation by the patient. Mann–Whitney statistic and confidence interval (97.5%-CI, one-sided)

tion mediators and inflammatory cells in the synovial fluid [22]. Several well-controlled clinical studies [3, 25] demonstrated that the intra-articular administration of sodium hyaluronate significantly reduced pain and improved joint function in patients with knee osteoarthritis. In addition, Bulstra et al. [26] showed that irrigation fluids damage cartilage metabolism for up to 2 weeks after irrigation and that HA administration restores this metabolism to the normal levels [9]. This provides further support for the use of a hyaluronic acid-containing synovial fluid substitute following arthroscopy.

Based on published data, we hypothesised that the HA present in Viscoseal would bind to HA-binding proteins on the cartilage surface and HA receptors on the synovial membrane [22] and thus recreate the barrier effect protecting underlying tissues from damage due to free radicals and pro-inflammatory cytokines liberated during the inflammatory process following surgery. In addition, the HA present in Viscoseal would shield the nociceptors and its meshwork would prevent the flow of pro-inflammatory molecules. Clinically, this would manifest as a reduction in pain and joint effusion with a subsequent NSAID-sparing effect, an improvement in joint function and a more rapid production of endogenous HA [27, 28].

Despite the small patient population in our study, the results appear to confirm our hypothesis and demonstrate that, compared to standard therapy, synovial fluid replacement with Viscoseal in patients undergoing arthroscopic partial meniscectomy caused a reduction in pain and joint effusion together with an improvement in daily activities. In this study we used both, a direct subjective measurement of pain (100 mm VAS) and indirect measure (analgesic consumption). In addition, the patients did not know what treatment they had received. Pain at rest on day 1 after surgery showed a lower increase (8.9 mm on the VAS) in the Viscoseal group compared to the control group (20.0 mm on the VAS) with the trend remaining in favour of Viscoseal for the first 3 days after surgery. Although diclofenac intake was slightly higher in the Viscoseal group on days 1 and 2, this decreased from day 3 to day 28 with a proven superiority in favour of the Viscoseal group on days 3, 4 and 7 indicating an NSAID-sparing effect.

Joint swelling also decreased rapidly during the study. By day 28, 60% of patients in the Viscoseal group had no swelling compared to 35% in the standard group (MW-S: $P=0.0072$). The Viscoseal group was superior to standard therapy at all times after surgery with a proven superiority at days 12 (MW-S: $P=0.015$) and 28 (MW-S: $P=0.0072$). This corresponded well with the increased capacity for performing daily activities observed in the Viscoseal group, which was greater on days 7 and 28 compared to the standard therapy group. The effect of intra-articular HA on joint swelling has already been observed in clinical studies in knee osteoarthritis [29]. Although there was a greater intake of diclofenac in the control group from day 3 onwards, this did not reduce joint swelling to the extent seen in the Viscoseal group.

Squatting is a function of painless or fairly painless joint movement. Pain on squatting decreased earlier in the Viscoseal group with an observed superiority on day 7 compared to the control group (MW-S: $P=0.2184$).

No significant between-group differences were observed for the Lysholm Score during the study. Although this score was designed to assess joint function after ligament repair, a much more invasive procedure, we tested its suitability in this study as no other appropriate scale to assess joint function after partial meniscectomy was available. Based on our results, we do not believe the Lysholm Score is suitable to assess joint function after partial meniscectomy.

The above results are interesting given that Viscoseal remained in the joint for only a short period of time after which most of the product most probably drained out of the joint through the redon drain. Thus, we can speculate that its presence in the joint was sufficient to coat the cartilage and synovial membrane, recreating the barrier effect. In addition, as the half-life of intra-articularly administered non-chemically modified sodium hyaluronate is about 17 h [30] it is possible that the HA in Viscoseal stimulated the earlier synthesis of endogenous HA. Indeed, it has been shown that the addition of exogenous HA to cultures of human osteoarthritic synoviocytes stimulated the synthesis of endogenous HA [27] and hence it is plausible that using a HA-based synovial fluid substitute would lead to an earlier reformation of synovial fluid.

This short-term (28-day) study demonstrated that patients in the Viscoseal group had a more rapid recovery from arthroscopic partial meniscectomy with less pain, less effusion, a lower intake of diclofenac and an earlier improvement in joint function, as shown by the earlier improvement in daily activities and pain on squatting, compared to the standard therapy group. The NSAID-sparing effect and faster recovery in activities of daily living indicates that the benefit–cost ratio is in favour of Viscoseal.

Recently, Hempfling [31] reported the results of a prospective, randomised, masked-observer clinical study comparing the long-term (12 months) effects of joint lavage alone and joint lavage followed by administration of Viscoseal in 80 patients with persistent pain (> 50 mm VAS for at least 6 months prior to the start of the study) due to degenerative knee OA. A similar number of patients in both groups also underwent cartilage debridement. Patients in the Viscoseal group received a single administration of 10 ml Viscoseal after final lavage and no drain was placed in the operated joint post-arthroscopy. At 12 months after surgery, 75% of the patients in the Viscoseal group and 42% in the control group had no pain on walking 100 m while 56% in the Viscoseal group

and 24% in the control group had no night pain. Finally, 27 patients (75%) in the Viscoseal group and 19 (50%) in the control group had recovered or had clearly improved. No adverse events due to Viscoseal were reported. The use of Viscoseal should be investigated in other knee arthroscopy procedures such as ligament repair, cartilage repair procedure or meniscal tissue repair.

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