Effect of Sodium Hyaluronate on Recovery after Arthroscopic Knee Surgery

Sanjeev Anand, FRCS (Tr&Orth)[1]   Kiran Singisetti, FRCS (Tr&Orth)[2]   Koppa N. Srikanth, FRCS (Tr&Orth)[3]
Cathy Bamforth[4]   Theophilus Asumu, FRCS (Tr&Orth)[5]   Keyur Buch, FRCS (Tr&Orth)[5]

[1] Department of Trauma and Orthopaedics, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
[2] Department of Trauma and Orthopaedics, University Hospital of North Tees, Stockton, United Kingdom
[3] Department of Trauma and Orthopaedics, Sarathi Superspeciality Orthopaedic Centre, Bangalore, India
[4] Department of Physiotherapy, The Royal Oldham Hospital, Oldham, United Kingdom
[5] Department of Trauma and Orthopaedics, The Royal Oldham Hospital, Oldham, United Kingdom

Address for correspondence Kiran Singisetti, FRCS (Tr&Orth), Department of Trauma and Orthopaedics, University Hospital of North Tees, Stockton-on-Tees TS19 8PE, United Kingdom (e-mail: kiransingisetti@gmail.com).

Abstract

The aim of this study was to evaluate the effect of a single immediate postoperative instillation of 10 mL of sodium hyaluronate (Viscoseal) into the knee following arthroscopy. A single-center, prospective, randomized, controlled study was undertaken. Consenting knee arthroscopy patients were randomized into two groups following surgery: the study group received 10 mL of sodium hyaluronate intra-articularly, while the control group received an intra-articular instillation of 10 mL of Bupivacaine. Pre- and postoperative visual analogue scale scores for pain and Western Ontario and McMaster Universities (WOMAC) scores for knee function were obtained. Overall, 48 patients under the care of a single surgeon were randomized into two groups of 24. There were no statistically significant demographic differences at baseline. Three patients were lost to follow-up. There was a statistically significant difference in pain scores favoring the study group compared with the control group at 3 and 6 weeks postoperatively ($p < 0.05$), and a statistically significant difference in WOMAC scores favoring the study group compared with the control group at 3 and 6 weeks postoperatively ($p = 0.01$). Synovial fluid replacement with sodium hyaluronate following arthroscopic knee surgery conferred statistically significant improvements in pain and function scores compared with Bupivacaine in the short term (3–6 weeks).

Keywords
► knee arthroscopy
► sodium hyaluronate
► randomized trial

Knee arthroscopy is a commonly performed procedure for the assessment and treatment of various knee conditions. The incidence of complications related to this procedure is low (0.56–1.68%) but patients may sometimes experience pain, swelling, and stiffness in the early postoperative period.[1–3] Although these postoperative issues may be attributed to a large extent to the surgical trauma, various reports have commented on the negative influence of irrigating fluid (saline) used during arthroscopy.[4–6] The irrigating fluid flushes out normal joint synovial fluid. It may take several days for the synovial fluid to be regenerated, although there are no published studies that offer conclusive data on exactly when the intra-articular fluid is restored to its normative consistency following arthroscopic washout. Irrigation fluids

have also been shown to have a detrimental effect on the metabolism of articular cartilage. This inhibition of cartilage metabolism by transient cellular stress can be reversed by a single injection of sodium hyaluronate.[7] There are studies which demonstrate that injecting hyaluronic acid (HA), also commonly referred to as sodium hyaluronate, into the knee leads to a significant decrease in pain and the utilization of rescue pain medication compared with saline.[8]

Sodium hyaluronate is an unbranched high-molecular-weight polysaccharide belonging to glycosaminoglycan group which is widely used in the treatment of osteoarthritic joints.[9] Its role is to maintain the structural and functional characteristics of the extracellular matrix of the cartilage and biological fluids. HA is the major hydrodynamic nonprotein component of joint synovial fluid. Its viscoelastic properties confer shock absorbing and lubricating abilities to synovial fluid, while its macromolecular size and amphiphilic nature serve to retain fluid in the joint cavity during articulation. HA also reduces the degradation and enhances the synthesis of aggrecan in joint tissues, a property that offers the symptomatic benefit to patients with knee osteoarthritis (OA) via its anti-inflammatory effect.[10] By modulating the activities of proinflammatory mediators released by activated synovial cells, the HA may improve the symptoms of OA. The biopharmacological activities of HA could account for the reported long-term clinical benefits associated with the intra-articular injection of HA (viscosupplementation) as a therapy for OA. The benefits have been reported to last from a few months to years.[11,12]

In addition, there are data which demonstrate that the injection of exogenous HA promotes tissue healing and protects the articular cartilage and synovial membrane from damage following the experimental initiation of joint disease.[13,14] HA is also known to reduce levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in the synovial fluid during the treatment of patients with knee osteoarthritis, thus exerting a marked anti-inflammatory effect.[15]

The infiltration of joints other than the knee with exogenous HA following arthroscopy has resulted in significant benefit to the patient with no reported complications.[16,17] There have been many studies supporting the benefits of HA in treating the symptoms of OA of the knee, but there is a paucity of literature on the use of HA following knee arthroscopy.[18–21] The aim of this study was to determine the effect of a single, immediately postoperative intra-articular infiltration of 10 mL sodium hyaluronate (Viscoseal, TRB Chemedica, TRB Chemedica AG, Haar/Munich, Germany; 0.5% sodium hyaluronate solution in a 10 mL single use container) on pain and joint function following knee arthroscopy.

Patients and Methods

The study was a prospective, randomized, controlled, single center, single surgeon clinical trial. The local hospital ethics and research committee approved it. The study was conducted over a period of 3 years to assess whether any differences in outcome could be attributed to using sodium hyaluronate (Viscoseal) following knee arthroscopy as opposed to Bupivacaine (standard practice).

Inclusion Criteria
Patients aged 18 years or older, who had a clinical indication for knee arthroscopy, for example, early OA with mechanical symptoms or young patients with meniscal tears, were invited to participate. Early OA was denominated for the purposes of this study as grade 1 or 2 on the Kellgren–Lawrence grading system. All participants granted informed consent.

Exclusion Criteria
Patients were excluded if they had anterior knee pain; severe OA, crystalline or inflammatory arthropathy; ligamentous instability on clinical examination; local infection; known hypersensitivity to Bupivacaine, HA or other constituents of Viscoseal. Patients with preoperative X-ray findings of moderate-to-complete joint space narrowing and/or subchondral sclerosis were excluded from the study.

Study Procedure
All patients underwent knee arthroscopic assessment followed by treatment directed to their pathology. All procedures were performed under general anesthesia and nerve blocks were not used. Similar arthroscopy portals were used in all the procedures. Meniscal tears were trimmed to a stable edge. Loose debris and articular cartilage flaps were removed. No chondroplasty, abrasion arthroplasty, or microfractures were performed. Patients were randomized into one of the two groups toward the end of their arthroscopy. Randomization to study (Viscoseal) or control (Bupivacaine) groups was determined via the use of a computerized random number algorithm to create 50 cards that were placed in sealed serially numbered opaque envelopes. Following arthroscopy, a theater practitioner who was not directly associated with the trial opened the envelopes in the theater. Opening of the envelope was considered to be the point of enrolment. The control group had 10 mL of 0.5% Bupivacaine injected into the joint after the procedure, following evacuation of saline (as was the standard practice), while the study group had 10 mL of sodium hyaluronate injected into the joint, following saline evacuation.

The needle for injection of both study and control fluid was placed via a superolateral approach under arthroscopic visualization to ensure correct placement. The fluid was injected after evacuation of saline in both groups of patients. The patient's allocated group was not revealed in the case notes and patients were kept blinded to their ultimate allocation. The assessor blinding was achieved by having a physiotherapist, unaware of the postoperative agent injected, examine the patient's knee, and fill the questionnaires for the clinical assessment. The surgeon was aware of the product administered, but he was blinded to the patient's allocation until the end of the surgery, when the product was injected into the knee. The surgeon did not participate in subsequent data collection and patient assessment.

All patients followed the same postoperative physiotherapy regimen. No walking aids were used and a graduated exercise program was initiated. Patients were given Co-dydramol (dihydrocodeine tartrate, 10 mg, plus paracetamol, 500 mg) as a rescue medication for pain control, and no anti-inflammatory medication was issued or allowed. Patients were asked to record the number of tablets used.

End Points

Outcome measures were recorded by patients who were given questionnaires to assess their pain and function at the time of admission and at various times during the follow-up: 2 hours, day 1, day 7, 3 weeks, and 6 weeks following their operation. The surgical team did not participate in the collection of the outcome data.

Primary Outcome Measures

Primary outcome measures include the patient's self-assessment of pain on a 10 cm visual analogue scale (VAS) at rest, on movement, and on weight bearing.

Secondary Outcome Measures

Secondary outcome measures include the Western Ontario and McMaster Universities (WOMAC) score questionnaire to assess pain, stiffness, and function; 12-Item Short Form Health Survey (SF-12) general health questionnaire and use of rescue medication (Co-dydramol). All measures were recorded preoperatively and at 2 hours, day 1, day 7, 3 weeks, and 6 weeks postoperatively except for SF-12 scores, which were recorded preoperatively and at 6 weeks following surgery. Finally, at 6 weeks postsurgery, patients reported with their questionnaires to the clinic, where a trained physiotherapist, who was blinded to the randomization, recorded the outcome scores. At this time, the extent of any knee swelling was also assessed and recorded on a five-point scale (none: no effusion; mild: swipe test positive; moderate: parapatellar fullness/patellar tap present; severe: suprapatellar swelling; and extreme: tense suprapatellar pouch). The physiotherapist also assessed the efficacy of pain relief and scored it on a five-point scale (1: no pain; 2: mild pain; 3: moderate; 4: severe pain; and 5: extreme pain).

Statistics

Power analysis had suggested at least 22 patients would be required in each group (44 in total) to achieve 90% power, assuming a difference in pain between groups of 1 cm on the VAS and a standard deviation (SD) of 1 cm in each group. Power analysis was based on the primary measure of outcome (VAS score). It was deemed impractical to power the study, for each of the secondary outcome measures. Outcome measures were analyzed using the difference of means test (unpaired two-tailed t-test; significance at $p < 0.05$ and chi-square test to determine the homogeneity of variance). StatsDirect 2006 (StatsDirect Ltd, Altrincham, Cheshire, United Kingdom) was used for all analysis; power analysis was based on the formula derived from StatsDirect. Data were anonymized and analyzed by an independent researcher on

an intention-to-treat basis. A nonparametric test (Mann–Whitney test) was performed for sensitivity analysis as to the distributions of the VAS scores, which were positively skewed.

Ethics

All human studies have been approved by the appropriate ethics committee (LREC 02/OL/58) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons involved in the study gave their informed consent before their inclusion in the study.

Results

A total of 72 patients were invited to participate, of whom 48 were consented and enrolled into the study. A total of 24 patients were assigned to each group after randomization. Follow-up data were available for 45 patients (23 in the study group and 22 in the control group). Three patients were lost to follow-up (►Fig. 1). Baseline demographic data are shown in ►Table 1. No statistically significant differences were observed between the two groups with regard to age, gender, or preoperative pain and function levels (as observed by VAS scores at rest, weight bearing and movement, SF-12 scores, and WOMAC scores). Both the groups had similar distribution of pathology and treatment procedures (►Table 1). There was a significant reduction of pain as evidenced by VAS scores on weight bearing in the study group compared with the control group at weeks 3 and 6 postoperatively ($p < 0.05$; ►Fig. 2). The outcomes at 6 weeks are summarized in ►Table 2. The primary outcome, that is, the VAS score for pain on weight bearing at 6 weeks decreased by a mean of 1.3 cm in the study group compared with control group (Viscoseal, −0.8; SD, −1.4; Bupivacaine, −2.1; SD, −1.8; $p = 0.01$, see ►Fig. 2). The VAS score at rest and movement achieved improvement between 3 and 6 weeks in the study group. There was no statistically significant difference in pain relief immediately following the operation between the two groups as shown by VAS scores taken at the time of discharge ($p = 0.60$). Significant improvement in SF-12 was seen in both the groups following arthroscopy (►Table 2). There was significant improvement in WOMAC scores in the study group compared with the control at 3 and 6 weeks (Viscoseal, −13.7; SD, −10.4; Bupivacaine, −22.9; SD, −13.1; $p = 0.01$, see ►Fig. 3). At 6 weeks SF-12 scores were significantly better ($p = 0.04$) in the study group compared with the control group (►Table 2). When further subgroup analysis of the data was undertaken, improvement in SF-12 and WOMAC scores were seen in the study group compared with the control group, even after excluding patients with OA (12 patients with early OA in the study group and 11 patients with early OA in the control group). The analgesic consumption by patients in the study group was significantly less than those in the control group at 3 and 6 weeks postoperatively ($p < 0.02$). At baseline, both groups were taking a similar amount of analgesics (►Table 2). There was also a significant difference in target joint swelling
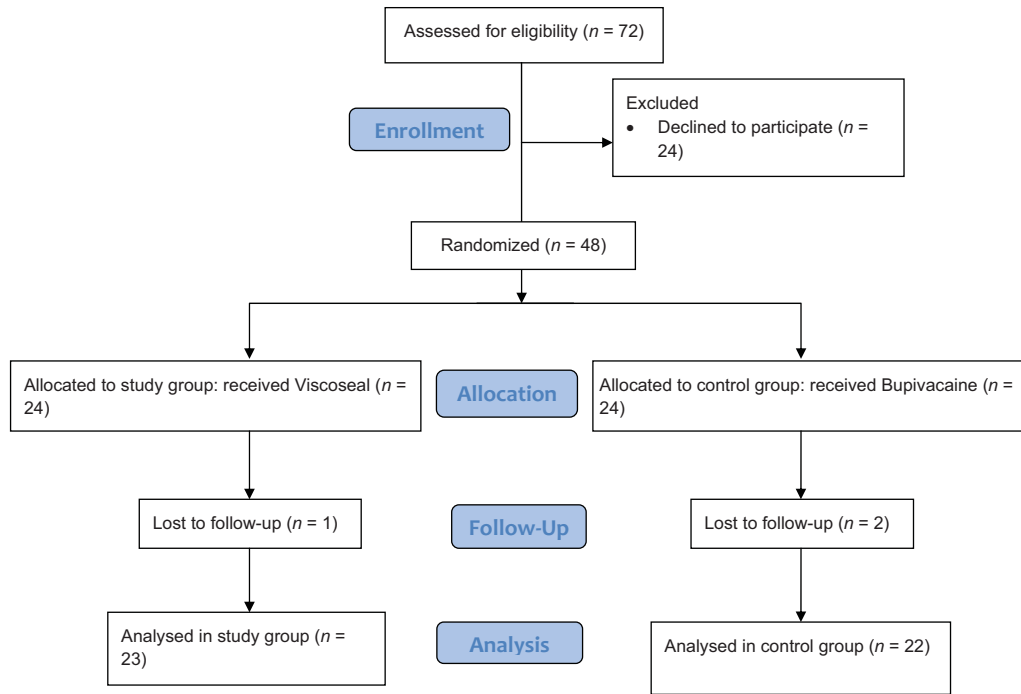
```
                    ┌─────────────────────────────────┐
                    │ Assessed for eligibility (n = 72) │
                    └─────────────────────────────────┘
                                    │
      ┌────────────┐                │        ┌──────────────────────────────┐
      │ Enrollment │────────────────┼───────▶│ Excluded                     │
      └────────────┘                │        │  • Declined to participate (n = │
                                    │        │    24)                       │
                                    ▼        └──────────────────────────────┘
                    ┌─────────────────────────┐
                    │   Randomized (n = 48)    │
                    └─────────────────────────┘
```


Fig. 1 The CONSORT flow diagram for randomized controlled trial. CONSORT, Consolidated Standards of Reporting Trials.

Table 1 Characteristics of randomized patients

Characteristics	Study (Viscoseal) group	Control (Bupivacaine) group
	n = 24	n = 24
Age		
Mean (SD)	43.5 (12.2)	43.3 (11.7)
Range	22–66	23–68
Sex		
Male n (%)	14 (58)	16 (67)
Female n (%)	10 (42)	8 (33)
Procedure		
Partial meniscectomy n (%)	12 (50)	12 (50)
Debridement n (%)	12 (50)	12 (50)
Knee with osteoarthritis		
n (%)	12 (50)	11 (46)
Preoperative pain at rest		
Mean (SD)	2.0 (1.6)	2.0 (1.8)
Preoperative pain on moving		
Mean (SD)	3.8 (2.0)	3.8 (1.9)
Preoperative pain on weight bearing		
Mean (SD)	4.8 (1.9)	5.0 (2.2)
Preoperative WOMAC score		
Mean (SD)	39.7 (13.5)	41.1 (13.6)
Preoperative SF-12		
Mean (SD)	33.2 (5.0)	32.0 (5.8)
Preoperative analgesic use (number of tablets per 24-h period)		
Median (range)	2 (0–6)	1 (0–6)

Abbreviations: SD, standard deviation; SF-12, 12-Item Short Form Health Survey; WOMAC, Western Ontario and McMaster Universities.
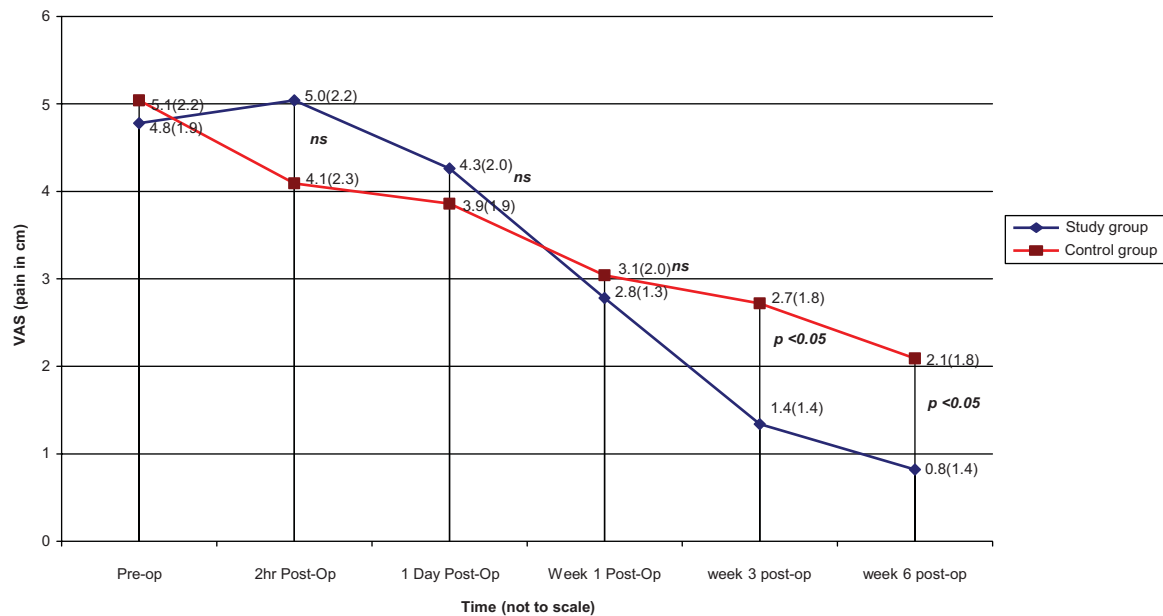
Fig. 2 Changes in mean pain scores on weight bearing, measured on the visual analogue scale. Values are given as mean (standard deviation).

Table 2 Outcomes at 6 weeks

	Study (Viscoseal) group	Control (Bupivacaine) group	Difference (95% CI)	p Value (t-test or chi-square)
	n = 23	n = 22		
Pain VAS on weight bearing				
Mean (SD)	0.8 (1.34)	2.0 (1.8)	1.2 (0.3–2.1)	0.01
WOMAC				
Mean (SD)	13.7 (10.2)	22.3 (12.7)	8.5 (1.8–15.2)	0.02
Number of patients with swelling (%)	5 (21%)	11 (46%)	25% (5–56%)	0.07
Resting pain VAS				
Mean (SD)	0.6 (1.1)	1.2 (1.0)	0.6 (−0.2 to 1.2)	0.06
Pain VAS on moving				
Mean (SD)	0.8 (1.2)	1.3 (1.1)	0.8 (0.1–1.6)	0.11
Analgesic use				
Mean (SD)	0.3 (0.8)	1.1 (1.6)	0.8 (0.1–1.5)	0.03
SF-12 scores				
Mean (SD)	41.3 (3.6)	38.3 (6.1)	−3.0 (−5.9 to −0.1)	0.04

Abbreviations: CI, confidence interval; SD, standard deviation; SF-12, 12-Item Short Form Health Survey; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities.

at 6 weeks between the two groups, favoring the study group, according to the independent assessment by a physiotherapist blinded to group allocation (►**Fig. 4**). Overall, 11 patients had swelling (moderate or more) in the control group while only 4 had swelling in the study group. The final conclusions were further supported by sensitivity analysis using the Mann–Whitney test.

Discussion

Pain, swelling, and stiffness are common problems in the early-postoperative period following arthroscopic knee surgery. Measures to alleviate these problems not only help in improving the morale of the patient, but also in aiding the patient to engage in rehabilitation, thus speeding recovery
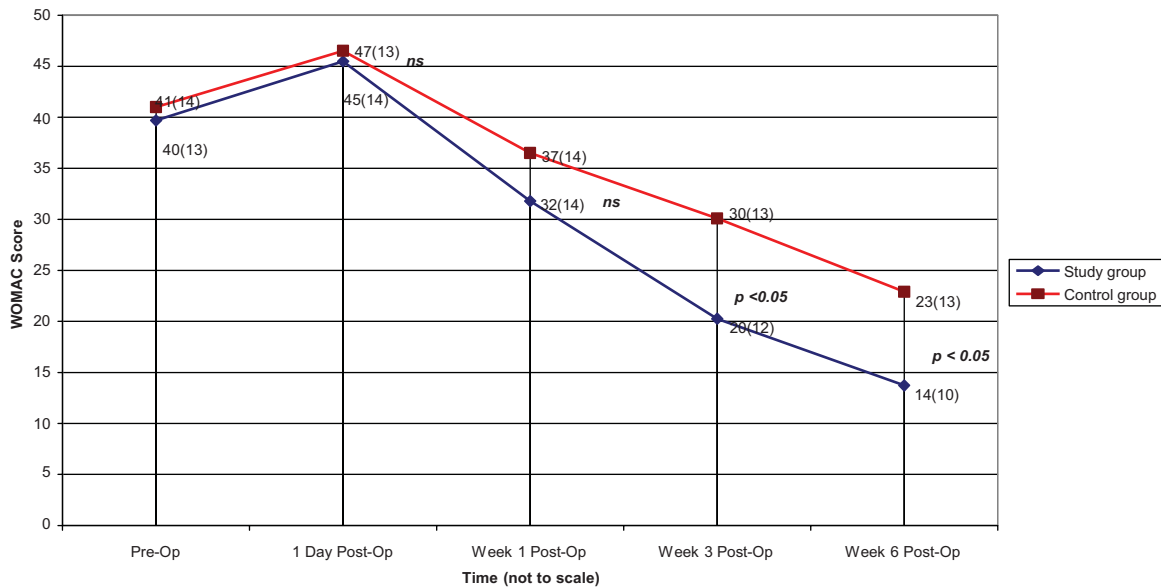
Fig. 3 Changes in mean WOMAC scores. WOMAC, Western Ontario and McMaster Universities. Values are given as mean (standard deviation).

after surgery. It has been demonstrated that intra-articular sodium hyaluronate delivers results comparable with arthroscopic washout in patients with knee osteoarthritis without mechanical symptoms.[22] This study was designed to determine whether an immediate postoperative infiltration of 10 mL of a proprietary sodium hyaluronate product (Viscoseal) into the knee would aid patient rehabilitation by significantly decreasing pain and improving function compared with 10 mL of Bupivacaine.

The analgesic effect of HA has been correlated to its molecular weight. The optimum molecular weight of HA for analgesia ranges from 860 to 2,300 kDa.[23] The molecular weight of Viscoseal, the sodium hyaluronate, used in our

study is listed as 1.8 million Da on the summary of product characteristics.

In relation to knee osteoarthritis and the therapeutic use of HA as an intra-articular injection, it has been demonstrated that HA leads to a reconstitution of the superficial amorphous layer of the cartilage, an improvement in the chondrocyte density, and a reduction in synovial inflammation, with a corresponding increase in the synovial repair process starting from as early as 3 weeks postinjection, and lasting for more than 6 months.[19,24]

The aim of our study was to assess any measurable differences in outcome during the immediate postoperative period, and in the short term, following arthroscopic knee surgery,
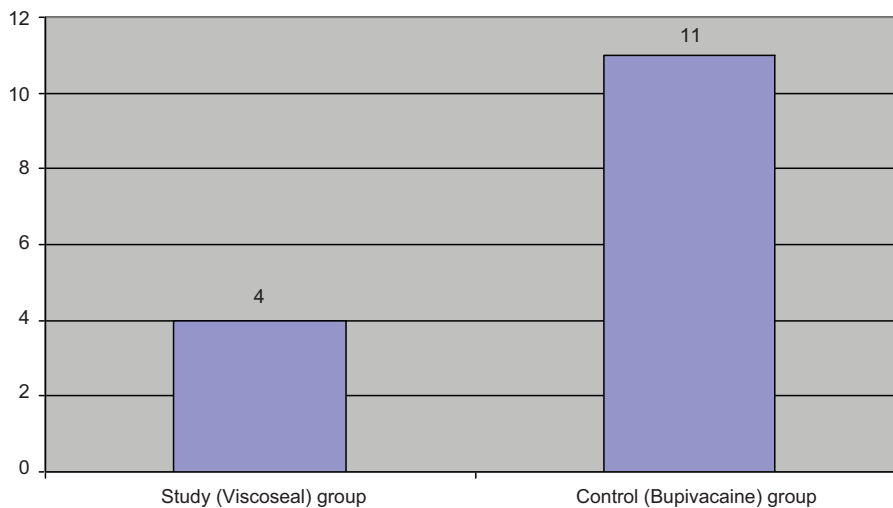

Fig. 4 Number of patients with swelling (moderate or more) at 6 weeks. ($p = 0.02$).

between a synthetic synovial fluid replacement and a local anesthetic. Our results were consistent with other published studies, which looked at the outcome of sodium hyaluronate infiltration following knee arthroscopy. These studies concluded that the postarthroscopic instillation of an HA-based synovial fluid substitute into the joint following arthroscopy was effective in achieving long-term stabilization of the joint.[18,20,21]

Several studies have demonstrated the analgesic efficacy of a single injection of intra-articular Bupivacaine following arthroscopic knee surgery.[25–27] Animal and laboratory studies, however, have reported a dose- and time-dependent local toxicity of Bupivacaine on chondrocytes. [28,29]. The potentially deleterious in vivo effects on human chondrocytes following a single intra-articular injection of local anesthetic are yet to be clearly defined.[30] In our study, no complications were encountered with the product used. The manufacturers claim that Viscoseal is devoid of animal proteins and hence has negligible allergenic potential. The rationale for the intra-articular infiltration of sodium hyaluronate at the end of an arthroscopic procedure was that it would reestablish the normal protective coating of HA over the surface of the articular cartilage and synovial membrane, thus acting as a mechanical barrier to nociceptive innervation and providing a hydrodynamic lubricant to enhance mobility. By enhancing joint mobility, it is postulated that the endogenous production of HA is stimulated.

Validated outcome measures were used to assess any change in patients' pain and function. In the immediate postoperative phase (2 hours), no statistically significant differences were observed between study and control groups. However, by 3 weeks postsurgery, all measures significantly favored the study group except for the mean VAS during the movement score, which, while numerically favoring the study group did not reach statistical significance.

Knee arthroscopic procedures have been shown to be cost effective when assessed for quality-adjusted life year.[31] However, the absence of physiological synovial fluid within the joint following knee arthroscopy may exacerbate postsurgical complications such as pain, effusion, and restricted mobility.[32] The relatively modest additional cost of providing a hyperviscous synovial fluid replacement following arthroscopic surgery has been shown to significantly reduce the need for opioid-based analgesia, thus reducing the requirement for overnight hospitalization due to opioid-induced emesis. In addition, Viscoseal been shown to significantly reduce time to discharge rates.[32] In younger, more active patients, a speedy return to work and normal activities is subjectively desirable, and has positive economic implications for the patient, the payer and the wider economy. To the best of our knowledge, no literature is available on cost-benefit analysis of viscosupplementation after knee arthroscopy.

The limitations of this study emanated mainly from a relatively small sample size. A prior power calculation confirmed a 90% degree of confidence in data generated by the primary measure of outcome, which informed the number of participants required to be enrolled into the study. Power was based on the primary outcome, rather than all the secondary outcome measures, as doing thus was impractical

with several secondary outcome measures. As posthoc power analysis gives no more information than p value and confidence interval and can also be misleading, it was decided not to do it for all the secondary outcome measures. A small number of patients decided to participate during the 3 years duration of study, as it was a single surgeon trial and had strict inclusion/exclusion criteria. However, statistical significance was observed in the nonparametric statistical analyses as outlined in the results already.

The recording and scoring of outcome parameters was conducted by a blinded assessor (physiotherapist), with subjective pain assessment recorded on a Likert-type scale, and a clinical examination—utilizing an ordinal scale of recognized manifestations of joint swelling—determining the swelling score. We only used patient reported outcome measures, except for assessment of swelling. Only one measurement of swelling was done for each patient at 6 weeks using defined observable clinical criteria, hence there was no need to look for inter- or intraobserver reliability.

There may be an argument about ideal study design comparing the groups with HA injection only versus no HA injection (i.e., without Bupivacaine) after arthroscopy. However, this would have been difficult to get ethical approval considering that the commonly accepted practice was to inject local anesthetic injection at the end of arthroscopy procedure. Authors acknowledge that a posthoc analysis based on specific joint pathology would have been very useful, meniscectomy with no degenerative change compared with meniscectomy with frank degenerative deficits being an example, and this is something that will hopefully emerge in future larger studies.

Conclusion

Intra-articular infiltration of Viscoseal following arthroscopic knee surgery conferred significantly improved pain relief and function in the short term postoperative period (3 to 6 weeks) compared with Bupivacaine. A larger study with specific attention to different subgroups of patients undergoing arthroscopic knee surgery may help elicit more specific information regarding the effect of sodium hyaluronate in the postoperative recovery period for different knee conditions.

References

1 DeLee JC; Committee on Complications of Arthroscopy Association of North America. Complications of arthroscopy and arthroscopic surgery: results of a national survey. Arthroscopy 1985;1(4):214–220

2 Small NC; Committee on Complications of the Arthroscopy Association of North America. Complications in arthroscopy: the knee and other joints. Arthroscopy 1986;2(4):253–258

3 Small NC. Complications in arthroscopic surgery performed by experienced arthroscopists. Arthroscopy 1988;4(3):215–221

4 Reagan BF, McInerny VK, Treadwell BV, Zarins B, Mankin HJ. Irrigating solutions for arthroscopy. A metabolic study. J Bone Joint Surg Am 1983;65(5):629–631

5 Bulstra SK, Kuijer R, Eerdmans P, van der Linden AJ. The effect in vitro of irrigating solutions on intact rat articular cartilage. J Bone Joint Surg Br 1994;76(3):468–470

6 Straehley D, Hellar A, Solomons C, et al. The effect of arthroscopic irrigating solutions on cartilage and synovium. Trans Orthop Res Soc 1985;10:260

7 Bulstra SK, Douw C, Kuijer R. Normal saline irrigation of the rat knee inhibits cartilage metabolism; hyaluronan restores this disturbed metabolism to normal. Presentation at: the 45th Annual Meeting of the Orthopaedic Research Society; 1–4 February, 1999; Anaheim, CA

8 Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther 1998;20(3):410–423

9 Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006;(2):CD005321

10 Kobayashi K, Matsuzaka S, Yoshida Y, Miyauchi S, Wada Y, Moriya H. The effects of intraarticularly injected sodium hyaluronate on levels of intact aggrecan and nitric oxide in the joint fluid of patients with knee osteoarthritis. Osteoarthritis Cartilage 2004; 12(7):536–542

11 Ghosh P, Guidolin D. Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects molecular weight dependent? Semin Arthritis Rheum 2002; 32(1):10–37

12 Theiler R, Brühlmann P. Overall tolerability and analgesic activity of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. Curr Med Res Opin 2005;21(11):1727–1733

13 Listrat V, Ayral X, Paternello F, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. Osteoarthritis Cartilage 1997;5(3): 153–160

14 Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. Osteoarthritis Cartilage 1993;1(2): 97–103

15 Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in knee osteoarthritis. Ann Clin Lab Sci 2004;34(3): 330–335

16 Miyamoto H, Sakashita H, Miyata M, et al. Arthroscopic management of temporomandibular closed lock. Aust Dent J 1998;43(5): 301–304

17 McCain JP, Balazs EA, de la Rua H. Preliminary studies on the use of a viscoelastic solution in arthroscopic surgery of the temporomandibular joint. J Oral Maxillofac Surg 1989;47(11): 1161–1168

18 Mathies B. Effects of Viscoseal, a synovial fluid substitute, on recovery after arthroscopic partial menisectomy and joint lavage. Knee Surg Sports Traumatol Arthrosc 2006;14(1):32–39

19 Cubukçu D, Ardiç F, Karabulut N, Topuz O. Hylan G-F 20 efficacy on articular cartilage quality in patients with knee osteoarthritis: clinical and MRI assessment. Clin Rheumatol 2005;24(4): 336–341

20 Hempfling H. Intra-articular hyaluronic acid after knee arthroscopy: a two-year study. Knee Surg Sports Traumatol Arthrosc 2007; 15(5):537–546

21 Thein R, Haviv B, Kidron A, Bronak S. Intra-articular injection of hyaluronic acid following arthroscopic partial meniscectomy of the knee. Orthopedics 2010;33(10):724

22 Forster MC, Straw R. A prospective randomised trial comparing intra-articular Hyalgan injection and arthroscopic washout for knee osteoarthritis. Knee 2003;10(3):291–293

23 Gotoh S, Onaya J, Abe M, et al. Effects of the molecular weight of hyaluronic acid and its action mechanisms on experimental joint pain in rats. Ann Rheum Dis 1993;52(11):817–822

24 Frizziero L, Govoni E, Bacchini P. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: clinical and morphological study. Clin Exp Rheumatol 1998;16(4):441–449

25 Waddell DD, Bert JM. The use of hyaluronan after arthroscopic surgery of the knee. Arthroscopy 2010;26(1):105–111

26 Sun QB, Liu SD, Meng QJ, Qu HZ, Zhang Z. Single administration of intra-articular bupivacaine in arthroscopic knee surgery: a systematic review and meta-analysis. BMC Musculoskelet Disord 2015;16:21

27 Wei J, Yang HB, Qin JB, Kong FJ, Yang TB. Single-dose intra-articular bupivacaine after knee arthroscopic surgery: a meta-analysis of randomized placebo-controlled studies. Knee Surg Sports Traumatol Arthrosc 2014;22(7):1517–1528

28 Chu CR, Coyle CH, Chu CT, et al. In vivo effects of single intra-articular injection of 0.5% bupivacaine on articular cartilage. J Bone Joint Surg Am 2010;92(3):599–608

29 Lo IK, Sciore P, Chung M, et al. Local anesthetics induce chondrocyte death in bovine articular cartilage disks in a dose- and duration-dependent manner. Arthroscopy 2009;25(7): 707–715

30 Piper SL, Kramer JD, Kim HT, Feeley BT. Effects of local anesthetics on articular cartilage. Am J Sports Med 2011;39(10):2245–2253

31 Lubowitz JH, Appleby D. Cost-effectiveness analysis of the most common orthopaedic surgery procedures: knee arthroscopy and knee anterior cruciate ligament reconstruction. Arthroscopy 2011;27(10):1317–1322

32 Marcheggiani Muccioli GM, Wykes P, Hundle B, Grassi A, Roatti G, Funk L. Effects of a synovial fluid substitute on early recovery after arthroscopic subacromial decompression of the shoulder. Musculoskelet Surg 2015;99(2):121–126