Original Article

Does Hyaluronan improve pain or function following Arthroscopic Subacromial decompression (ASD) surgery of Shoulder? Results of a level 1 RCT

Abstract

Background: Sodium hyaluronate (hyaluronan) can be used as a synovial fluid substitute following arthroscopic surgery. In this study, we examined its effect on pain and function following arthroscopic subacromial arthroscopic decompression (ASAD). **Methodology:** A prospective, randomized, and single-blinded design was used (13/LO0427) to compare the effect of a single postprocedure subacromial instillation of 10 ml hyaluronan, against 10 ml saline control. All patients had interscalene block along with general anesthesia and followed standard postoperative rehabilitation protocol. A power calculation for a 6-point difference in Oxford Shoulder Score (OSS) indicated a minimum sample size of 44. Participants were assessed preoperatively, and at 12 weeks using the following outcome measures -Oxford Shoulder Score (OSS), visual analog score (VAS), European quality of life score (EUROQOL), and Disability of the arm, shoulder, and hand (DASH) scores. **Results:** 46 patients were included for analysis. Both groups showed a mean improvement in OSS of 9 points ($P = 0.0001$), DASH (10 points, $P < 0.05$), and EUROQOL (0.13, $P < 0.05$). No significant difference was observed between groups in any of the recorded outcomes. Apart from one case of frozen shoulder in each group, no other complications were noted. **Conclusion:** While both groups showed improved pain and function scores after ASAD, no significant difference was seen between groups receiving placebo or hyaluronan. The intervention is safe but, in this study, has not been shown to improve postoperative pain or function over ASAD alone. Level of evidence: I.

Keywords: *Arthroscopic subacromial decompression, hyaluronan, shoulder impingement syndrome, sodium hyaluronate, viscoseal*

Praveen Sarda, David Butt[1], Sherif Elnikety[1], Claire Fitzgerald[1], Steven Corbett[1]

Department of Orthopaedics, Manchester University Hospital NHS Trust, Manchester, [1]Department of Orthopaedics, Guy's and St Thomas Hospital NHS Trust, London, UK

Introduction

The shoulder girdle consists of three main components – the glenohumeral joint, the subacromial joint space, and scapulothoracic articulation, all of which are involved during the full range of motion at the shoulder. Pathology in any one of these can result in pain and restriction of movements. Pain originating in the subacromial space due to bursitis and subacromial impingement is the most common reason for surgical intervention in the shoulder.

Arthroscopic subacromial arthroscopic decompression (ASAD) is a widely practiced operation involving removal of inflamed subacromial bursa and any acromial spurs, aiming to produce a flat undersurface for the acromion, thus enlarging the supraspinatus outlet and deterring impingement. ASAD has been shown to be effective in reducing pain and improving function in the short and long term,[1,2] although a recent study has challenged this internationally held viewpoint.[3]

As with any surgical intervention, arthroscopy can be associated with complications including pain, swelling, and loss of joint mobility/stiffness. Most of the subacromial bursa is mechanically removed during ASAD, thus reducing the lubrication until the bursa reforms. Pain can be a direct result of the surgery itself, but the irrigation solution used during arthroscopy can contribute indirectly[4,5] by negatively affecting the metabolism and lubricating properties of the bursa.

Hyaluronan is an unbranched high molecular weight polysaccharide and is

How to cite this article: Sarda P, Butt D, Elnikety S, Fitzgerald C, Corbett S. Does Hyaluronan improve pain or function following Arthroscopic Subacromial decompression (ASD) surgery of Shoulder? Results of a level 1 RCT. Indian J Orthop 2019;53:595-601.

Address for correspondence:
Dr. Praveen Sarda, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL, UK.
E-mail: shipra22@gmail.com

Access this article online

Website: www.ijoonline.com

DOI: 10.4103/ortho.IJOrtho_50_19

Quick Response Code:

a vital constituent of both articular cartilage and synovial fluid. It helps maintain the structural and functional characteristics of the extracellular matrix of articular cartilage, and – in its unaggregated form – to polymerize the synovial fluid. This imparts the shock-absorbing and lubricating function to synovial fluid, while its macromolecular size and amphiphilic nature serve to retain fluid in the joint cavity during articulation. It is present throughout the human body in the interstitial space.[6]

The properties of hyaluronan substitutes are useful in the conservative treatment of osteoarthritic joints.[6] The inhibition of cartilage metabolism by transient cellular stress can be reversed by a single injection of sodium hyaluronate.[7] In addition, reports have shown that exogenous hyaluronan promotes tissue healing[8,9] and protects articular cartilage and synovial membrane from damage following the experimental initiation of joint disease.[10]

Viscoseal™ (TRB Chemedica (UK) Ltd., Newcastle-under-Lyme, UK) is one of the hyaluronan substitutes in the market that purportedly improves recovery by displacing residual saline and debris from the surrounding soft tissue and exposed cancellous bone. Some studies have shown comparable results to arthroscopic washout in patients with knee osteoarthritis without mechanical symptoms.[11,12]

By establishing a viscous, protective barrier over localized nociceptors, it is hypothesized that a more favorable outcome following ASAD will be achieved with administration of Viscoseal, than that observed with the administration of 10 ml of normal saline which we used as control. A previous audit in the department[13] had confirmed that the effect of interscalene block wears off between 24 and 48 h after surgery, and it was hypothesized that using Viscoseal would provide longer pain relief, improving early rehabilitation.

Methodology

Ethics approval

Prospective, single-blinded, randomized multicenter study sponsored by the research department at Guy's and St Thomas' NHS Trust and approved by the Regional ethics committee (13/LO/0427, project ID 121063).

Objectives

To determine the effect of a single postoperative subacromial instillation of a 0.5% concentration of sodium hyaluronate of fermentative origin (Viscoseal) on pain and function following arthroscopic subacromial decompression surgery.

Inclusion criteria

Patients aged 30–60 years, listed for ASAD after failure of conservative treatment. All patients were provided with an information leaflet, and informed consent was obtained for inclusion in the trial.

Exclusion criteria

Patients were excluded if they had any local infections, rotator cuff tears confirmed on preoperative scan or during surgery, shoulder instability, known cervical pathology, past history of treatment under pain team, systemic arthritis, known hypersensitivity to hyaluronic acid or other constituents of Viscoseal, Marcaine, and allergy to codeine phosphate or paracetamol. Patients were proposed to be withdrawn from the study if they wished to discontinue the study prematurely or developed any serious adverse event such as infection or regional pain syndrome.

Intervention

All patients underwent ASAD surgery using standard technique including bursectomy and acromioplasty. Sealed envelopes were used to randomly allocate them to intervention or control groups and were only opened at the end of the procedure with the arthroscopic cannula still in the subacromial space.

All patients received general anesthesia with interscalene block using 10–20 ml 0.5% Marcaine and standardized postoperative analgesia on discharge. At the end of the ASAD procedure, residual saline was evacuated form the subacromial space. Through the retained arthroscopic cannula, the study group received 10 ml of Viscoseal (0.5% sodium hyaluronate) and the control group received 10 ml of normal saline. The surgical treatment, physiotherapy instruction, and followup were the same for both groups. Patients were given codeine and paracetamol for pain control.

The surgeon could not be blinded since the consistency of Viscoseal is different from normal saline. The patients were blinded to the intervention, and all the data were collected independently by a research fellow without any influence from the operating surgeon.

Patients were assessed on subjective pain levels and function at the time of admission using the Oxford Shoulder score (OSS), Visual analog score (VAS), European quality of life score (EUROQOL), and Disability of the arm, shoulder, and hand score (DASH). Following surgery, patient recorded VAS and amount of rescue medication required at days 1–30 on a pain diary. VAS scores were also collected at 6 weeks and 12 weeks postoperatively. Oxford, EUROQOL, and DASH scores were collected preoperatively and at 12 weeks.

Range of movement (ROM) was recorded at each physiotherapy visit. Change in VAS and ROM components which have repeated measures were analyzed using a mixed model repeated measures (MMRM) model, assuming that the missing outcomes are "Missing at Random." This is summarized in Table 1. In what follows, comparisons are Group 2 - Group 1. Difference in change in all criteria was assessed using linear regression of change in the scores

adjusting for Group and cubic polynomial of baseline score (preoperation).

Statistics

A publication in 2013 reported postoperative OSS following ASAD at 3 months to be 38 (range 35–42).[2] Using OSS as our primary outcome measure, a 6-point difference between groups was chosen for power calculation.[14,15] Assuming 95% confidence level (P = 0.05) and a Beta of 0.2 (20%) giving a power level of 80% (100%-b), to detect 6-point difference with SD of 7, there was a requirement of 22 patients per group and 44 patients for the trial. To account for withdrawal, loss to followup, etc., it was proposed to recruit 10% extra patients, and 50 patients were recruited in total. All scores were tested for homogeneity of variance (Chi-square/F-test), mean scores were calculated, and then *t*-tested. All the calculations were carried out by a professional statistician.

Secondary outcomes included subjective assessment of pain by patients using VAS, time taken to achieve full active ROM, and difference in EUROQOL and DASH scores. Change in VAS and ROM components which have repeated measures were analyzed using a MMRM model, assuming that the missing outcomes are "Missing at Random." The analysis utilizes all the available data on all patients. Different covariance structures were considered for each variable based on Akaike's information criterion. Performing multiple tests will increase the chance of Type I error (false positive). This effect should be kept in mind when interpreting the results (a lower significance level [lower than nominal 5%] should be considered).

Results

A total of 88 patients were invited to participate, of whom 50 were enrolled into the study. 4 were excluded for various reasons [Consort Diagram Table 2], leaving 46 patients included in the trial for analysis. After exclusions, 24 and 22 patients were left in Group 1 (Viscoseal) and 2 (saline), respectively. In Table 2, summary statistics for each variable is reported for the both groups. There was equal distribution of sex and side with 23 each. Data were confirmed to be normally distributed.

When compared to preoperative scores, both groups improved significantly at the 3-month followup. The

Table 1: Summary statistics pre- and post-operation*

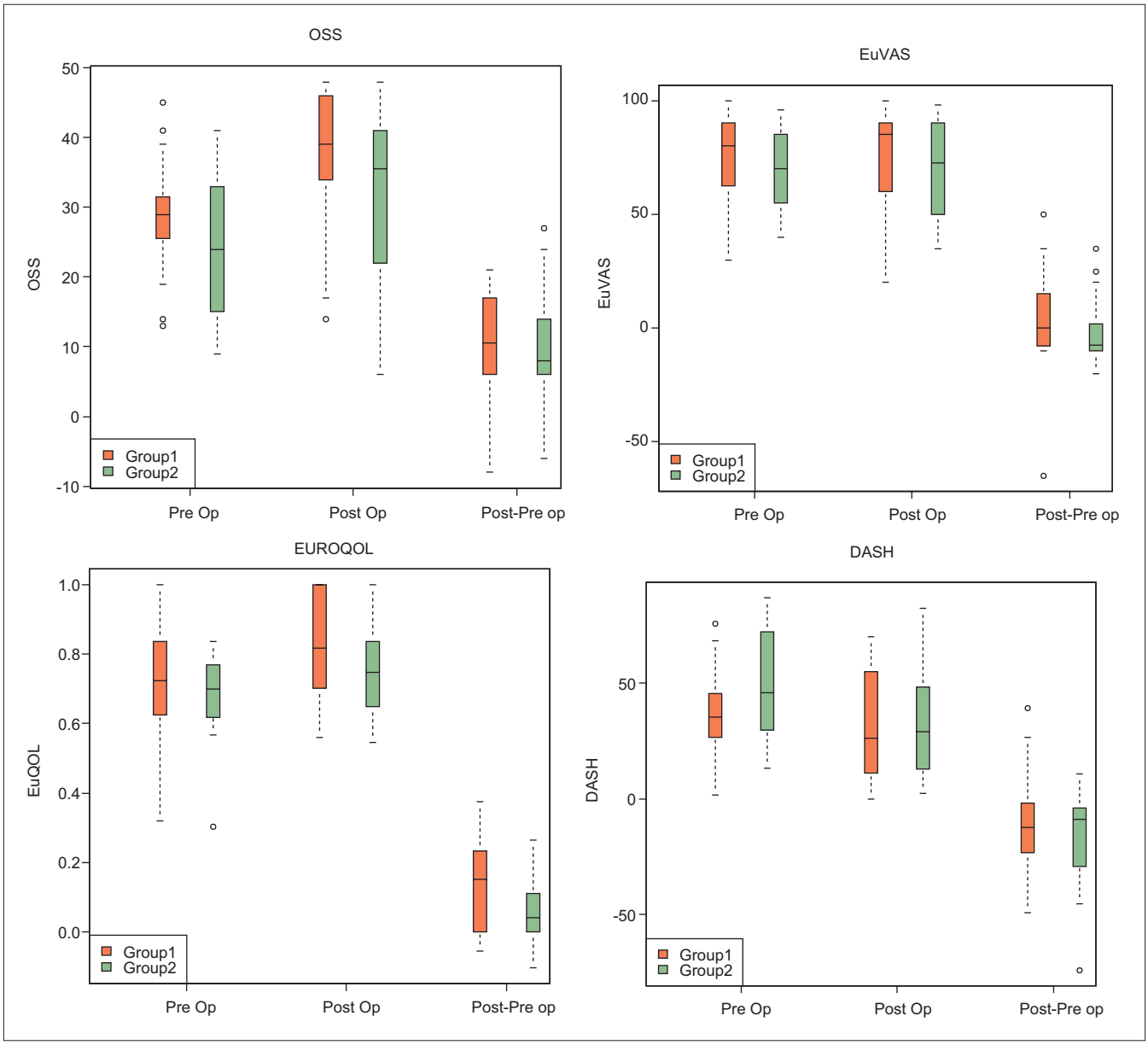
	Group 1 (*n*=24)	Group 2 (*n*=22)	*P*
Age Median (IQR) [range] mean (SD)	45 (41.75, 52.00) [30.0, 60.0] 45.92 (8.0)	47 (44, 55.5) [28, 60] 47.45 (8.98)	0.54
Length of surgery Median (IQR) [range] mean (SD)	45 (40, 51) [30, 58] 44.64 (8.404)	42 (39.5, 52.25) [25, 69] 44.95 (11.564)	0.92
Preoperative OSS, (1, 1 missing) Median (IQR) [range] mean (SD)	29.0 (25.5, 31.50) [13.0, 45.0] 28.83 (7.637)	24.0 (15.0, 33.0) [9.0, 41.0] 24.24 (10.237)	0.158
Week -12 OSS, (6, 4 missing) Median (IQR) [range]	39.0 (34.0, 45.5) [14.0, 48.0]	35.5 (23.75, 41.0) [6.0, 48.00]	0.274
Difference week 12 from baseline, mean (95% CI) *P* value^	9.72 (5.42, 14.02) 0.0001	10.35 (5.74, 14.96) 0.0002	0.78
Preoperative DASH, (1 missing) Median (IQR) [range] mean (SD)	35.30 (26.66, 45.40) [1.67, 75.80] 37.44 (18.28)	45.84 (30.5, 72.12) [13.3, 87.10] 50.89 (22.84)	0.0356
Week - 12 DASH, (6, 4 missing) Median (IQR) [range] mean (SD)	26.25 (11.53, 50.42) [0.0, 70.0] 30.44 (25.069)	29.2 (13.84, 48.08) [2.50, 82.50] 33.71 (24.397)	0.694
Difference week 12 from baseline, mean (95% CI) *P* value^	−10.31 (−10.90, 0.27) *P*=0.055	−17.48 (−27.67, −7.29) *P*=0.002	0.57
Preoperative EuROQOL, (2 missing) Median (IQR) [range] mean (SD)	0.723 (0.624, 0.827) [0.321, 1.0] 0.7189 (0.1526)	0.69 (0.63, 0.77) [0.30, 0.84) 0.688 (0.117)	0.456
week - 12 EuROQOL (8, 5 missing) Median (IQR) [range] mean (SD)	0.817 (0.704, 1.0) [0.56, 1] 0.813 (0.162)	0.75 (0.65, 0.84) [0.546, 1.0] 0.7508 (0.133)	0.233
Difference week 12 from baseline, mean (95% CI) *P* value^	0.134 (0.065, 0.203) 0.0009	0.043 (−0.004, 0.091) 0.071	0.037
Preoperative Eu VAS, (1 missing) Median (IQR) [range]	80.0 (62.5, 90.0) [30.0, 100.0]	70.0 (56.25, 83.75) [40.0, 96.0]	0.222
Week-12 Eu VAS, (7, 8 missing) Median (IQR) [range]	85 (60, 90) [20, 100]	72.5 (50.0, 87.5) [35.0, 98.0]	0.180
Difference week 12 from baseline, mean (95% CI) *P* value^	2.18 (−10.58, 14.94) 0.722	−1.5 (−11.14, 8.14) 0.74	0.35
Preoperative VAS, (5, 3 missing) Median (IQR) [range]	6.0 (5.0, 7.0) [1.0, 10.0]	7.0 (5.0, 8.0) [2.0, 10.0]	0.23

Contd..

Table 1: Contd...

	Group 1 (*n*=24)	Group 2 (*n*=22)	*P*
Week- 2 VAS, (6, 3 missing) Median (IQR) [range]	4.0 (4.0, 7.0) [0.0, 9.0]	4.0 (2.5, 6.0) [0.0, 8.0]	0.28
Difference week 2 from baseline, mean (95% CI)	−1.85 (−3.39, −0.31)	−2.97 (−4.23, −1.72)	0.326
P value^	0.022	0.0001	

*For those with (nearly) normal distribution, median (IQR) [range], mean (SD) are given and the comparison is done by *t*-test. Those with skewed only, median (IQR) [range] is given and comparisons are by Mann-Whitney U-test, ^Paired *t*-test change from baseline in each group. Note that since the missing data in the two time points are different, mean of difference is not the difference of means. SD=Standard deviation, IQR=Interquartile range, VAS=Visual analog score, DASH=Disability of the arm, shoulder, and hand score, OSS=Oxford Shoulder Score, EUROQOL=European quality of life score, CI=Confidence interval



primary outcome measure OSS improved by over 9 points in each group. However, the difference between the groups was not statistically validated**.** Among the secondary outcome measures, Euro QOL showed significant improvement in the test group at 3 months. The difference between the two groups was − 0.087 (*P* = 0.037, 95% confidence interval = −0.167, −0.006,). All the outcomes are documented in Table 1. Considering the effect of multiple testing, this result cannot be considered as significant nevertheless it indicates area for more investigation.

ROM at all time points (2, 6, and 12 weeks) were modeled, with group and baseline movements included as covariates, and an independent covariance matrix. Apart from forward flexion at week 2 favoring the test group, there was no statistically significant difference between the two groups [Table 3]. This difference was not maintained at 3 months. There were no complications apart from one patient in each group developing postoperative frozen shoulder.

Table 2: Consort 2010 flow diagram - Viscoseal trial

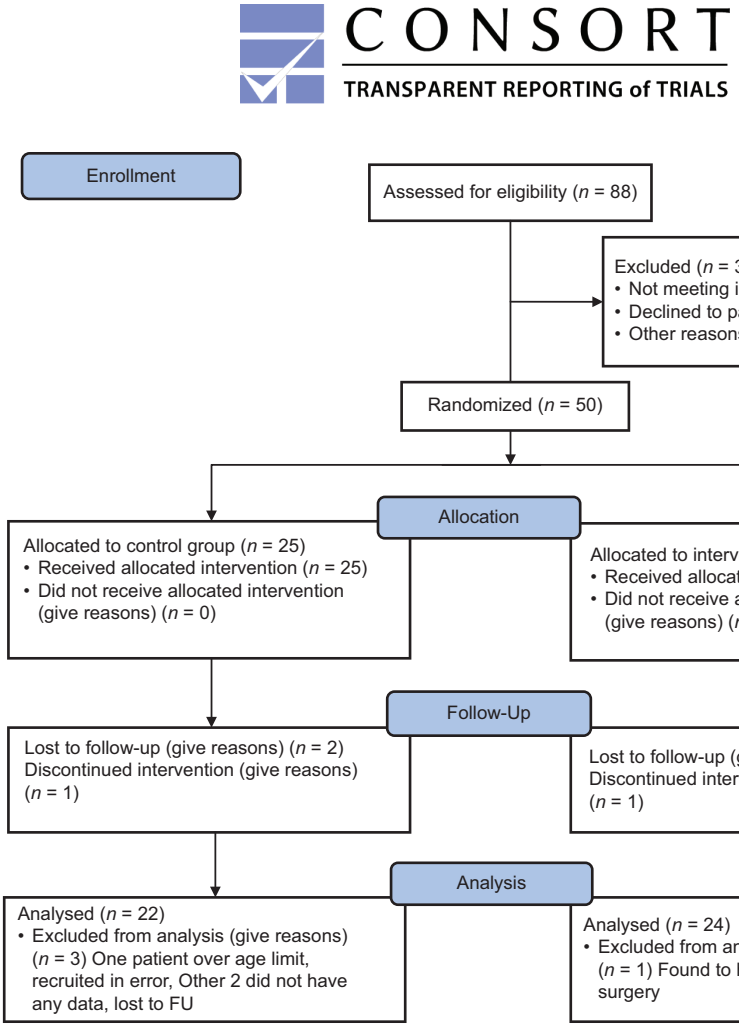


Table 3: ROM analysis pre and postop

ROM	Test Group	Control Group	*P*
Pre op ER, Median (IQR)[range]	70.0 (50.0, 80.0)[30.0,90.0]	80.0 (60.0,80.0)[40.0,130.0]	0.45
week2 ER, (2,4 missing) Median (IQR)[range] Mean (sd)	47.5 (40.0,60.0)[20.0,80.0] 50.68 (17.13)	55.0 (40.0,77.5)[20.0,80.0] 55.0 (21.14)	0.5
Pre op IR, (missing) Median (IQR)[range]	70 (60,80)[20,90]	65 (60,80)[15,90]	0.57
week2 IR, (4,4 missing) Median (IQR)[range] Mean (sd)	50 (40,80)[20,90] 53.75 (22,59)	50 (41.25,77.50)[10,80] 54.72 (21.04)	0.87
Pre op ABD, (missing) Median (IQR)[range]	172.5 (137.5, 180.0)[90,180]	160 (117.5,180)[45, 180]	0.24
week2 ABD, (2,3missing) Median (IQR)[range] Mean (sd)	140(82.5,180)[45, 180]	90 (70, 115)[40,180]	0.072
Pre op FF, (missing) Median (IQR)[range]	177.5 (160, 180) [90.0, 180.0]	165 (140, 180)[80.0, 180]	0.3
week2 FF, (2,3missing) Median (IQR)[range] Mean (sd)	150(92.5, 180.0)[70.0, 180.0]	100(80.0, 160)[40.0, 180.0]	0.05

Discussion

There have been previous publications[1,2,16] showing improved function after ASAD procedure, and it continues to be a popular procedure for patients with impingement syndrome after failed conservative treatment. Pain, swelling, and soreness are common problems that can hamper recovery and rehabilitation for a few weeks after ASAD. This could be caused by a combination of surgical trauma, loss of the lubricating function of the bursa, and a raw undersurface of acromion.

Viscoseal® (TRB Chemedica [UK] Ltd, Newcastle-under-Lyme, UK) is a 0.5% concentration isotonic solution of hyaluronan of fermentative origin. Instilled into the joint immediately after surgery, it purportedly acts as a temporary substitute for the natural lubrication fluid that has been lost during arthroscopy[17] (TRB website 2018). In addition, it is claimed to reestablish the protective coating of hyaluronan over the exposed bony surface which may help reduce pain by binding free nerve endings.[18]

Hyaluronan has been used extensively in the treatment of osteoarthritic joints and has been demonstrated to be useful in relieving pain and improving function in degenerative knee joints in randomized controlled trials. Basic science literature in the last 2 decades shows that hyaluronan leads to a reconstitution of the superficial amorphous cartilage layer, an improvement in the chondrocyte density, and a reduction in synovial inflammation, with no serious adverse effects.[6,19-23] Clinical trials with use of hyaluronan following knee arthroscopies have shown significant decrease in pain and reduction of the rescue pain medication compared with saline.[21,24-26]

It is hypothesized that this lubrication property may also be utilized after ASAD to replace the function of the temporarily absent bursa. The literature is more limited with regard to its use in shoulder arthroscopy. A previous smaller study into the effects of instilling hyaluronan following subacromial decompression[27] showed improved pain and function and no adverse events. We designed this trial as a prospective randomized single-blinded intervention in a larger cohort, allowing a more robust statistical analysis of outcome measures.

We aimed to study any difference in the immediate and early outcome by comparing the instillation of Viscoseal when compared with saline. We used validated outcome scores such as OSS, EUROQOL, DASH, and VAS score. OSS was used as the primary outcome, while the others were used as secondary measures for detecting any difference in the immediate and early postoperative period. Review of literature suggests a minimum of 6 points on the OSS as smallest detectable change[14,15] for statistical significance, and this number was used for power calculation of the study. Patients in both groups showed significant improvement in every single parameter [Table 1], but there was no statistically significant difference between the two groups.

All the patients were day cases and were taught how to fill in the daily VAS diary at home. Unfortunately, the compliance rate in returning the VAS diary was very low (12 out of 46), making any conclusions statistically untenable. This also reflects the problems in placing the burden of data collection on patients.

Our results do not mirror the benefits of Viscoseal reported after knee arthroscopy. One reason maybe the universal usage of interscalene block in all our procedures, making the procedure virtually pain free in the first 24 hours. While blocks are now standard for all shoulder arthroscopic procedures, it has inherent risks such as temporarily reduced pulmonary function, pneumothorax, injection site pain, and rarely permanent nerve damage. In addition, it increases theater time per procedure and it would be interesting to conduct a three-arm trial comparing nerve block to Viscoseal or local anesthetic infiltration.

A recent publication in the Lancet[3] concluded that subacromial decompression is no better than placebo surgery, or nonoperative treatment. This has renewed the focus on the efficacy (or the lack of it) of this procedure. While this study was set up to detect difference in two groups of patients undergoing ASAD, the outcomes in both groups indicate patients improved significantly in almost all the parameters tested [Table 2]. Thus, this study reinforces the beneficial effect of ASAD as a procedure, even though the intervention using hyaluronan did not significantly improve short term function.

Limitations of study

The sample size was determined based on primary outcome measure, but it is insufficient for statistical validation of secondary outcomes. There was poor compliance with the VAS score sheets; as a result of which, no meaningful data could be obtained for daily pain scores in the first 1 month. This could be ascribed to user fatigue in filling in multiple questionnaire in postoperative phase when most patients are in a degree of pain and discomfort and anxious as a result. Perhaps rationalization of the information collected and an app to collect real time data would be more user-friendly and ensure better compliance.

Conclusion

Subacromial instillation of sodium hyaluronate does not improve the function or movement after subacromial decompression procedure, when compared to placebo.

Acknowledgments

Help from Azita Rajai, Medical Statistician at Research and Innovation department of Manchester foundation trust is gratefully acknowledged.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Lunsjö K, Bengtsson M, Nordqvist A, Abu-Zidan FM. Patients with shoulder impingement remain satisfied 6 years after arthroscopic subacromial decompression: A prospective study of 46 patients. Acta Orthop 2011;82:711-3.
2. Magaji SA, Singh HP, Pandey RK. Arthroscopic subacromial decompression is effective in selected patients with shoulder impingement syndrome. J Bone Joint Surg Br 2012;94:1086-9.
3. Beard DJ, Rees JL, Cook JA, Rombach I, Cooper C, Merritt N, *et al.* Arthroscopic subacromial decompression for subacromial shoulder pain (CSAW): A multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial. Lancet 2018;391:329-38.
4. DeLee JC. Complications of arthroscopy and arthroscopic surgery: Results of a national survey. J Arthroscopic Relat Surg 1985;1:214-20.
5. Small NC. Complications in arthroscopic surgery performed by experienced arthroscopists. Arthroscopy 1988;4:215-21.
6. 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;1:97-103.
7. 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;76:468-70.
8. 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;2:190-210.
9. Wiig 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;8:425-34.
10. Ghosh P, Holbert C, Read R, Armstrong S. Hyaluronic acid (hyaluronan) in experimental osteoarthritis. J Rheumatol Suppl 1995;43:155-7.
11. Anand S, Singisetti K, Srikanth KN, Bamforth C, Asumu T, Buch K. Effect of sodium hyaluronate on recovery after arthroscopic knee surgery. J Knee Surg 2016;29:502-9.
12. Forster MC, Straw R. A prospective randomised trial comparing intraarticular hyalgan injection and arthroscopic washout for knee osteoarthritis. Knee 2003;10:291-3.
13. Moscuzza F. Postoperative analgesia for shoulder surgery. In: Guy's and St Thomas'. London: NHS Trust; 2012.
14. Moser JS, Barker KL, Doll HA, Carr AJ. Comparison of two patient-based outcome measures for shoulder instability after nonoperative treatment. J Shoulder Elbow Surg 2008;17:886-92.
15. van Kampen DA, Willems WJ, van Beers LW, Castelein RM, Scholtes VA, Terwee CB, *et al.* Determination and comparison of the smallest detectable change (SDC) and the minimal important change (MIC) of four-shoulder patient-reported outcome measures (PROMs). J Orthop Surg Res 2013;8:40.
16. Järvelä S, Järvelä T, Aho H, Kiviranta I. Arthroscopic subacromial decompression: Outcome comparison between outpatient and hospitalized patients with 2- to 5-year followup. Scand J Surg 2010;99:50-4.
17. Description. Available from: http://www.viscoseal.trbchemedica.co.uk/product-information/viscoseal. [Last accessed on 2019 Jan 24].
18. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: A systematic review. BMC Musculoskelet Disord 2015;16:321.
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;24:336-41.
20. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: A randomized clinical trial. Hyalgan study group. J Rheumatol 1998;25:2203-12.
21. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology (Oxford) 1999;38:602-7.
22. Lohmander LS, Dalén N, Englund G, Hämäläinen M, Jensen EM, Karlsson K, *et al.* Intraarticular hyaluronan injections in the treatment of osteoarthritis of the knee: A randomised, double blind, placebo controlled multicentre trial. Hyaluronan multicentre trial group. Ann Rheum Dis 1996;55:424-31.
23. Puhl W, Bernau A, Greiling H, Köpcke W, Pförringer W, Steck KJ, *et al.* Intraarticular sodium hyaluronate in osteoarthritis of the knee: A multicenter, double-blind study. Osteoarthritis Cartilage 1993;1:233-41.
24. Baker JF, Solayar GN, Byrne DP, Moran R, Mulhall KJ. Analgesic control and functional outcome after knee arthroscopy: Results of a randomized double-blinded trial comparing a hyaluronic acid supplement with bupivacaine. Clin J Sport Med 2012;22:109-15.
25. Mathies B. Effects of viscoseal, a synovial fluid substitute, on recovery after arthroscopic partial meniscectomy and joint lavage. Knee Surg Sports Traumatol Arthrosc 2006;14:32-9.
26. 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;20:410-23.
27. 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;99:121-6.