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Effect of sodium hyaluronate/carboxymethyl cellulose (Guardix-sol) on retear rate and postoperative stiffness in arthroscopic rotator cuff repair patients: A prospective cohort study

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Abstract

Purpose: Hyaluronate-based anti-adhesive agents are expected to enhance rotator cuff healing; however, their effect on the incidence and extent of postoperative complications such as stiffness and retears has not been investigated. **Methods:** From July 2012 to February 2013, 80 patients undergoing arthroscopic rotator cuff repair surgery were prospectively enrolled. Forty patients were assigned to the control group, while the other 40 were assigned to the injection group and received a Guardix-sol injection immediately after surgery. Passive range of motion, pain visual analog scale, and functional score were assessed at 8 weeks, 6 months, and 24 months postoperatively. Gliding motion between the deltoid muscle and the greater tuberosity of the proximal humerus was evaluated using ultrasonography at 2 and 8 weeks postoperatively, and tendon integrity was evaluated using magnetic resonance imaging at 6 months postoperatively. **Results:** We found no significant difference between the groups regarding gliding motion at 2 weeks postoperatively. However, at 8 weeks, the incidence of poor gliding motion was 2.5% and 15% for the injected patients and control group, respectively, which was statistically significant. At 6 months after surgery, the retear rate between the two groups was not statistically significant. We found no statistically significant difference between the two groups regarding retear rate and clinical score throughout the follow-up period. We noted no complications related to the use of Guardix-sol. **Conclusions:** Patients who received the Guardix-sol injection showed improved gliding motion between the deltoid muscle and the greater tuberosity in the early postoperative period.

Keywords

arthroscopic rotator cuff repair, clinical score, Guardix-sol, postoperative stiffness, retear rate, sodium hyaluronate

Introduction

Despite advancements in arthroscopic rotator cuff repair techniques, postoperative shoulder stiffness is still one of the most frequently reported postoperative complications.[1] A review of the literature shows that the incidence of stiffness following rotator cuff repair surgery ranges anywhere from 4.9% to 32.7%. The stiffness arises from capsular contracture of the implant and postsurgical adhesion to the surrounding soft tissues. Risk factors for stiffness following rotator cuff repair include diabetes mellitus, thyroid disorders, preoperative shoulder stiffness, operative technique, prolonged immobilization, and decreased compliance with postoperative rehabilitation protocols.[2] Therefore, regardless of the degree of rotator cuff healing, postoperative stiffness should be treated due to its negative effect on the satisfaction of the patient after arthroscopic surgery.[3]

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It has been reported that hyaluronate, the commercially available form of hyaluronan, prevents fibrosis and scar formation in fetuses, as well as in the early phase of wound healing, and moreover modulates cell proliferation, migration, and gene expression. An important anti-inflammatory effect has also been reported,[4] based on which sodium hyaluronate (SHA) is emerging as an alternative intra-articular regimen in the treatment of adhesive capsulitis of the shoulder joint.[5] Hyaluronate has been reported to act as an anti-adhesive agent during tendon surgery and abdominal surgery, where it reduced adhesions and post-operative ileus.[6,7] In addition, several studies have reported the enhanced rotator cuff healing potential of SHA in vitro.[8] However, to our knowledge, there are few reports on the anti-adhesive effect, incidence of retears (radiologic outcome), and clinical outcome of SHA in vivo applied as a subacromial injection immediately after the arthroscopic rotator cuff repair procedure.

In our study, we used SHA in combination with carboxymethyl cellulose (CMC), a polymer known to act as a mechanical barrier,[3] as it is not absorbed immediately, and remains on the surface of the implant during wound healing. Moreover, the CMC used in combination with SHA had been chemically modified in order to increase the time before the anti-adhesion agents are absorbed.[9] This combination of SHA and CMC is commercially available under the name Guardix-sol.

The aim of this study is to evaluate the effects of Guardix-sol in terms of retear rate (radiologic outcome), clinical outcomes, and postoperative stiffness. We hypothesized that patients injected with Guardix-sol would have better total range of motion (ROM; including forward elevation, external rotation, and internal rotation) in the early postoperative period, with no effect on tendon integrity.

Materials and methods

Patient selection

Between July 2012 and February 2013, a total of 80 patients who had undergone arthroscopic rotator cuff repair were prospectively enrolled. Prior approval was obtained from the hospital ethics committee and a written informed consent was taken from all patients. This is a hospital-based study. The patients were assigned to either the injection group ($n = 40$) or to control group ($n = 40$), and this assignment of patients to groups was not randomized. The first 40 consecutive patients did not receive the Guardix-sol injection and were assigned to the control group, while the following 40 patients received the Guardix-sol injection and were assigned to the injection group. The study included only patients with a full-thickness rotator cuff tear who underwent arthroscopic suture bridge (transosseous equivalent (TOE) double row) repair of the rotator cuff. We excluded patients with degenerative arthritis, infection, revision of the rotator cuff repair, open surgery, rheumatoid arthritis, incomplete, or partial repair[10] (type III or IV repair). The rotator cuff tears were labeled according to their size, from small to large. Among the patients in the injection group, 2 had small tears, 36 had medium tears, and 2 had large tears. Among the patients in the control group, 2 had small tears, 34 had medium tears, and 4 had large tears.

Surgical technique and injection

All surgeries were performed by a single surgeon. During surgery, the patient lay in the lateral decubitus position. Intra-articular pathologies were managed after creating the routine posterior and anterior portals. Additional capsular release was performed with a radiofrequency device (AthroCare, Austin, Texas, USA) in patients who had showed preoperative limitation in ROM ($n = 26$ for the injection group and $n = 31$ for the control group). Thereafter, the arthroscope was inserted into the subacromial space. Acromioplasty was performed on patients with anterior osteophyte of the acromion and prominent anterolateral acromial spur. After debridement of pathologic tissue, the medial–lateral tear size was measured using a calibrated probe with 5-mm-spaced markings through the lateral portal, and the anterior–posterior tear size was measured using the same probe through the anterior portal. Depending on the tear size, two or three double-loaded suture anchors (GENESYS; ConMed Linvatec, Largo, Florida, USA) were inserted in the medial portion of the footprint, adjacent to the cartilage. Sutures were passed through the tendon edge by shuttling with size 0 polydioxanone (Ethicon), and not all sutures were tied. Usually, only two knots (out of four medial row suture passages) were tied in the medial row. One limb from each suture loop pair was selected and fixed in the lateral row by a knotless suture anchor (POPLOK; ConMed Linvatec). Similarly, the other limbs were fixed by using another suture anchor. The repair constructs did not differ between the two groups. All patients underwent complete repair (type I or type II repair)[11] using 1×2 or 2×2 TOE techniques (Figure 1).

The injection protocol was also the same for both groups. After finishing the rotator cuff repair procedures, a spinal needle attached with a syringe containing Guardix-sol was inserted into the lateral sub-deltoid and acromion area, but no solution was injected (Figure 2). Afterwards, the shoulder was squeezed in order to remove some of the normal saline present in the shoulder joint. Subsequently, the skin portal was sutured. Finally, Guardix-sol was injected for patients in the injection group just before the complete dressing was applied to the wound. The patients in the injection group received a single dose of Guardix-sol (i.e. 5 g of SHA/CMC mix), while the patients in the control group were not injected.

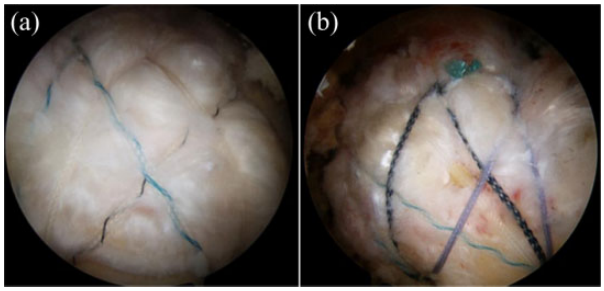

Figure 1. Arthroscopic picture of the transosseous equivalent repair: (a) 1 × 2 and (b) 2 × 2.

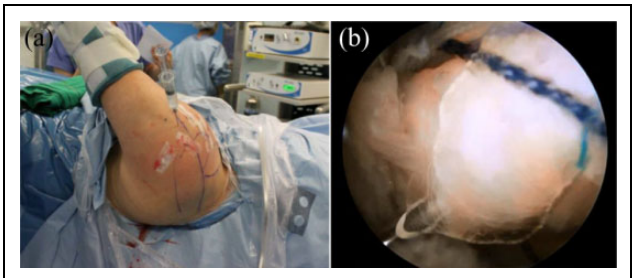

Figure 2. Setup of the injection system (a) and arthroscopic picture of Guardix-sol injection (b) following the rotator cuff repair procedure.

Rehabilitation protocol

All patients were immobilized for 4–5 weeks after the rotator cuff repair surgery, depending on the tear size (4 weeks for small or medium tears and 5 weeks for large tears), without any passive or active ROM exercise. A sling with an abduction pillow was applied during that period. After the removal of the sling and pillow, gentle passive ROM exercise was started using a rope and pulley and a cane. During two or three outpatient visits, rehabilitation was supervised by a professional therapist from the authors' institution. Those patients who were not able to come to our clinic after the initial two or three visits were educated with respect to home exercise rehabilitation.

Outcome assessments

The primary outcome assessed was ROM measured by an independent, blinded researcher preoperatively and at 8 weeks, 6 months, and 24 months after surgery. The secondary outcomes assessed were clinical scores, magnetic resonance imaging (MRI), and ultrasonographic findings. Secondary outcomes were also measured preoperatively and at 8 weeks, 6 months, and 24 months after surgery. With respect to clinical scores, patients were evaluated for passive ROM (forward elevation, abduction, internal rotation to the back, and external rotation) and were assigned a pain score on a visual analog scale (VAS), an American Shoulder and Elbow Surgeons (ASES) score, and a Constant score. In addition, we have gathered VAS and ASES score data outcomes via telephone surveys only from those patients whose had not had a follow-up for the last 2 years.

The gliding motion (graded poor or good) in the space between the deltoid muscle and the greater tuberosity of the proximal humerus was examined using ultrasonography at 2 and 8 weeks postoperatively. The transducer was placed in the area of the greater tuberosity, and the sonographer examined the gliding motion during passive external and internal rotations at the side. We measured the GT that moves laterally or medially with the rotary movements of the arm. If GT is moving toward lateral side less than 5 mm during the external rotation, we assessed it as "poor." It has been seen that the external rotation is the first and most severely affected movement in the acromioclavicular joint, followed by abduction and internal rotation, with forward flexion being the least diminished movement.

At approximately 6 months after surgery, MRI examinations of both groups were performed using 3.0 T scanners (Gyroscan Intera Achieva, Philips Medical Systems, Best, the Netherlands). The MRI data were reviewed independently by two orthopedic surgeons on two separate occasions, 2 weeks apart. The MRI evaluations focused on postoperative complications and rotator cuff retears, with retear findings being graded according to the classification suggested by Sugaya et al.[12]

Statistical analysis

The expected difference between the injection and control groups with respect to the mean values for follow-up forward elevation would be 15°, with a standard deviation of 21°, given a 0.05 two-sided significance level and a power of 80%.[13] Based on the *t*-test, the minimum sample size for each group was determined to be 32 patients (nQuery Advisor 3.0; Statistical Solutions, Cork, Ireland). Considering a dropout rate of 20%, the optimal sample size was determined to be 40 patients.[14] Student's *t*-test was used to compare the pain VAS, ROM, and functional scores between the two groups. The χ^2 test was used for categorical variables. The significance threshold was set at 0.05 for all analyses. Inter-observer reliability was evaluated using the value and the intraclass correlation coefficient for categorical variables and continuous variables, respectively. The evaluated measurements were compared between the injection group and the control group. All statistical analyses were performed using SPSS v. 12.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Table 1 shows the patient demographics. The mean age of patients in the injection group ($n = 40$) was 59.9 ± 8.4 years (range, 40–77 years), and 15 patients were male. The mean age of patients in the control group ($n = 40$) was

Table 1. Demographic and preoperative data for all patients included in this study.

		Injection group	Control group	*p* Value
Number of patients		40	40	NS
Age		59.9 ± 8.4	61.9 ± 7.5	NS
Sex (male/female)		15/25	19/21	$p < 0.05$
Operation site (right/left)		27/13	26/14	NS
Past medical history	Diabetes mellitus	5	4	NS
	Cardiovascular	12	11	NS
	Thyroid disorders	3	4	NS
	Smoking	14	12	NS

Table 2. Comparisons between the injection group and the control group with respect to ROM and clinical outcomes, preoperatively and 8 weeks postoperatively.

	Injection group ($n = 40$)	Control group ($n = 40$)	*p* Value
Preoperatively			
Range of motion (°)			
Forward elevation	137.0 ± 33.5	129.3 ± 28.1	0.266
Internal rotation	10.2 ± 3.7	11.4 ± 4.6	0.177
External rotation	44.1 ± 18.9	38.5 ± 14.2	0.137
Clinical scores			
Pain VAS	5.4 ± 2.4	5.2 ± 2.2	0.717
Constant	48.2 ± 20.5	48.1 ± 19.3	0.804
ASES score	44.7 ± 16.4	43.8 ± 18.4	0.743
Postoperatively (8 weeks)			
Range of motion (°)			
Forward elevation	112.1 ± 31.3	102.0 ± 22.9	0.105
Internal rotation	14.1 ± 3.9	14.8 ± 3.4	0.391
External rotation	12.2 ± 14.9	17.5 ± 15.1	0.126
Clinical scores			
Pain VAS	4.5 ± 2.1	4.8 ± 1.8	0.624
Constant	39.8 ± 14.5	39.7 ± 17.2	0.942
ASES score	46.5 ± 16.3	34.1 ± 21.2	0.574

ROM: range of motion.

61.9 ± 7.5 years (range, 48–76 years), and 19 patients were male. There was no significant difference in terms of age between the two groups, but there was a significant difference with respect to gender ratio. Other demographic factors did not significantly differ between the groups.

For the patients in the injection group, MRI examinations were performed at 5.2 ± 0.5 months after surgery, and four patients did not undergo MRI examinations. For patients in the control group, MRI examinations were performed at 5.1 ± 0.6 months after surgery, and six patients did not undergo MRI examinations. We considered MRI findings graded as Sugaya[15] type IV and V as retears. Interobserver reliability was strongest for retear detection (range, 0.81–1.00; = 0.97). The incidence of retears was 2.7% ($n = 1$) in injection group and 11.8% ($n = 4$) in the control group. Although not statistically significant, there was a tendency to have a higher incidence of retears in the control group than in the injection group ($p = 0.192$).

There was no significant difference between the injection and control groups regarding the quality of the gliding motion in the interspace between the deltoid muscle and the greater tuberosity, which was evaluated by ultrasonography at 2 weeks postoperatively. However, there was a significant difference regarding gliding motion in the sub-deltoid space at 8 weeks postoperatively ($p < 0.05$). The incidence of poor gliding motion was 2.5% (1/40) for patients in the injection group and 15% (6/40) for patients in the control group.

There were no differences between groups with regard to passive ROM and clinical scores preoperatively or at 8 weeks, 6 months, or 24 months postoperatively (Tables 2–4). At the 2-year follow-up, three patients from the injection group and four patients from the control group were absent. Regarding forward elevation, there was a tendency for faster recovery in patients from the injection group than in those from the control group at 8 weeks postoperatively (Figures 3 and 4), but this difference was not statistically significant ($p = 0.105$).

Discussion

This study demonstrates that the patients who received a subacromial injection of Guardix-sol resulted in no

Table 3. Comparison between the injection group and the control group with respect to ROM and clinical outcomes at 6 months postoperatively.

	Injection group ($n = 36$)	Control group ($n = 34$)	p Value
Postoperatively (6 months)			
Range of motion (°)			
Forward elevation	124.6 ± 22.0	119.6 ± 23.0	0.418
Internal rotation	10.6 ± 2.9	11.9 ± 3.4	0.148
External rotation	28.6 ± 13.0	24.8 ± 11.6	0.272
Clinical scores			
Pain VAS	2.9 ± 1.1	3.3 ± 1.4	0.492
Constant	58.7 ± 14.1	53.0 ± 19.2	0.136
ASES score	65.1 ± 16.3	57.7 ± 23.3	0.105

ROM: range of motion; VAS: visual analog scale; ASES: American Shoulder and Elbow Surgeons.

Table 4. Comparison between the injection group and the control group with respect to ROM and clinical outcomes at 2 years postoperatively.

Final follow-up (2 years)	Injection group ($n = 37$)	Control group ($n = 36$)	p Value
Range of motion (°)			
Forward elevation	153.6 ± 11.3	148.8 ± 18.6	0.261
Internal rotation	7.4 ± 2.1	7.9 ± 1.9	0.348
External rotation	38.2 ± 10.6	48.0 ± 16.6	0.825
Clinical scores			
Pain VAS	1.5 ± 1.3	1.7 ± 1.5	0.576
Constant	82.6 ± 16.4	80.9 ± 18.9	0.194
ASES score	75.6 ± 16.3	70.1 ± 19.9	0.189

ROM: range of motion; VAS: visual analog scale; ASES: American Shoulder and Elbow Surgeons.

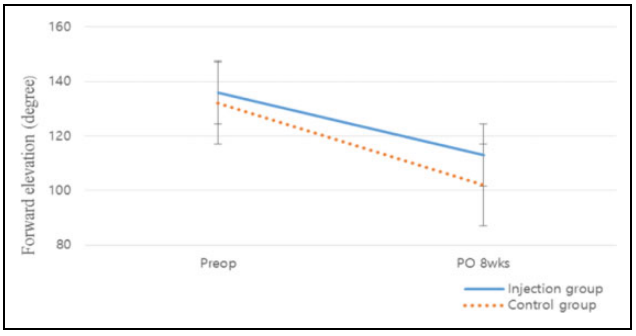

Figure 3. Forward elevation showed a tendency for fast recovery in the injection group (112.1° ± 31.3°) than in the control group (102.0° ± 22.9°) at 8 weeks postoperatively but there was no statistically significant difference ($p = 0.105$).

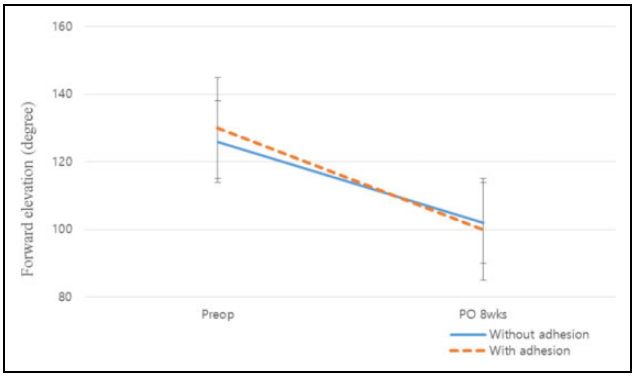

Figure 4. Forward elevation showed no significant difference between patients without subacromial adhesion (100° ± 23.7°) and those with adhesion in the control group (102.6° ± 22.5°; $p > 0.05$).

improvement of clinical outcomes over a 2-year follow-up period, compared with the control group. Despite this, patients who received the injection had a relatively lower incidence of retears even though a single injection might not have had any influence on stiffness or tendon integrity during the immediate postoperative period. However, patients who received a subacromial injection of Guardix-sol showed a tendency for faster improvement in forward elevation and improved sono-guided sub-deltoid gliding motion at 8 weeks postoperatively. That is, the early postoperative phase has shown that Guardix-sol can be an effective way to decrease stiffness.

Hyaluronan is an anionic, non-sulfated glycosaminoglycan widely distributed throughout connective, epithelial, and neural tissues.[16] As one of the chief components of the extracellular matrix, hyaluronan contributes significantly to cell proliferation and migration. The inflammation process that ensues after surgical trauma leads to the generation of many biologic factors, including growth factors, cytokines, and eicosanoids. These biologic factors are necessary for subsequent wound healing as they promote the migration of inflammatory cells, fibroblasts, and

endothelial cells to the wound site.[17] During the early inflammatory phases of wound repair, the wounded tissue contains high concentrations of hyaluronan, probably because of increased synthesis.[17] Hyaluronan acts as a promoter of early inflammation, which is crucial for the entire wound healing process. Hyaluronan may also function in the negative feedback loop of inflammatory activation through its specific interactions with the biologic factors of inflammation.[17]

Furthermore, the efficacy and safety of SHA use in abdominal and gynecologic surgery have already been reported.[6] Kumar et al.[18] reported that an SHA/CMC membrane was the only effective anti-adhesiogenesis agent in general surgical patients. Several relevant reports have also been published in the field of orthopedic surgery, with many showing a decrease in the number of paratendinous adhesions when using seprafilm or hyaluronate gel after repair of the flexor tendons in animal models.[19] The use of sodium hyaluronate as nonsurgical therapy in shoulder disorders has also been reported.[20,21] However, considering that shoulder stiffness is one of the important complications after surgical repair,[1,22] it is surprising that there are only a few reports regarding the anti-adhesive effects of hyaluronate after shoulder surgery, particularly after rotator cuff repair.

Postoperative stiffness is recalcitrant to treatment, and it limits the patient's daily activities because of the restricted motion and pain.[23] Additionally, it is well known that postoperative stiffness discourages functional improvements. Trenerry et al.[24] evaluated postoperative ROM recovery comparing an early motion recovery group and a postoperative stiffness group and observed a gradual, full ROM recovery in the postoperative stiffness group within 76 weeks. However, many surgeons contemplate how to prevent early postoperative stiffness after rotator cuff repair. In this context, we carried out the Guardix-sol injection experiment in order to determine whether the use of Guardix-sol can encourage faster recovery of early ROM or less adhesion in the subacromial joint space. However, we did not observe statistically significant recovery of early ROM in patients from the injection group. Nonetheless, these patients showed a tendency for faster recovery compared to that of the control group at 8 weeks postoperatively (Table 2), but this difference was not statistically significant ($p > 0.05$).

Wiig et al.[25] showed that hyaluronate inhibited cell proliferation of rabbit flexor tendons in vitro in a dose-dependent manner, which can be attributed to its anti-adhesive property. In another study, Yamada et al.[8] showed that hyaluronate modulates cell proliferation and expression of mRNA for procollagen α1 (III), which is a precursor for type III collagen, but not for that of procollagen α1 (I), which is a precursor for type I collagen and may allow healing of the rotator cuff tendon with minimal adhesion. Oryan et al.[26] also showed that SHA decreased post-surgical hyperemia, edema, and inflammation at the injured area of rabbit superficial flexor digitalis tendon compared to the control group. We feel that all these effects might have influenced our results regarding the lower incidence of retears and that SHA might have some positive effects in healing as it causes less inflammation and cell proliferation.

Usually, several postoperative adhesions are seen in the subacromial, subcoracoid, and subdeltoid space, with capsular contraction. Subacromial adhesion is known to play an important role in postoperative stiffness.[27] Therefore, it is crucial to have some anti-adhesive agents in these spaces. This is why we decided to inject the agent in this area. However, we feel that the space is too wide for a single injection of 5 g to be efficient, and higher doses are required in order to observe a measurable effect. However, due to relatively high cost of even a single injection, we were not able to administer additional injections. As proven in the Gliding movement, it helps the external rotation during the early postoperative period. A high cost may become a concern to some patients, so it may be selectively used upon patient's consent. Also lowering the cost of the agent and conducting more conclusive and positive studies on rotator cuff tears are important steps to improve the understanding of its action under different circumstances.

One unique aspect of this study was to examine the gliding motion in the interspace between the deltoid muscle and the greater tuberosity of the proximal humerus using ultrasonography. It was difficult to measure subacromial adhesion, so we measured the deltoid adhesion. Because SHA decreases friction against soft tissue,[26] the SHA injection was favored by the authors in the hope of decreasing subacromial fibrous adhesion. However, at 8 weeks after surgery, patients without subacromial adhesion in the control group did not significantly differ in their ROM when compared with those with subacromial adhesion (Figure 2). This might be due to many other variables. As mentioned above, a single injection might be sufficient to help the entire shoulder ROM since it might have helped the gliding motion of the subdeltoid area. Another factor would be that the effect might be too small to be both detected and measured by conventional tools.

There were several limitations in this study. First, this study was not a randomized study, which might introduce sample bias since the results only pertain to certain cases of Guardix injection. Second, at the 2-year follow-up, although we had more than 80% follow-up patients, 12 patients in the injection group and 11 patients in the control group could not visit the outpatient clinic. Therefore, a phone survey was conducted to collect the data. Accordingly, the ROM data could not be obtained for these patients, resulting in a lower follow-up rate. Third, there is always measure error and performance bias. Although we tried to reduce each of these by evaluating MRI findings twice by two observers, there is bound to be some residual bias. The same issue is present for ultrasonographic measurements. Fourth, although we looked at several

preoperative demographic factors for both groups, some unchecked variables might have been different between the groups. Since women had more pain and slower recovery of shoulder motion compared with men during the first 3 months after rotator cuff repair; the gender difference might have played some role.[28] Fifth, when there is no difference in comparing two groups of small sample size, one is always subjected to beta-error. Finally, it is not clear whether one dose of Guardix injection is sufficient to prevent adhesion. Therefore, in order to clarify this issue, dose-dependent studies need to be carried out in the future.

Conclusion

Compared to the patients in the control group, patients who received the Guardix-sol injection showed improved gliding motion between the deltoid muscle and the greater tuberosity in the early postoperative period, as evaluated by ultrasonography. In addition, patients who received the injection tended to show better healing rate (lower retear rate, as evaluated by postoperative MRI) and improved forward elevation, even though these differences were not statistically significant. The results of other clinical measurements did not show any differences between the postoperative progress of the injection group and that of the control group.

Authors' note

The study was approved by the Institutional Review Board at the Sungkyunkwan University College of Medicine, Samsung Medical Center: no. SMC 2012-03-056-012.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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