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 Bamforth4  Theophilus Asumu, FRCS (Tr&Orth)5  Keyur Buch, FRCS (Tr&Orth)5

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

Sodium hyaluronate is an unbranched high-molecular-weight polysaccharide belonging to glycosaminoglycan group which is widely used in the treatment of osteoarthritic joints. 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. 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.

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. 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.

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. 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. 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 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 (Fig. 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 the 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 \((n = 72)\)

Excluded
- Declined to participate \((n = 24)\)

Randomized \((n = 48)\)

Allocated to study group: received Viscoseal \((n = 24)\)

Lost to follow-up \((n = 1)\)

Analysed in study group \((n = 23)\)

Allocated to control group: received Bupivacaine \((n = 24)\)

Lost to follow-up \((n = 2)\)

Analysed in control group \((n = 22)\)

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

**Table 1** Characteristics of randomized patients

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

Abbreviations: SD, standard deviation; SF-12, 12-Item Short Form Health Survey; 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.
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.

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**Fig. 3** Changes in mean WOMAC scores. WOMAC, Western Ontario and McMaster Universities. Values are given as mean (standard deviation).

**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 produc-
tion 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 How-
ever, the absence of physiological synovial fluid within the joint
following knee arthroscopy may exacerbate postsurgical com-
lications such as pain, effusion, and restricted mobility.32 The
relatively modest additional cost of providing a hypertonic
synovial fluid replacement following arthroscopic surgery has
been shown to significantly reduce the need for opioid-based
analgesia, thus reducing the requirement for overnight hospital-
ization 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 confi-
dence 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 signifi-
cance 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. How-
ever, 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 arthro-
scopic 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 hyalur-
onate 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
214–220
2. Small NC; Committee on Complications of the Arthroscopy Asso-
ciation of North America. Complications in arthroscopy: the knee
3. Small NC. Complications in arthroscopic surgery performed by
4. Reagan BF, McInerny VK, Treadwell BV, Zarins B, Mankin HJ.


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


