Presented at the 9th World Congress of the Osteoarthritis Research Society International, Chicago, IL, USA, 2–5 December 2004.

Effect of sodium hyaluronate on recovery after arthroscopic knee surgery – a randomised controlled trial

Correspondence:
K Buch
Department of Orthopaedics, Royal Oldham Hospital, Oldham, UK
E-mail: keyur.buch@pat.nhs.uk

Poster number: 342

Anand S, Mitchell S, Bamforth C, Asumu T, Buch K

Department of Orthopaedics, Royal Oldham Hospital, Oldham, UK.

Introduction

Arthroscopic knee surgery is a commonly performed day case procedure, associated with rapid recovery. Though the incidence of complications is low, patients may experience side-effects such as pain, swelling and loss of joint mobility in the early postoperative period. Although these side-effects may be attributed to a large extent to the surgical trauma, various reports have commented on the negative influence of irrigating fluid (saline) used in arthroscopy.[1–4]

Sodium hyaluronate (HA) is a synovial fluid substitute widely used in the treatment of osteoarthritic joints. Intra-articular injection of exogenous HA can help to relieve pain and improve function in osteoarthritic knees.[5] In addition, reports have shown that exogenous HA promotes tissue healing[6,7] and protects articular cartilage and synovial membrane from damage following the experimental initiation of joint disease.[8] Injected HA can augment the flow of synovial fluid, normalise its synthesis and inhibit the degradation of endogenous HA.[9]

Exogenous HA has been used with arthroscopy in other joints with good benefits and no reported complications.[10,11]

Aim

The aim of this study was to determine the effects of a single postoperative, intra-articular injection of sodium HA (Viscoseal®, TRB Chemedica (UK) Ltd, 0.5% sodium HA solution in a 10 ml single use container) on pain and joint function, following arthroscopic knee surgery.

Methodology

This study was conducted at Royal Oldham Hospital, Oldham, UK, between 2002 and 2004. It was approved by the local ethics and research committee.

Study design

A single centre, randomised, blinded prospective clinical trial.

Inclusion criteria: Patients aged older than 18 years, who had a clinical indication for knee arthroscopy and none of the exclusion criteria, were invited to participate. Patients with osteoarthritis (OA) were included if they had mechanical symptoms suggesting a degenerative meniscal tear. Informed consent was provided.

Exclusion criteria: Patients were excluded if they had anterior knee pain; severe OA, as shown by radiographic signs of 'bone-on-bone OA'; crystalline or inflammatory arthropathy or ligamentous instability on clinical examination; local infection; known hypersensitivity to bupivacaine, HA or other constituents of Viscoseal®. Pregnant or lactating patients were also excluded from the study.

Study procedure

Following arthroscopic knee surgery, patients were randomised to one of two groups. The control group had 10 ml of 0.5% bupivacaine injected into the joint after the procedure, following evacuation of saline (as is the current practice in our centre), while the study group had 10 ml of Viscoseal® injected into the joint.

Randomisation was achieved with the use of a computerised random number algorithm to create 50 cards that were placed in sealed opaque envelopes. Following arthroscopy, envelopes were opened in theatre by a theatre practitioner who was not connected with the trial. Opening of the envelope was considered to be the point of enrolment. The patient's allocated group was not revealed in the case notes and patients were kept blinded to their ultimate allocation.

Each injection of fluid was given via a superolateral approach, under arthroscopic visualisation. All patients had diagnostic arthroscopy followed by treatment directed to their pathology. Similar arthroscopy portals were used in all cases. Meniscal tears were trimmed to a stable rim. Loose debris and articular cartilage flaps were removed. No chondroplasty, abrasion arthroplasty or microfracture was performed. The same postoperative physiotherapy regimen was followed by all patients. No walking aids were used and a graduated exercise programme was initiated. Patients were given co-dydramol (dihydrocodeine tartrate, 10 mg, plus paracetamol, 500 mg) as rescue medication for pain control and 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 treatment. The surgical team did not participate in the collection of outcome data.

Primary efficacy parameters: Patient's self-assessment of pain on a 10 cm visual analogue scale (VAS) at rest, on movement and on weight bearing.

Secondary efficacy parameters: WOMAC questionnaire to assess pain, stiffness and function; SF-12 general health questionnaire and use of rescue medication (co-dydramol).

All measures except SF-12 were recorded preoperatively and at Day 1, Day 7, 3 weeks and 6 weeks after surgery. In addition, pain was recorded 2 h after surgery and at the time of discharge in order to compare the postoperative response to Viscoseal® with that of bupivacaine. SF-12 scores were recorded preoperatively and at 6 weeks following surgery.

Finally, at 6 weeks, patients reported with their questionnaires to the clinic, where a trained physiotherapist, who was blinded to the randomisation, recorded the outcome scores. At this time, the extent of any knee swelling was also assessed and recorded on a 5-point scale (none: no effusion; mild: swipe test positive; moderate: parapatellar fullness/patellar tap present; severe: suprapatellar swelling; extreme: tense suprapatellar pouch). The physiotherapist also assessed the efficacy of pain relief and scored it on a 5-point scale (1: no pain; 2: mild pain; 3: moderate; 4: severe pain; 5: extreme pain).

Statistical analysis

Prior power analysis had suggested that, assuming a difference in pain between groups of 1 cm on the VAS, and a standard deviation of 1 cm in each group, at least 22 patients would be required in each group (44 in total). Demographic and outcome measures were analysed using the difference of means test (unpaired two-tailed t-test; significance at $p < 0.05$)

Results

A total of 72 patients were invited to participate, of whom 48 agreed to participate in the study. After randomisation, 24 patients were assigned to each group. Follow-up was available for 45 patients (23 in the study group and 22 in the control group). Baseline demographic data are shown in Table 1. No significant difference was found between the two groups as regards to age, sex and their preoperative pain and function levels (as seen by VAS scores at rest, weight bearing and movement, SF-12 scores, WOMAC scores and analgesic usage). Both groups had similar distribution of pathology and treatment procedures (Table 1). Patients were considered to be in the OA group if radiographic evidence of a loss of more than 75% of articular cartilage was noted or if, during arthroscopy, ≥ grade 3 OA changes were noted in more than one compartment.

	Viscoseal group (n = 23)	Bupivacaine group (n = 22)	$p < 0.05$
Age (years) Mean (SD) Range	43.95 (12.33) 23–68	43.13(11.84) 22–66	ns
Gender (male/female)	Males, 13 Females, 10	Males, 14 Females, 8	ns
Procedure Partial meniscectomy Debridement	 11 12	 11 11	ns
Number of knees with osteoarthritis	12	11	ns

Table 1: *Baseline demographics (ns, not significant).*

Figures 1, 2 and 3 show comparative trends in VAS scores between the two groups. A significant improvement in SF-12 and WOMAC scores was seen in both groups. On comparing SF-12 values at 6 weeks, results in the study group were significantly improved compared with the control group ($p = 0.04$; Figure 4). The improvement in WOMAC scores for the study group compared with those of the control group approached significance at 3 and 6 weeks (Figure 5). Figure 6 shows that patients in the control group used fewer analgesics in the immediate postoperative period while less analgesic consumption was noted in the study group at 3 and 6 weeks. There was also a significant difference in pain and swelling at 6 weeks between the two groups, according to assessment by the independent physiotherapist (Figure 7).

Discussion

Arthroscopic knee surgery is a safe procedure with a low incidence of complications,[12] but it is associated with pain, swelling and loss of joint mobility in the early postoperative period. This not only has an important bearing on patient comfort but may determine the speed of recovery after surgery. A low level of pain has a very positive effect on the morale of the patient, which in turn aids rehabilitation. This study was designed to determine whether a postoperative injection of sodium HA would aid the rehabilitation of a patient by decreasing pain and improving function.

HA is an unbranched, high molecular weight polysaccharide belonging to the family of glycosaminoglycans and is a normal vital constituent of both articular cartilage and synovial fluid. The principal role of HA is to maintain the structural and functional characteristics of the extracellular matrix of the cartilage and of the biological fluids.[13] HA provides synovial fluid with its remarkable physical properties, allowing it to act as a lubricant, a shock absorber and a filter, hindering the movement of potentially damaging cells and molecules through the joint space.[14] Viscosupplementation with HA is postulated to protect matrix components and functional cells of cartilage and synovial tissue from mechanical stress and to give symptomatic pain relief by covering the nociceptors in the joint capsule.[15] Exogenous HA has been used with arthroscopy in other joints with good benefits and no reported complications.[10,11] In our study, no complications were encountered with the use of Viscoseal®. The manufacturers claim that Viscoseal® is devoid of animal proteins and hence has negligible allergenic potential.

We injected 10 ml of Viscoseal® into the joint at the end of the operation. This displaced saline in the joint, preventing this solution from impairing cartilage metabolism. The supposition was that it would re-establish the normal protective coating of HA over the joint surface of the articular cartilage and synovial membrane. By enhancing joint mobility, moreover, it may help maintain production of endogenous HA.

Validated outcome measures were used to assess any change in patient's pain and function. In the immediate postoperative phase (2 h), outcome measures appear to favour the control group, though patients in the study group appear to have a better outcome over a longer duration. This early bias in favour of the control group would be explained by the local anaesthetic action of bupivacaine in controlling pain. Subsequently, tissue protective properties of HA appear to confer advantage to the study population. This benefit appears to be larger in patients with degenerative changes, though our study did not have adequate numbers to allow us to draw any such statistically significant conclusion.

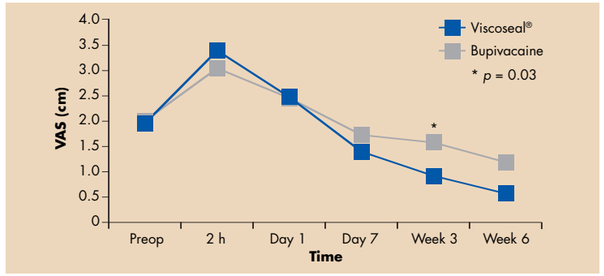

Figure 1: *Changes in mean pain scores at rest, measured on the visual analogue scale (VAS).*

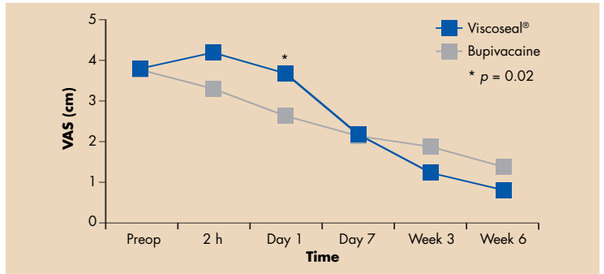

Figure 2: *Changes in mean pain scores on movement, measured on the VAS.*

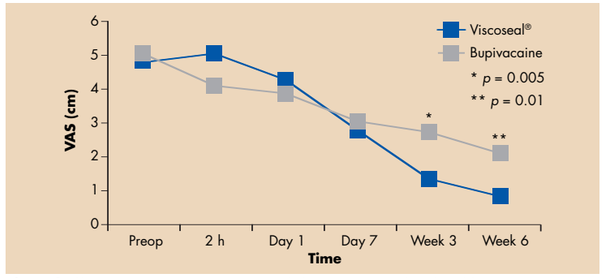

Figure 3: *Changes in mean pain scores on weight bearing, measured on the VAS.*

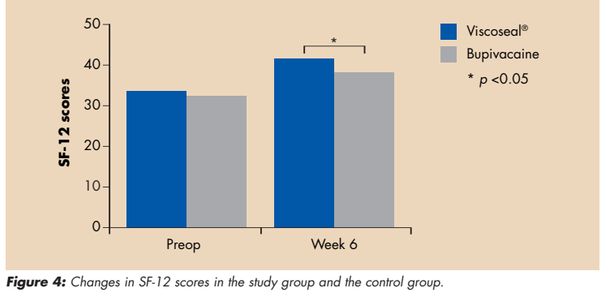

Figure 4: *Changes in SF-12 scores in the study group and the control group.*

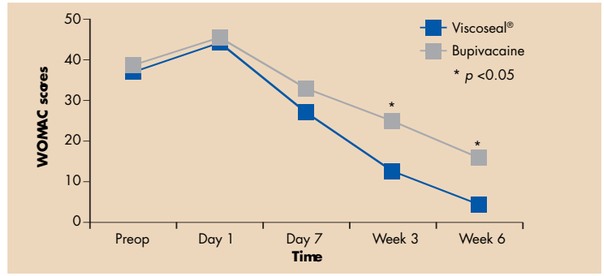

Figure 5: *Changes in mean WOMAC scores.*

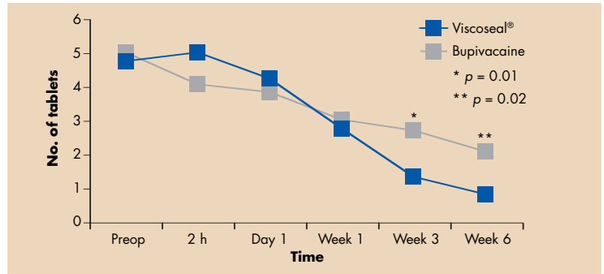

Figure 6: *Analgesic use in the study group and the control group.*

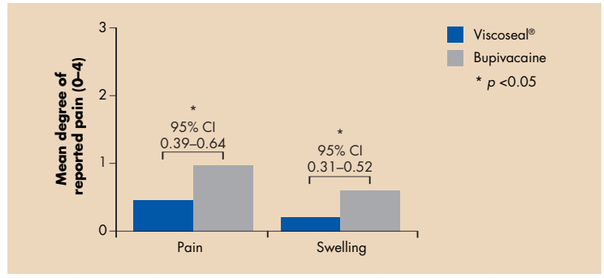

Figure 7: *Comparison of physiotherapist-assessed pain and swelling scores at 6 weeks postoperatively.*

Conclusion

- Viscosupplementation after arthroscopic knee surgery offers significantly improved function and pain relief over the medium term (3–6 weeks).
- Larger studies would help to identify differences of effect in different subgroups of patient populations.

Acknowledgements

Our special thanks are due to Mr David Lamb for help with statistical analysis. For any further information on the project, contact keyur.buch@pat.nhs.uk

References

1 Reagen BF, McInerny MD, Treadwell BV, Zarins B, Mankin HJ. Irrigating solutions for arthroscopy. A metabolic study. *J Bone Joint Surg* 1983;65-A:629–31.
2 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-B:468–70.
3 Straehley D, Hellar A, Solomons C, Fisher R, Halanowska A, Wiedel J. The effect of arthroscopic irrigating solutions on cartilage and synovium. *Trans Orthop Res Soc* 1985;10;260.
4 Bulstra SK, Douw C, Kuijer R. NaCL irrigation of the rat knee inhibits cartilage metabolism; hyaluranon restores this disturbed metabolism to normal. Presentation at the 45th Annual Meeting of the Orthopaedic Research Society, Anaheim, USA, 1–4 February 1999.
5 Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee – a meta-analysis of randomised controlled trials. *J Bone Joint Surg [Am]* 2004;86: 538–45.
6 Frank C, Shrive N, Hiraoka H, Nakamura N, Kaneda Y, Hart D. Optimisation of the biology of soft tissue repair. *J Sci Med Sport* 1999;2(3):190–210.
7 Wig ME, Amiel D, VandeBerg J, Kitabayashi L, Harwood FL, Arfors KE. The early effect of high molecular weight hyaluronan (hyaluronic acid) on anterior cruciate ligament healing: an experimental study in rabbits. *J Orthop Res* 1990;8(3):425–34.
8 Ghosh P, Holbert C, Read R, Armstrong S. Hyaluronic acid (hyaluronan) in experimental osteoarthritis. *J Rheumatol* 1995;43 (Suppl.):155–57.
9 Rydell N, Balazs EA. Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of osteoarthritis and granulation tissue formation. *Clin Orthop.* 1971;80:25–32.
10 Miyamoto H, Sakashita H, Miyata M, *et al.* Arthroscopic management of temperomandibular closed lock. *Austr Dent J* 1998;43: 301–4.
11 McCain JP, Balazs EA, Rua HDL. Preliminary studies on the use of a viscoelastic solution in arthroscopic surgery of the temporomandibular joint. *J Oral Maxillofac Surg* 1989;47:1161–68.
12 DeLee JC. Complications of arthroscopy and arthroscopic surgery: results of a national survey. *J Arthroscopic Rel Surg* 1985;1:214–20.
13 Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluranate (hyalectin) in osteoarthritis of the knee; a 1 year placebo-controlled trial. *Osteoarthritis Cartilage* 1993;1:97–103.
14 Scott JE. In: Evered D, Whelan J, eds. *The biology of hyaluronan. Ciba Foundation Symposium 143.* Chichester: John Wiley, 1989: pp 6–20.
15 Balazs EA, Denlinger JL. In: Evered D, Whelan J, eds. *The biology of hyaluronan. Ciba Foundation Symposium 143.* Chichester: John Wiley, 1989: pp 265–75.