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Comparative analysis of intra-articular injection of steroid and/or sodium hyaluronate in adhesive capsulitis: prospective, double-blind, randomized, placebo-controlled study

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Background: Few studies have reported the effects of simultaneous injections of corticosteroid (CS) and hyaluronic acid (HA) on adhesive capsulitis (AC) of the shoulder. This study investigated the synergistic effects of simultaneous intra-articular injections of CS and compared them to those of CS or HA alone.
Method: Sixty patients with AC were enrolled in this randomized, placebo-controlled trial. The participants were divided into 4 groups: saline, CS, HA, and CS with HA groups. The primary outcome measure was changes in the Shoulder Pain and Disability Index (SPADI) scores at one month. The secondary outcome measures included changes in pain, range of motion, muscle strength, and additional shoulder functional scores at 1 day, 1 week, and 1, 3, and 6 months after injection.
Results: After 1 month, changes of the SPADI scores were significantly higher in the CS with HA group (−58.4%) than those in the saline (−7.7%) and HA (−14.4%) groups. The score changed more in the CS with HA group than that in the CS group (−43.7%), but there was no significant difference. In the changes in pain, the CS with HA group showed significantly better and faster effects than the saline and HA groups. In the changes of range of motion, functional scores, the CS with HA group showed better results than the saline and HA groups.
Conclusion: In the treatment of AC, the simultaneous injection of CS and HA was more effective in improving SPADI scores at one month after injection than a single injection of CS or HA.

Adhesive capsulitis (AC) of the shoulder is characterized by the spontaneous onset of shoulder pain and the gradual loss of active and passive shoulder motion and is known to occur in 2%-5% of the general population.[37] AC is a painful condition and causes disability and sleep disorders.[26] The socioeconomic burden of AC was reported to be £3954 per patient in England and €4521 in the Netherlands.[25,39] AC is considered a self-limiting disease that resolves in one to three years. However, 20%-50% of patients suffer long-term deficits in range of motion (ROM) within ten years.[3,25,28,36]

AC is reported to proceed as freezing, frozen, and thawing stages, but the stages can overlap.[26,27] The patients are classified as pain-predominant and stiffness-predominant. The stiffness-predominant phase is treated with physical therapy, and the pain-dominant phase is treated in various ways. The known treatment methods are analgesia, physical therapy, corticosteroid (CS) or hyaluronic acid injection (HA), manipulation under anesthesia, hydrodilatation, and arthroscopic release, but there is no one standard of treatment.[14,20,43] Although the optimal treatment method is controversial, intra-articular injections are one of the most commonly used treatments.[1,7,9,10,24,26,40] The purpose of the injection is to relieve pain early, help ROM exercises, and ultimately improve function quickly.[26] Among the various injection materials, the intra-articular injection of CS is known to be an effective treatment,[31] and HA is also reported to be effective and similar to CS.[14,22,23] CS increases the transcription of genes coding for anti-inflammatory proteins such as liporcortin-1, interleukin-10, and interleukin-1 receptor antagonist and inhibits the expression of multiple inflammatory genes.[17] CS has a greater short-term effect for AC, but only a small long-term effect.[4,26] HA has an

Seoul Metropolitan Governance—Seoul National University Boramae Medical Center Institutional Review Board approved this study (IRB No. 06-2008-44).

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Table I
Patient characteristics before injection of different regimens.

Variables	Saline group (n = 15)	CS group (n = 15)	HA group (n = 15)	CS with HA group (n = 15)	*P* value[†]
Mean age[*]	49.4 ± 4.9	52.3 ± 8.5	54.5 ± 5.1	53.5 ± 7.5	.182
Sex (male:female)	3:12	5:10	9:6	4:11	.133
Dominance (yes:no)	5:10	6:9	7:8	8:7	.819
Duration (mo)[*]	7.4 ± 5.9	7.6 ± 8.6	6.8 ± 8.3	10.2 ± 8.9	.683
Aggravation (mo)[*]	1.6 ± 1.0	1.8 ± 1.4	1.8 ± 1.4	2.7 ± 1.5	.605
Follow-up (mo)[*]	6.2 ± 0.6	6.4 ± 0.8	6.3 ± 0.8	6.3 ± 0.6	.932
Accuracy (success:fail)	15:0	14:1	15:0	15:0	.148

HA group, hyaluronic acid group; *CS group,* corticosteroid group; *CS with HA group,* combination of corticosteroid and hyaluronic acid group.
There is no difference between groups in all variables.
[*]The values are given as mean difference ± standard deviation.
[†]By analysis of variance, $P < .05$ was defined as statistically significant.

anti-inflammatory effect and is known to protect damaged cartilage and improve synovial abnormalities.[31,33,36] HA has a delayed onset between 2 and 5 weeks and continues to be effective for 6 months.[2] Both CS and HA have anti-inflammatory effects as described previously. The simultaneous administration of both in orthopedic treatment is reported to be more effective than each medication alone because their onset and action mechanisms are different. However, the level of evidence of studies on these injection treatments for AC is limited, and the number of injections, follow-up periods, and medication dose were different in each study, making it difficult to interpret the results.[26]

Only one previous study compared the simultaneous injection of CS and HA to an injection of CS alone.[33] In that study, injections were administered seven times, but treatment effect of simultaneous injections was not clear because of the lack of a control group. To the best of our knowledge, no studies have systematically analyzed the effects of CS with HA, CS alone, and HA alone. Accordingly, the purpose of our study was to address the clear evidence for the treatment effect of simultaneous injections of CS and HA. Our hypothesis is that the simultaneous injection of CS and HA is more effective for improving Shoulder Pain and Disability Index (SPADI) scores one month after injection than a single injection of CS or HA.

Method

Study design and eligibility criteria

A single-center, placebo-controlled, randomized clinical trial with a blinded outcome assessor was conducted at a university hospital enrolling patients with unilateral AC. Between 2010 and 2013, patients aged between 25 and 75 years were eligible if they had painful limitations in shoulder movements. AC was diagnosed as the presence of shoulder pain and limitations in both active and passive ROM more than 25% in at least two planes of forward flexion (FF), abduction (ABD), external rotation (ER), and internal rotation (IR) compared to the contralateral shoulder or normal values.[10] As it was the freezing stage of active capsulitis, the duration of the symptoms was less than a year.[26] We excluded patients if they had bilateral symptoms, uncontrolled diabetes mellitus, overt hypothyroidism or hyperthyroidism, previous shoulder surgery, any other previous glenohumeral joint injections, trauma to the

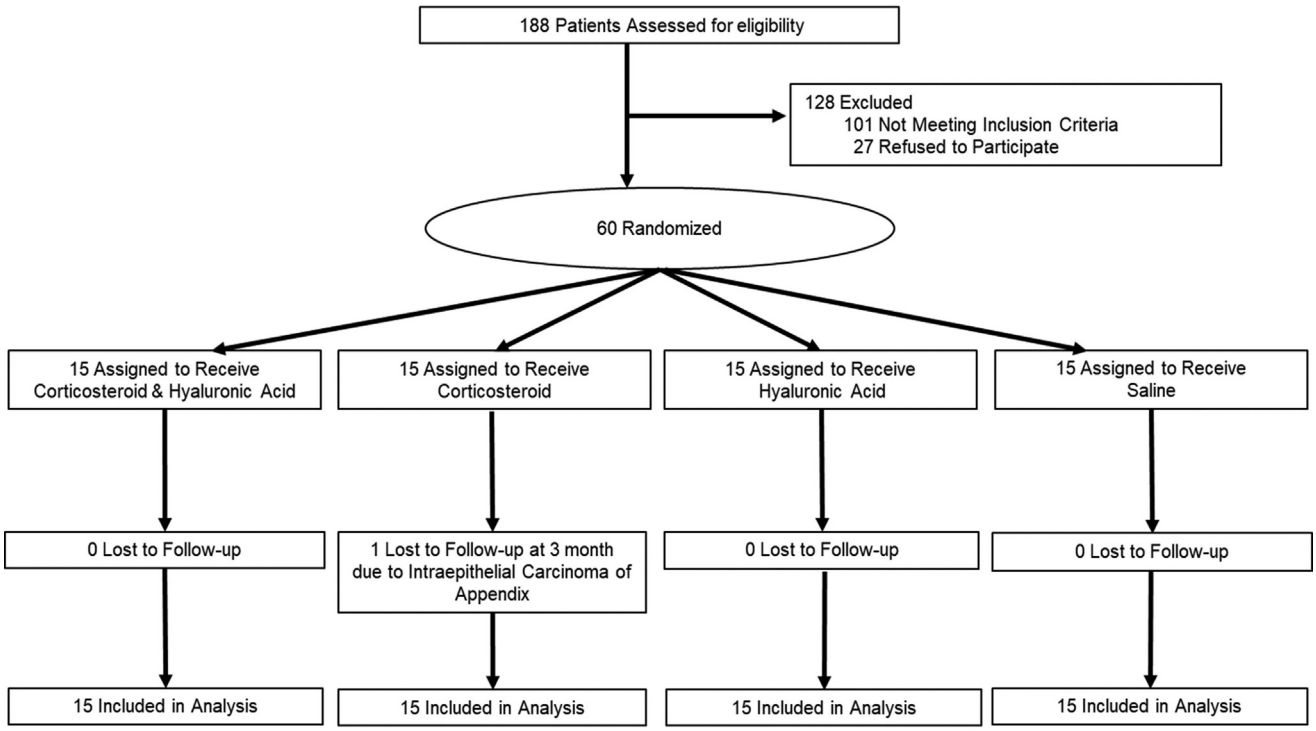

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patient randomization to each regimen of the injection treatment groups.

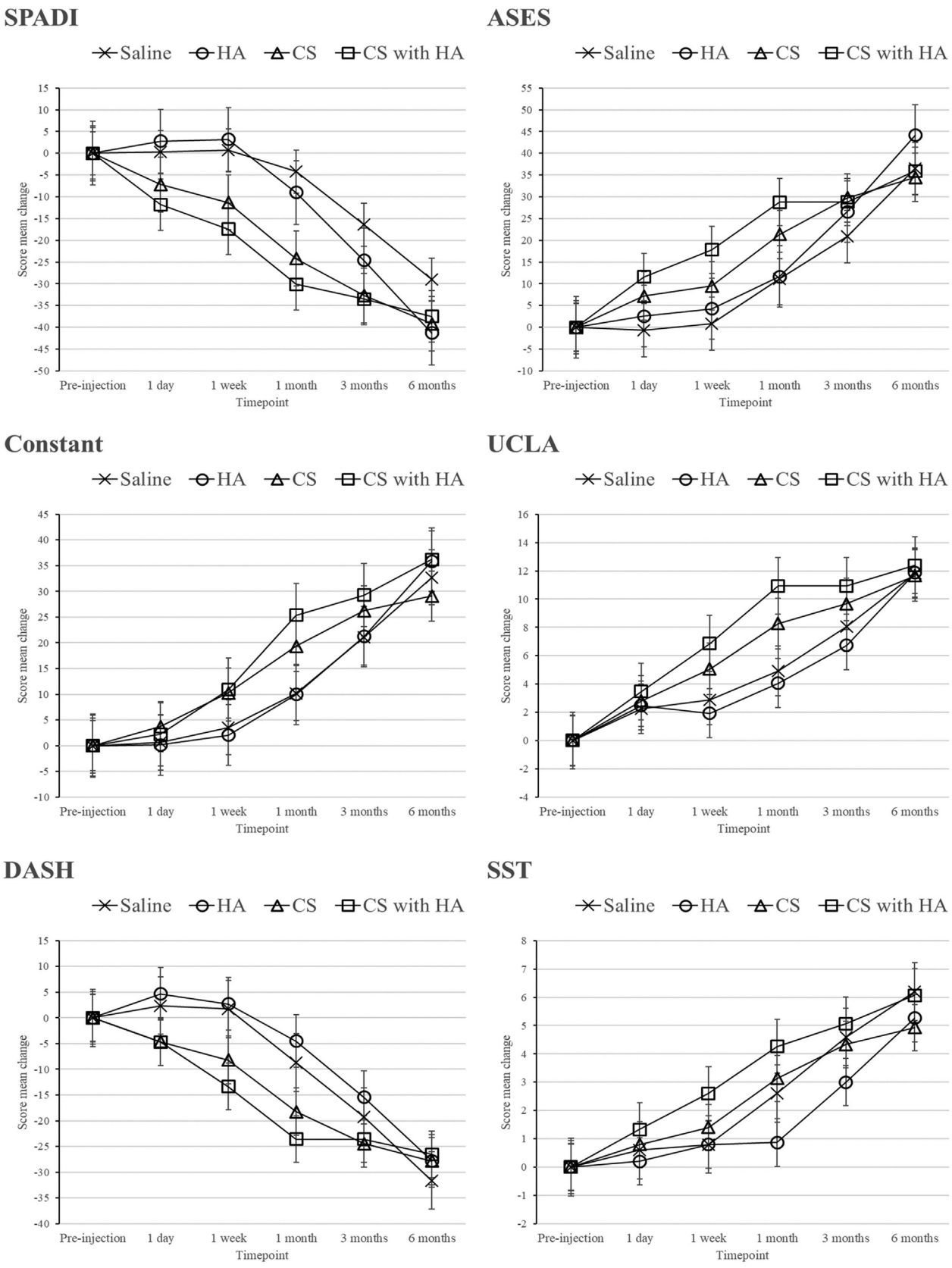

Figure 2 Mean changes in functional scores after intra-articular injections of different regimens. For UCLA and DASH scores, there was no significant difference between the groups. *HA*, hyaluronic acid; *CS*, corticosteroid; *CS with HA*, combination of corticosteroid and hyaluronic acid; *SPADI*, Shoulder Pain and Disability Index; *ASES*, American Shoulder and Elbow Surgeons; *Constant*, Constant system; *UCLA*, University of California at Los Angeles system; *DASH*, Disabilities of the Arm, the Shoulder and Hand system; *SST*, Simple Shoulder test.

Table II
Meanchanges of functional scores after intra-articular injections of different regimens.

Measurement	Saline group	HA group	CS group	CS with HA group	*P* value*
SPADI					.006
Preinjection	54.9 ± 25.5	55.9 ± 17.6	55.5 ± 21.8	51.6 ± 12.9	
1 d	0.3 ± 11.9	2.8 ± 10.7	−7.2 ± 10.7	−11.8 ± 14.5‡	.002
1 week	0.7 ± 13.0	3.2 ± 15.2	−11.3 ± 16.9‡	−17.4 ± 12.9†,‡	<.001
1 mo	−4.2 ± 22.3	−8.0 ± 28.1	−24.2 ± 16.8†	−30.1 ± 10.7†,‡	<.001
3 mo	−16.4 ± 28.3	−24.6 ± 25.4	−32.7 ± 20.3	−33.5 ± 19.0	.061
6 mo	−29.0 ± 42.8	−41.3 ± 18.9	−39.2 ± 25.9	−37.5 ± 18.5	.683
ASES					.034
Preinjection	43.9 ± 20.9	42.7 ± 18.8	44.4 ± 20.9	47.9 ± 19.2	
1 d	−0.6 ± 9.1	2.5 ± 11.6	7.1 ± 15.9	11.6 ± 16.2†	.021
1 week	0.8 ± 15.8	4.3 ± 16.1	9.5 ± 16.8	17.8 ± 14.1†,‡	<.001
1 mo	11.2 ± 16.2	11.7 ± 23.4	21.3 ± 15.1	28.8 ± 18.6†,‡	.001
3 mo	20.9 ± 20.6	26.6 ± 23.0	29.8 ± 20.1	28.8 ± 22.3	.381
6 mo	36.5 ± 26.3	44.1 ± 20.8	34.4 ± 26.7	35.9 ± 21.2	.466
Constant					.015
Preinjection	34.9 ± 11.6	38.7 ± 14.0	36.5 ± 15.3	38.2 ± 13.3	
1 d	0.6 ± 5.4	0.1 ± 8.6	3.7 ± 5.8	2.2 ± 5.7	.357
1 week	3.6 ± 10.4	2.1 ± 7.5	10.2 ± 10.2	10.9 ± 7.8‡	<.001
1 mo	10.2 ± 10.1	10.0 ± 14.3	19.3 ± 9.0†	25.4 ± 12.3†,‡	<.001
3 mo	21.1 ± 17.9	21.2 ± 17.3	26.2 ± 12.5	29.3 ± 15.5	.295
6 mo	32.7 ± 22.1	35.9 ± 15.2	29.1 ± 21.9	36.2 ± 15.6	.520
UCLA score					.234
Preinjection	16.1 ± 4.6	16.1 ± 3.8	15.6 ± 3.8	16.9 ± 5.2	
1 d	2.3 ± 5.3	2.5 ± 4.1	2.8 ± 5.3	3.5 ± 4.4	
1 week	2.9 ± 5.9	1.9 ± 3.1	5.1 ± 5.1	6.9 ± 4.5	
1 mo	4.9 ± 6.3	4.1 ± 5.2	8.3 ± 5.1	10.9 ± 6.0	
3 mo	8.1 ± 7.4	6.7 ± 5.9	9.7 ± 6.3	10.9 ± 6.2	
6 mo	11.8 ± 7.2	11.9 ± 5.0	11.7 ± 7.6	12.4 ± 6.8	
DASH					.001
Preinjection	46.6 ± 26.3	39.4 ± 22.5	43.8 ± 15.2	39.1 ± 12.1	
1 d	2.4 ± 8.8	4.7 ± 12.8	−4.6 ± 9.5	−4.7 ± 10.2	.043
1 week	1.7 ± 10.7	2.7 ± 13.8	−8.2 ± 11.1	−13.3 ± 7.9†,‡	<.001
1 mo	−8.7 ± 14.2	−4.5 ± 17.7	−18.2 ± 10.0	−23.6 ± 13.1†,‡	<.001
3 mo	−19.2 ± 23.4	−15.4 ± 15.4	−24.4 ± 13.3	−23.6 ± 15.6	.226
6 mo	−31.6 ± 26.7	−27.8 ± 17.0	−27.8 ± 14.1	−26.5 ± 12.9	.933
SST					.357
Preinjection	3.3 ± 2.7	4.9 ± 3.2	4.2 ± 3.0	4.3 ± 2.6	
1 d	0.6 ± 1.5	0.2 ± 1.7	0.8 ± 2.2	1.3 ± 1.9	
1 week	0.8 ± 2.0	0.8 ± 2.5	1.4 ± 2.4	2.6 ± 2.3	
1 mo	2.6 ± 2.4	0.9 ± 3.0	3.1 ± 2.4	4.3 ± 2.6	
3 mo	4.6 ± 2.8	3.0 ± 1.2	4.3 ± 3.4	5.1 ± 2.7	
6 mo	6.2 ± 3.4	5.3 ± 3.5	4.9 ± 3.5	6.1 ± 2.7	

HA group, hyaluronic acid group; *CS group,* corticosteroid group; *CS with HA group,* combination of corticosteroid and hyaluronic acid group; *SPADI,* the Shoulder Pain and Disability Index; *ASES,* the American Shoulder and Elbow Surgeons; *Constant*, the Constant system; *UCLA,* the University of California at Los Angeles system; *DASH,* the Disabilities of the Arm, the Shoulder and Hand system; *SST,* the Simple Shoulder test.
The values are given as mean difference ± standard deviation. There was no significant difference between the CS with HA group and the CS group.
*By analysis of variance, $P < .05$ was defined as statistically significant.
†Significantly greater than that in the saline group.
‡Significantly greater than that in the HA group.

shoulder (including fracture or dislocation) that required hospital care within recent six months, neurological symptoms, allergies to injection materials, secondary AC, systemic inflammatory disease including rheumatoid arthritis, infection or osteoarthritis of the shoulder joint, blood coagulation diseases, a full-thickness rotator cuff tear, serious mental illness, pregnancy, and cerebrovascular accidents. The study was approved by the Seoul Metropolitan Government Seoul National University Boramae Medical Center Institutional Review Board (IRB no.: 06-2008-44). The trial protocol is shown in Supplement 1.

Randomization and blinding

After providing consent and undergoing baseline assessment, the enrolled patients were randomly allocated at a 1:1:1:1 ratio with block sizes of 8 and 12 using the randomization sequence created using SAS 9.1 statistical software (SAS Institute Inc., Cary, NC, USA), which was performed by a biostatistician. The patients were assigned to receive either HA injection, CS injection, CS and HA injection, or saline injection as a sham treatment. The assignment was delivered to the assistant who prepared the injection, and the injection assignment was sealed. The patients, as well as the main investigator, were blinded to the treatment assignments. The outcome assessor was blinded to the group allocations and not involved in providing the interventions.

Intervention

A single physician performed all the injections as previously described.[18] To compare the exact effects of each drug, all drugs were injected only once at the same dose. The patient in the saline group received 4 mL of saline and 4 mL of contrast media (ioxitalamate); the CS group received 1 mL of triamcinolone acetonide (40mg/mL), 3 mL of saline, and 4 mL of contrast media; the HA group received 2 mL of high-molecular-weight hyaluronic acid with an average molecular weight of 3000 kD (Hyruan Plus; LG Life Sciences Ltd, Seoul, Korea), 2 mL of saline, and 4 mL of contrast media; and the CS with HA group received 1 mL of triamcinolone

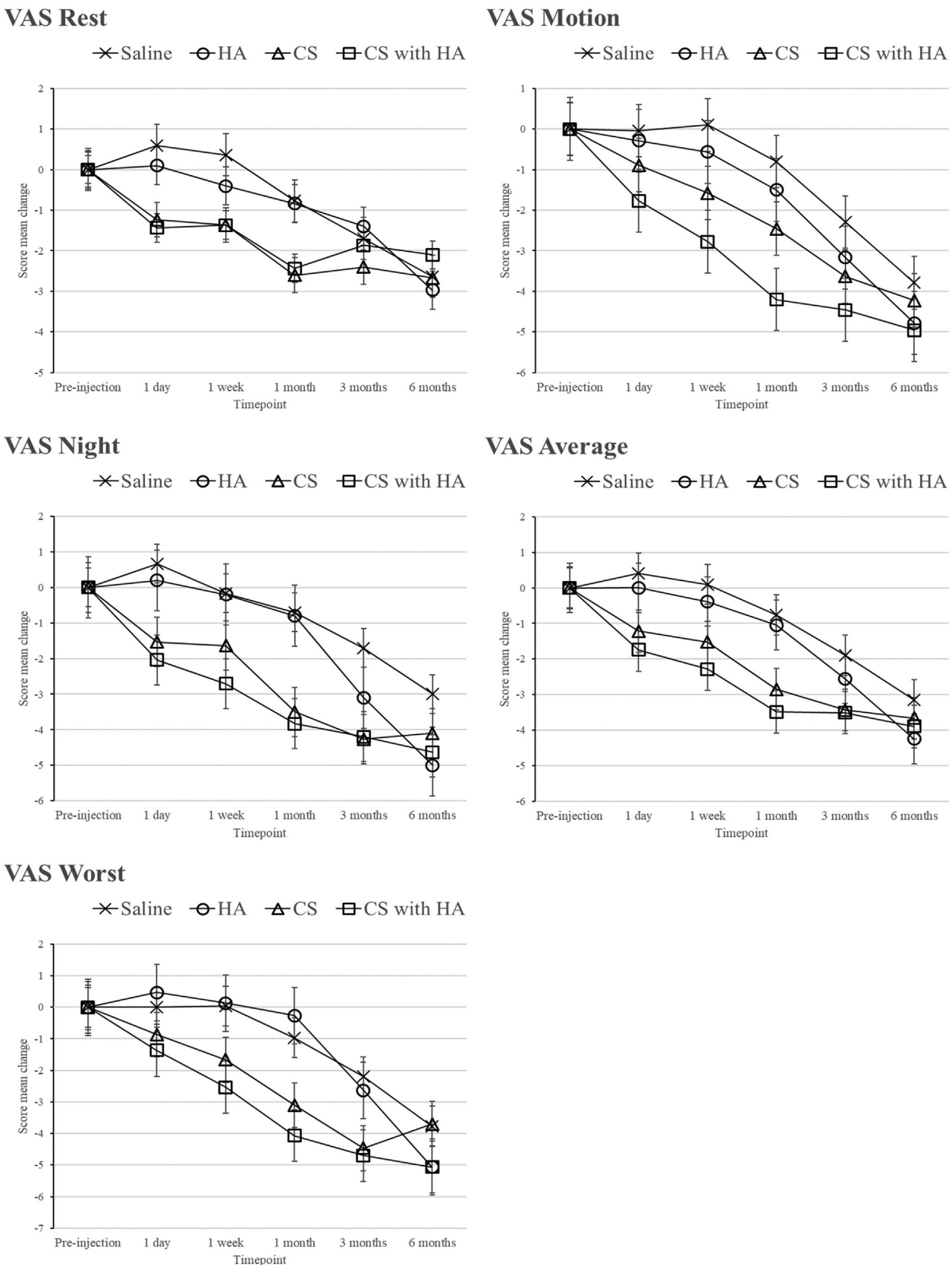

Figure 3 Mean changes in pain after intra-articular injections of different regimens. For VAS motion, there was no significant difference between the groups. *VAS*, visual analog scale; *HA*, hyaluronic acid; *CS*, corticosteroid; *CS with HA*, combination of corticosteroid and hyaluronic acid.

Table III
Mean changes of pain after intra-articular injections of different regimens.

Measurement	Saline group	HA group	CS group	CS with HA group	*P* value*
Pain-rest					.001
Preinjection	3.3 ± 2.6	3.7 ± 2.4	3.9 ± 2.9	2.9 ± 2.0	
1 d	0.6 ± 1.3	0.1 ± 1.8	−1.2 ± 2.5	−1.4 ± 1.4†,‡	<.001
1 week	0.4 ± 2.1	−0.4 ± 2.3	−1.4 ± 2.5	−1.4 ± 1.8†	.017
1 mo	−0.8 ± 2.4	−0.8 ± 2.8	−2.6 ± 3.3	−2.4 ± 2.0†,‡	.001
3 mo	−1.7 ± 3.1	−1.4 ± 2.5	−2.4 ± 3.5	−1.9 ± 1.8	.488
6 mo	−2.6 ± 2.6	−3.0 ± 2.4	−2.7 ± 3.4	−2.1 ± 1.8	.796
Pain-motion					.146
Preinjection	6.3 ± 2.4	6.3 ± 2.3	6.5 ± 2.4	6.8 ± 2.3	
1 d	0.0 ± 1.8	−0.3 ± 1.8	−0.9 ± 1.4	−1.8 ± 2.1	
1 week	0.1 ± 1.8	−0.6 ± 1.9	−1.6 ± 2.2	−2.8 ± 1.7	
1 mo	−0.8 ± 2.1	−1.5 ± 2.9	−2.5 ± 2.0	−4.2 ± 2.8	
3 mo	−2.3 ± 2.0	−3.2 ± 2.5	−3.6 ± 2.3	−4.5 ± 2.6	
6 mo	−3.8 ± 3.6	−4.8 ± 2.5	−4.2 ± 2.7	−5.0 ± 2.9	
Pain-night					.004
Preinjection	5.2 ± 2.8	6.0 ± 2.2	6.8 ± 3.0	5.8 ± 1.8	
1 d	0.7 ± 1.5	0.2 ± 1.4	−1.5 ± 2.6	−2.0 ± 2.5†,‡	.005
1 week	−0.2 ± 2.6	−0.2 ± 1.4	−1.6 ± 2.6	−2.7 ± 2.2‡	.003
1 mo	−0.7 ± 2.3	−0.8 ± 3.3	−3.5 ± 2.6	−3.8 ± 1.9†,‡	<.001
3 mo	−1.7 ± 3.1	−3.1 ± 3.0	−4.3 ± 3.1	−4.2 ± 2.2	.074
6 mo	−3.0 ± 4.0	−5.0 ± 2.3	−4.1 ± 3.3	−4.6 ± 1.7	.185
Pain-average					.024
Preinjection	5.0 ± 2.4	5.3 ± 2.0	5.7 ± 2.4	5.2 ± 1.6	
1 d	0.4 ± 1.1	0.0 ± 1.3	−1.2 ± 2.0	−1.7 ± 1.8†,§	<.001
1 week	0.1 ± 1.8	−0.4 ± 1.6	−1.5 ± 2.2	−2.3 ± 1.5†,§	.001
1 mo	−0.8 ± 2.0	−1.0 ± 2.6	−2.9 ± 2.1	−3.5 ± 1.8†,§	.001
3 mo	−1.9 ± 2.4	−2.6 ± 2.4	−3.4 ± 2.6	−3.5 ± 1.7	.377
6 mo	−3.1 ± 3.2	−4.2 ± 2.2	−3.7 ± 2.8	−3.9 ± 1.6	.495
Pain-worst					.037
Preinjection	7.8 ± 1.5	8.0 ± 1.8	8.8 ± 1.4	8.3 ± 1.2	
1 d	0.0 ± 1.3	0.5 ± 1.2	−0.9 ± 2.6	−1.4 ± 2.4†,‡	.002
1 week	0.0 ± 1.3	0.1 ± 1.7	−1.7 ± 2.4	−2.5 ± 2.1†,‡	<.001
1 mo	−1.0 ± 1.8	−0.3 ± 2.9	−3.1 ± 2.8	−4.1 ± 2.7†,‡	<.001
3 mo	−2.2 ± 2.4	−2.6 ± 2.6	−4.5 ± 2.5	−4.7 ± 2.7	.098
6 mo	−3.8 ± 3.7	−5.1 ± 2.7	−3.7 ± 2.4	−5.1 ± 2.3	.472

HA group, hyaluronic acid group; *CS group,* corticosteroid group; *CS with HA group,* combination of corticosteroid and hyaluronic acid group.
The values are given as mean difference ± standard deviation.
*By analysis of variance, $P < .05$ was defined as statistically significant.
†Significantly greater than that in the saline group.
‡Significantly greater than that in the HA group.
§Significantly greater than that in the CS group.

acetonide, 2 mL of hyaluronic acid, 1 mL of saline, and 4 mL of contrast media. Three images were obtained after the injection to ascertain whether a true intra-articular injection was made: a standard shoulder anteroposterior view, a lateral scapular view, and a shoulder axillary view. The accuracy of the injection was judged as previously described[18] (Supplement 1).

Outcome assessments

Follow-up was at 1 day, 1 week, 1 month, 3 months, and 6 months after injection using patient-reported questionnaires and performance tests at a clinic visit. We concluded that 6 months of follow-up was sufficient because previous studies reported no differences between treatment groups after 6 months.[10,24,41]

The primary outcome measure was changes in the mean SPADI from baseline to 1 month after treatment. SPADI scores decrease as pain and patient function improve. The SPADI has been widely used for assessing AC.[10,38,44]

The secondary outcome measures were assessed according to changes in the mean (1) pain, (2) ROM, (3) strength, (4) functional scores, and (5) overall satisfaction from baseline to the follow-up period. A visual analog scale (VAS) was used to evaluate pain at rest, on motion, and at night and the worst pain. The patients were asked to use a 10-cm scale marked from 0 as "no pain" to 10 as "unbearable pain". The average pain scores were also calculated and compared. ROM was measured with a goniometer in active FF, ABD, ER with the arm at the side, and IR. IR was measured using vertebral levels, and these were translated into numbers from 1 for the buttocks to 17 for the T2 spinous process. The strength of the supraspinatus, infraspinatus, and subscapularis muscles was measured using a hand-held electronic scale (CHS; CAS, Yangju, Korea). The functional scoring systems used were the American Shoulder and Elbow Surgeons (ASES) system, the Constant system, the University of California at Los Angeles system, the Disabilities of the Arm, Shoulder and Hand (DASH) system, and the Simple Shoulder test. Functional scores except DASH scores increase as pain, function, and patient satisfaction improve. DASH scores decrease as pain and patient function improve. To evaluate overall satisfaction, the patients were asked to answer "yes" or "no" to questions concerning their willingness to undergo intervention again, whether they were prepared to recommend the intervention to another, and whether they were able to work as they did before injury. In addition, VAS scores were obtained for overall shoulder function and satisfaction. The patients were asked to use a 10-cm scale marked from "I can't use it" to "I feel normal" for function, and from "very unsatisfied" to "very satisfied" for satisfaction.[32]

After the injection, the investigator handed out picture leaflets and instructed the participants on a home exercise program for

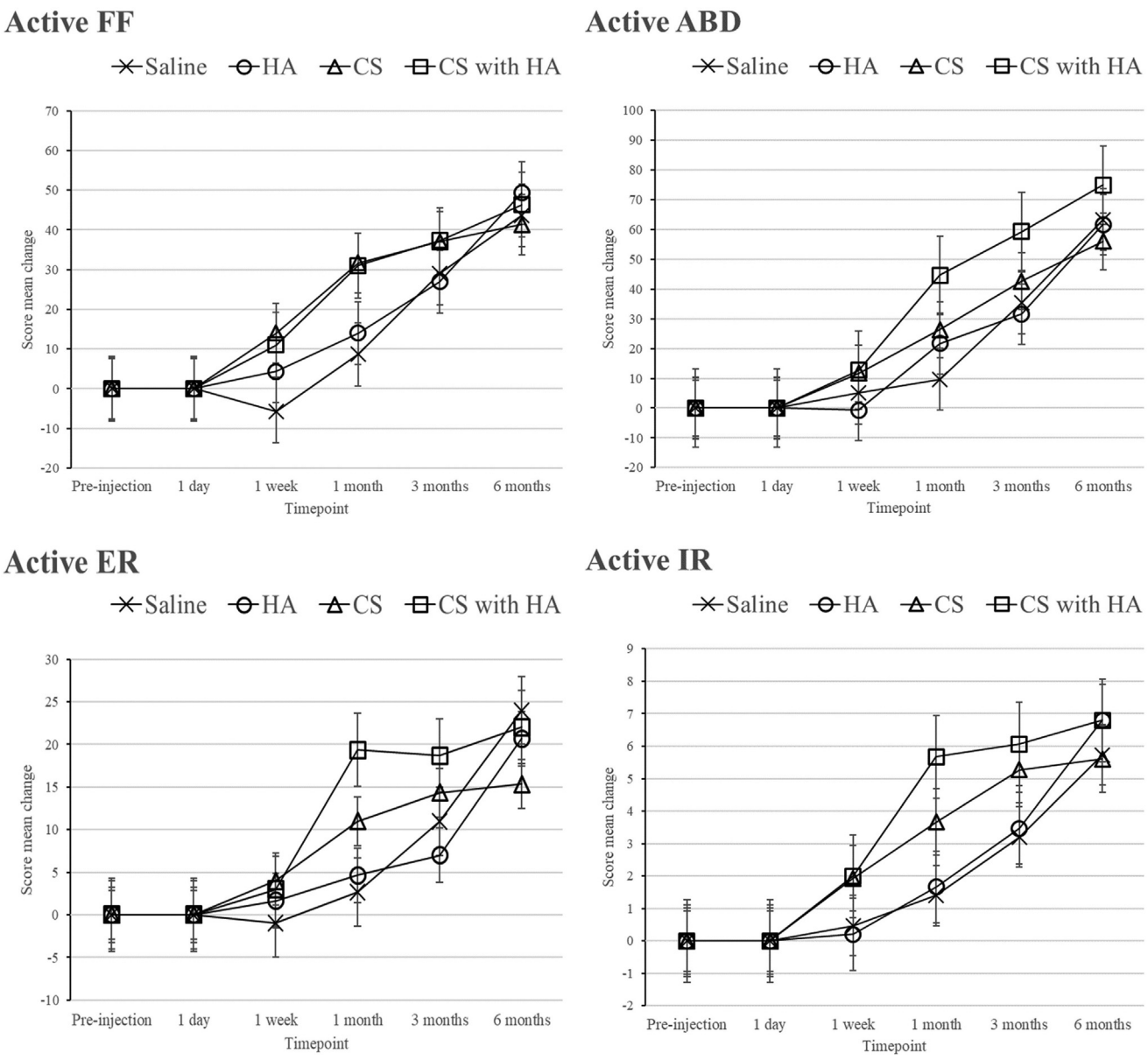

Figure 4 Mean changes in active range of motions after intra-articular injections of different regimens. *FF*, forward flexion; *Abd*, abduction; *ER*, external rotation; *IR*, internal rotation; *HA*, hyaluronic acid; *CS*, corticosteroid; *CS with HA*, combination of corticosteroid and hyaluronic acid.

increasing the ROM of the joint. A recommendation was also given at each follow-up visit to keep exercising. Exercises were to be performed twice a day, with each round lasting 10 to 15 minutes. The patients were also prohibited from taking any additional physical therapy or medication. Adverse effects of the intervention experienced by the participants were elicited with the use of open-ended questions.

Sample size

The required sample size was calculated based on the study of AC treatment by Carrette et al.[10] Using the results of that study, a sample size calculation was performed to provide a statistical power of 80% at an α level of 0.05 with a standard deviation of 25. We obtained a minimum sample size of 48 patients (12 patients in a group). Taking a failure rate of 20% into consideration, 60 patients (15 patients in a group) were required.

Statistical analysis

The statistician who conducted the data analyses was blinded to the group allocations. The outcome measures were analyzed based on the intention-to-treat principle. The continuous variables were compared using the Kruskal-Wallis test or analysis of variance. The categorical variables were compared using the Chi-squared test or Fisher's exact test. The linear mixed-effect model for repeated measures was used to examine the curative means of short acting duration in the primary and secondary analyses.[6]

In the linear mixed-effect model, group, time, and group-by-time interaction were included as fixed factors with subject variabilities as a random factor. If the group-by-time interaction was significant, post-hoc tests for comparisons between the groups were conducted to assess the group differences at each time. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA), and the significance level was set at a *P* value of 0.05.

Table IV
Mean changes of active and passive range of motion after intra-articular injections of different regimens.

Measurement	Saline group	HA group	CS group	CS with HA group	*P* value*
Active FF					<.001
Preinjection	115.7 ± 23.5	114.3 ± 16.9	111.0 ± 28.0	121.7 ± 26.8	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.709
1 week	−5.7 ± 20.0	4.3 ± 18.6	14.0 ± 25.2	11.1 ± 15.4†	.023
1 mo	8.7 ± 18.1	14.0 ± 17.2	31.7 ± 20.8†	31.0 ± 27.0†,‡	<.001
3 mo	29.0 ± 28.7	27.0 ± 21.8	37.0 ± 28.7	37.3 ± 22.0	.171
6 mo	43.7 ± 35.6	49.3 ± 23.7	41.3 ± 41.0	46.3 ± 23.5	.614
Active AB					.002
Preinjection	86.7 ± 16.1	93.3 ± 18.1	93.0 ± 27.3	90.7 ± 29.3	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.726
1 week	5.0 ± 16.3	−0.7 ± 6.8	11.7 ± 16.2	12.7 ± 19.0‡	.007
1 mo	9.7 ± 26.0	21.7 ± 19.7	26.3 ± 21.9	44.7 ± 33.4†	.002
3 mo	35.3 ± 37.5	31.7 ± 24.7	42.7 ± 31.0	59.3 ± 34.0	.049
6 mo	63.3 ± 40.6	61.7 ± 31.1	56.0 ± 47.1	75.0 ± 34.5	.412
Active ER					.001
Preinjection	23.7 ± 13.2	21.3 ± 6.4	24.7 ± 11.9	24.7 ± 16.0	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.709
1 week	−1.0 ± 13.0	1.7 ± 3.1	4.0 ± 8.3	3.0 ± 8.2	.221
1 mo	2.7 ± 14.3	4.7 ± 12.9	11.0 ± 15.9	19.3 ± 8.6†,‡	<.001
3 mo	11.0 ± 22.0	7.0 ± 15.3	14.3 ± 14.3	18.7 ± 13.9	.054
6 mo	24.0 ± 25.0	20.7 ± 18.3	15.3 ± 15.5	22.0 ± 21.7	.537
Active IR					<.001
Preinjection	2.7 ± 2.0	2.4 ± 2.0	2.7 ± 2.1	3.0 ± 1.9	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.867
1 week	0.5 ± 1.7	0.2 ± 0.9	1.9 ± 2.3‡	2.0 ± 1.8‡	<.001
1 mo	1.4 ± 1.4	1.7 ± 2.1	3.7 ± 2.3†	5.7 ± 2.6†,‡	<.001
3 mo	3.2 ± 3.4	3.5 ± 2.8	5.3 ± 2.7	6.1 ± 2.2†,‡	.001
6 mo	5.7 ± 3.5	6.8 ± 2.4	5.6 ± 4.0	6.8 ± 2.5	.445
Passive FF					.002
Preinjection	121.7 ± 21.2	120.3 ± 17.5	117.7 ± 28.6	128.3 ± 26.0	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.688
1 week	1.3 ± 15.9	5.7 ± 19.3	13.0 ± 23.0	9.0 ± 15.0	.144
1 mo	11.3 ± 15.2	13.3 ± 17.2	31.0 ± 21.3†,‡	31.0 ± 23.2†,‡	<.001
3 mo	29.3 ± 25.6	27.7 ± 23.4	35.7 ± 25.3	36.0 ± 22.2	.180
6 mo	41.3 ± 31.7	45.7 ± 25.8	38.3 ± 39.8	44.3 ± 25.1	.509
Passive AB					<.001
Preinjection	91.7 ± 18.3	100.0 ± 19.5	97.3 ± 25.5	95.3 ± 26.6	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.682
1 week	7.7 ± 17.2	−3.0 ± 8.4	15.3 ± 18.2‡	12.0 ± 20.3	.003
1 mo	15.7 ± 26.1	18.3 ± 24.0	28.0 ± 18.8	53.3 ± 28.4†,‡,§	<.001
3 mo	37.3 ± 34.9	24.5 ± 37.5	43.7 ± 29.4	60.0 ± 32.6‡	.027
6 mo	62.0 ± 37.9	58.3 ± 34.5	54.7 ± 44.6	74.0 ± 27.7	.214
Passive ER					.004
Preinjection	28.7 ± 12.7	25.0 ± 8.0	27.0 ± 10.8	29.0 ± 18.6	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.736
1 week	−1.0 ± 13.4	0.7 ± 1.8	4.7 ± 8.8	2.3 ± 8.4	.215
1 mo	1.3 ± 12.9	3.3 ± 12.2	14.0 ± 15.1	19.7 ± 13.8†,‡	<.001
3 mo	8.3 ± 22.2	9.0 ± 15.3	18.7 ± 15.6	20.3 ± 19.3	.034
6 mo	23.3 ± 25.3	20.3 ± 19.0	18.3 ± 18.0	23.7 ± 28.3	.719
Passive IR					<.001
Preinjection	3.3 ± 2.3	3.3 ± 3.1	3.4 ± 2.2	3.9 ± 2.3	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.856
1 week	0.3 ± 1.9	−0.5 ± 3.0	2.1 ± 2.1‡	1.7 ± 1.4†,‡	.001
1 mo	1.1 ± 1.7	0.7 ± 1.4	3.9 ± 2.2†,‡	5.1 ± 2.4†,‡	<.001
3 mo	3.4 ± 3.5	3.1 ± 3.6	5.4 ± 2.2	5.4 ± 2.6	.013
6 mo	6.1 ± 3.9	6.3 ± 3.2	5.6 ± 3.5	6.7 ± 2.3	.491

HA group, hyaluronic acid group; *CS group,* corticosteroid group; *CS with HA group,* combination of corticosteroid and hyaluronic acid group; *FF,* forward flexion; *AB,* abduction; *ER,* external rotation; *IR,* internal rotation.
The values are given as mean difference ± standard deviation.
*By analysis of variance, $P < .05$ was defined as statistically significant.
†Significantly greater than that in the saline group.
‡Significantly greater than that in the HA group.
§Significantly greater than that in the CS group.

Results

Demographics and accuracy

Sixty patients were randomized and treated with one of the four interventions according to the assigned group. There were 39 female and 21 male patients, with a mean age of 52.4 years and mean symptom duration of 8.0 months. Table I shows the demographic and outcome variables of the 4 intervention groups at baseline. Before injection, none of the demographic and outcome variables were different between the four intervention groups. Except for the CS groups, which showed 93.3% injection accuracy

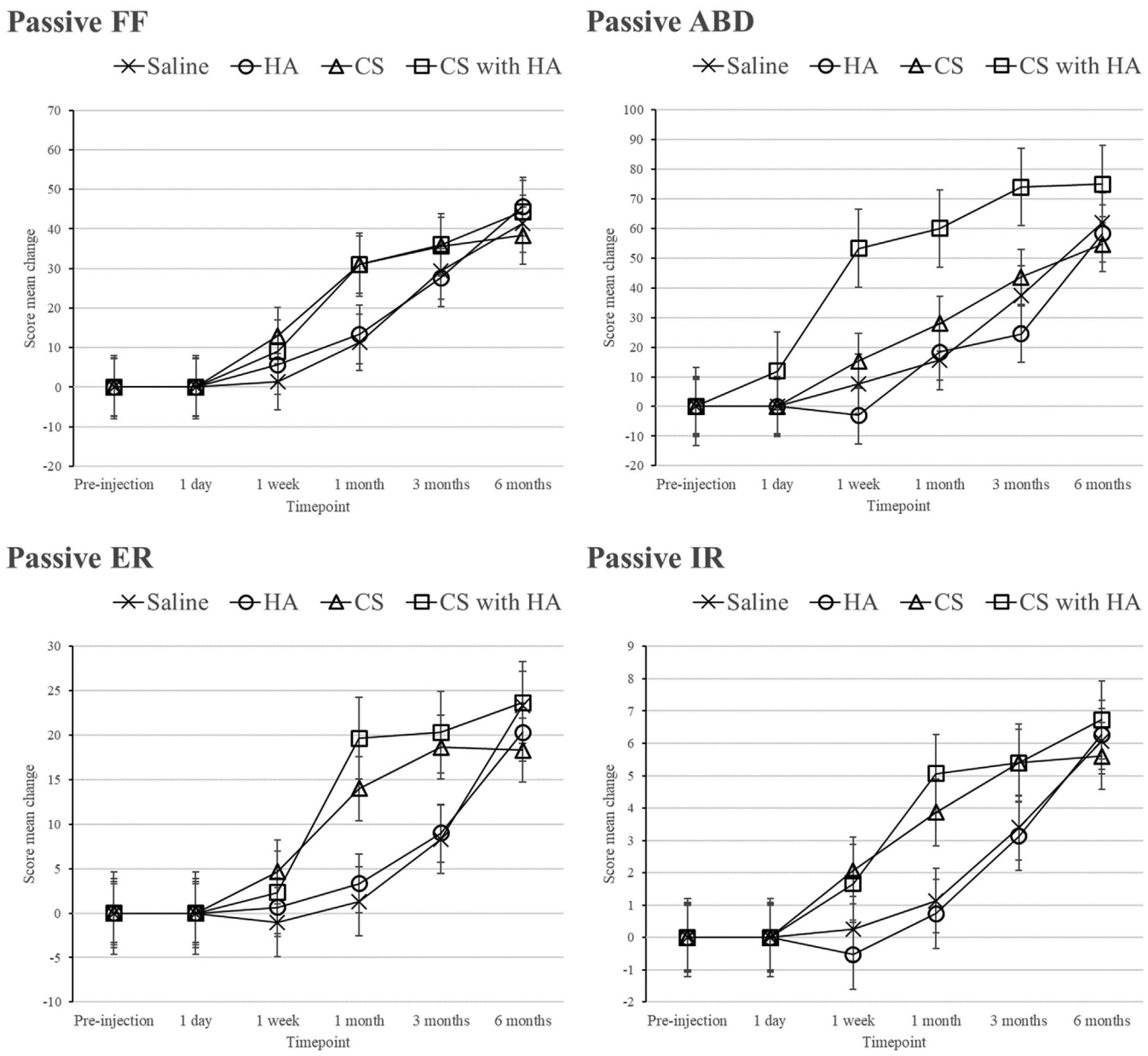

Figure 5 Mean changes of in passive range of motions after intra-articular injections of different regimens. *FF*, forward flexion; *Abd*, abduction; *ER*, external rotation; *IR*, internal rotation; *HA*, hyaluronic acid; *CS*, corticosteroid; *CS with HA*, combination of corticosteroid and hyaluronic acid.

due to one failed injection, all other groups showed an injection accuracy of 100% without any significant differences between the four groups ($P = .15$; Table I).

Among 60 patients, 1 patient with steroid injections was lost to the follow-up after 3 months, who went to a different hospital because of the intraepithelial carcinoma of appendix. Thus, follow-up data were obtained for 59 of 60 participants (98.3%) after 6 months (Fig. 1).

Primary outcome measure

The primary outcome measure, the mean change in SPADI scores, is shown in Figure 2 and Table II. One month after injection, the SPADI scores of the CS with HA group decreased the most compared to those in the other groups. The SPADI scores improved by a mean (percentage %) of −30.1 points (−58.4%) in the CS with HA group, which was significantly superior to the improvements of −4.2 (−7.7%) and −8.0 points (−14.4%) observed in the saline group and the HA group, respectively ($P < .001$ and $P = .03$, respectively). The CS group showed a significantly greater change by −24.2 points (−43.7%) than the saline group ($P = .009$). A week after injection, the SPADI scores improved by −17.4 points (-33.6%) in the CS with HA group, which was superior to the improvements of 0.7 (1.3%) and 3.2 points (5.7%) observed in the saline group and HA group, respectively ($P < .001$ and $P < .001$, respectively). The CS group showed a significantly greater change by −11.3 points (−20.4%) than the saline group ($P = .023$). There was no significant difference between the CS with HA group and the CS group, but the score was decreased much more in the CS with HA group. There was no difference between the groups after 3 and 6th months.

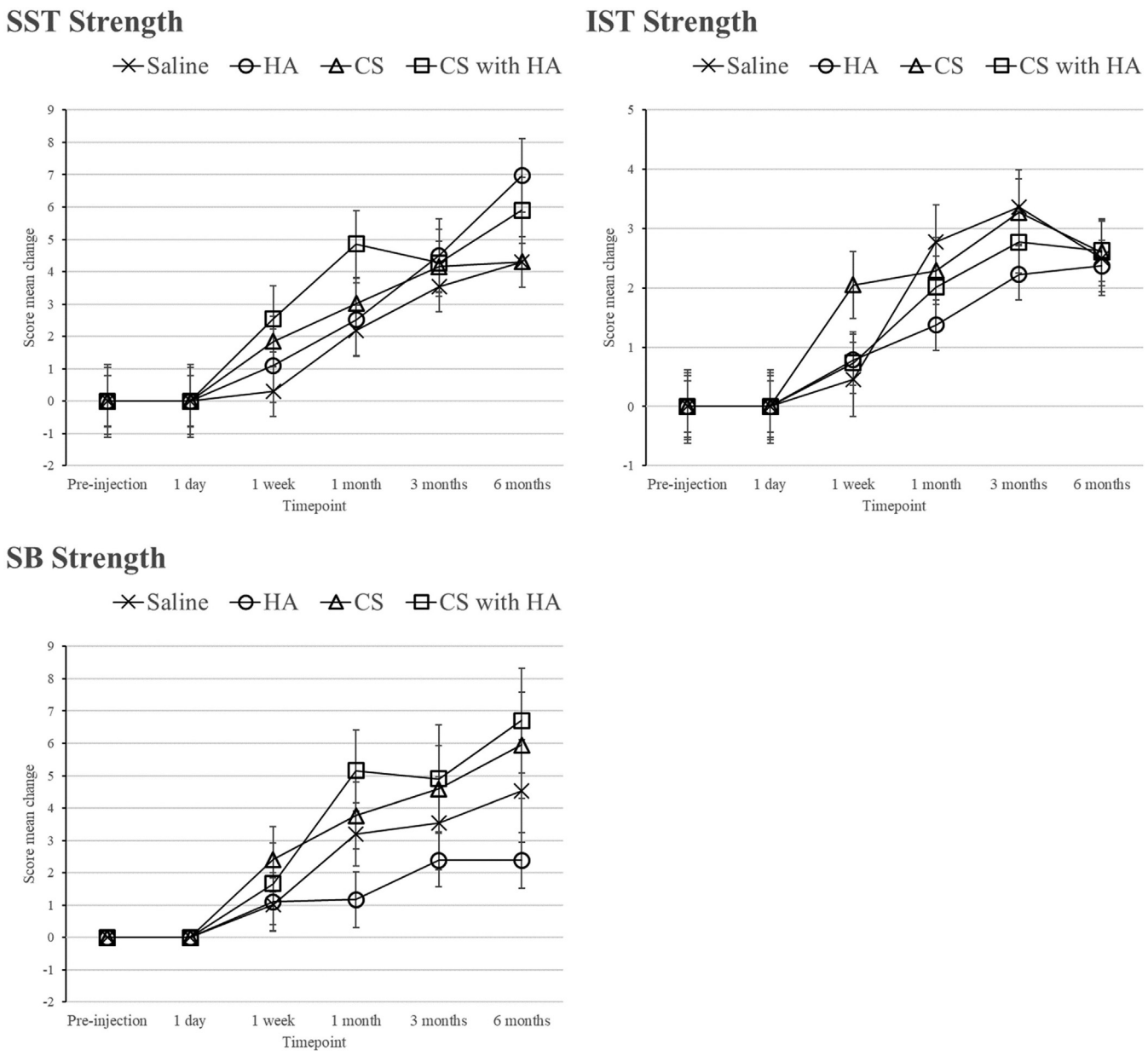

Figure 6 Mean changes in strength of SST, IST, and SB muscles after intra-articular injections of different regimens. There was no significant difference between the groups. *SST*, supraspinatus muscle; *IST*, infraspinatus muscle; *SB*, subscapularis muscle; *HA*, hyaluronic acid; *CS*, corticosteroid; *CS with HA*, combination of corticosteroid and hyaluronic acid.

Secondary outcome measures

Pain

The VAS scores at rest and at night, and the worst and average VAS scores, differed between the groups over time, but there was no difference in VAS scores at motion between the groups (Fig. 3 and Table III). In all VAS scores except the VAS scores at motion, the CS with HA group showed faster pain relief than the saline group, whereas the CS group and the HA group showed no difference from the saline group in pain relief at any point. One day and 1 month after injection, the VAS scores at rest and at night and the worst scores were improved in the CS with HA group, which were significantly superior to the improvements in the saline and HA groups. One week after injection, improvements in the worst VAS scores in the CS with HA group were significantly superior to those in the saline group and the HA group. From one day to 1 month after injection, improvements in VAS scores at rest and at night and the worst scores in the CS with HA group were higher than those of the CS group, but there were no significant differences. The mean change in average VAS scores in the CS with HA group was superior to that in the saline group and the CS group after 1 day, 1 week, and 1 month. Three and 6 months after injection, there was no significant difference between the groups in any pain scores.

Range of motion

The mean change in the active ROM differed between the groups over time (Fig. 4 and Table IV). After 1 month, the mean change in the active FF and ER in the CS with HA group was significantly higher than that in the saline and HA groups. The mean change in the active ABD in the CS with HA group was superior to that in the saline group. In the CS group, the mean change

Table V
Mean changes of power of rotator cuff muscle after intra-articular injections of different regimens.

Measurement	Saline group	HA group	CS group	CS with HA group	*P* value*
Power-SST					.072
Preinjection	5.3 ± 4.5	6.6 ± 2.9	5.4 ± 2.8	5.3 ± 4.5	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
1 week	0.3 ± 2.7	1.1 ± 2.3	1.8 ± 2.6	2.5 ± 3.4	
1 mo	2.2 ± 2.7	2.5 ± 3.3	3.0 ± 2.0	4.9 ± 4.4	
3 mo	3.5 ± 3.4	4.5 ± 4.3	4.2 ± 3.1	4.3 ± 6.3	
6 mo	4.3 ± 4.6	7.0 ± 4.1	4.3 ± 3.2	5.9 ± 4.1	
Power-IST					.309
Preinjection	5.3 ± 4.0	6.2 ± 3.6	5.0 ± 2.4	6.7 ± 3.8	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
1 week	0.5 ± 2.5	0.8 ± 2.7	2.1 ± 2.3	0.7 ± 3.6	
1 mo	2.8 ± 2.9	1.4 ± 2.7	2.3 ± 3.1	2.0 ± 3.3	
3 mo	3.4 ± 3.8	2.2 ± 3.1	3.3 ± 3.3	2.8 ± 2.7	
6 mo	2.5 ± 5.8	2.4 ± 2.9	2.6 ± 3.7	2.6 ± 3.4	
Power-SB					.032
Preinjection	8.5 ± 4.1	11.4 ± 3.9	7.6 ± 4.8	10.1 ± 6.0	
1 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.229
1 week	1.0 ± 3.1	1.1 ± 3.5	2.4 ± 3.9	1.7 ± 4.9	.738
1 mo	3.2 ± 3.8	1.2 ± 3.3	3.8 ± 4.0	5.2 ± 4.8	.098
3 mo	3.5 ± 5.5	2.4 ± 3.2	4.6 ± 5.2	4.9 ± 6.5	.627
6 mo	4.5 ± 6.1	2.4 ± 3.4	5.9 ± 6.4	6.7 ± 6.3	.114

HA group, hyaluronic acid group; *CS group,* corticosteroid group; *CS with HA group,* combination of corticosteroid and hyaluronic acid group; *SST,* supraspinatus; *IST,* infraspinatus; *SB,* subscapularis.
The values are given as mean difference ± standard deviation. There was no significant difference between groups.
*By analysis of variance, $P < .05$ was defined as statistically significant.

in the active FF and IR was superior to that of the saline group. Three and 6 months after injection, there was no significant difference between the groups in active FF, ABD, or ER. One and 3 months after injection, the mean change in the active IR in the CS with HA group was superior to that in the saline and HA groups. Six months after injection, there was no significant difference between the groups in active IR.

The mean change in passive ROM also differed between the groups over time (Fig. 5 and Table IV). After a month, the mean changes in all passive ROM in the CS with HA group were significantly higher than those in the saline and HA groups. For passive ABD, the CS with HA group was superior to the CS group. The mean change in the passive FF and IR in the CS group were superior to those of the saline and HA groups after a month. Three months after injection, the mean change in the passive ABD in the CS with HA group was superior to that of the HA group. Six months after injection, there was no significant difference between the groups in any passive ROM.

Strength

The strength of the supraspinatus, infraspinatus, and subscapularis muscles increased over time in all groups, but there was no significant difference between the groups (Fig. 6 and Table V).

Functional scores

In the mean changes in ASES, Constant, and DASH scores, the CS with HA group was superior to the saline group and the HA group after a month. The CS with HA group also showed superior improvement in the ASES and DASH scores compared to the saline

Table VI
Positive responder about overall satisfaction after intra-articular injections.

Measurement	Saline group	HA group	CS group	CS with HA group	*P* value*
Injection again					.89
1 d	66.7%	86.7%	60.0%	86.7%	
1 week	80.0%	66.7%	73.3%	93.3%	
1 mo	80.0%	66.7%	93.3%	93.3%	
3 mo	86.7%	80.0%	80.0%	93.3%	
6 mo	100.0%	86.7%	86.7%	93.3%	
Recommend injection					.699
1 d	66.7%	93.3%	60.0%	80.0%	
1 week	80.0%	80.0%	80.0%	80.0%	
1 mo	80.0%	66.7%	93.3%	93.3%	
3 mo	86.7%	80.0%	73.3%	93.3%	
6 mo	100.0%	86.7%	80.0%	93.3%	
Can work as before getting injured					.805
1 d	60.0%	73.3%	80.0%	80.0%	
1 week	60.0%	80.0%	80.0%	80.0%	
1 mo	80.0%	93.3%	80.0%	80.0%	
3 mo	66.7%	73.3%	93.3%	80.0%	
6 mo	80.0%	93.3%	93.3%	86.7%	

HA group, hyaluronic acid group; *CS group,* corticosteroid group; *CS with HA group,* combination of corticosteroid and hyaluronic acid group.
The values are given as percentage. There was no difference between groups.
*By analysis of variance, $P < .05$ was defined as statistically significant.

Table VII
Mean changes of overall shoulder function (VAS) after intra-articular injection and values of overall satisfaction (VAS) after intra-articular injections of different regimens.

Measurement	Saline group	HA group	CS group	CS with HA group	*P* value*
Overall Shoulder Function (VAS)					.192
Preinjection	4.4 ± 2.2	4.2 ± 1.8	3.9 ± 1.9	3.3 ± 1.9	
1 d	−0.7 ± 2.0	0.3 ± 2.2	0.5 ± 3.2	2.4 ± 2.9	
1 week	−0.5 ± 1.8	0.3 ± 2.4	1.1 ± 2.5	2.5 ± 3.2	
1 mo	0.3 ± 3.5	1.1 ± 2.9	2.6 ± 2.3	3.5 ± 3.0	
3 mo	1.6 ± 3.4	2.1 ± 2.1	3.0 ± 2.4	3.8 ± 2.6	
6 mo	2.7 ± 3.2	3.5 ± 2.2	3.3 ± 2.5	4.1 ± 2.5	
Overall Satisfaction (VAS)					.085
1 d	5.4 ± 2.1	5.1 ± 2.1	5.3 ± 2.3	6.7 ± 2.5	
1 week	6.5 ± 1.9	5.3 ± 2.4	6.6 ± 2.3	8.3 ± 1.7	
1 mo	7.1 ± 2.4	5.6 ± 2.2	6.9 ± 1.6	8.5 ± 2.0	
3 mo	6.9 ± 2.3	6.3 ± 2.4	7.3 ± 2.2	7.9 ± 2.1	
6 mo	7.7 ± 2.6	7.8 ± 2.2	6.9 ± 2.6	8.3	

HA group, hyaluronic acid group; *CS group,* corticosteroid group; *CS with HA group,* combination of corticosteroid and hyaluronic acid group; *VAS,* visual analogue scale.
The values are given as mean difference ± standard deviation. There was no difference between groups.
*By analysis of variance, $P < .05$ was defined as statistically significant.

and HA groups one week after injection. Three and 6 months after injection, there was no significant difference between the groups.

Overall satisfaction

The responses to the questions were not different between the groups at any time point (Table VI). The VAS scores for overall shoulder function and overall satisfaction improved in all groups with time, but there was no significant difference between the groups (Table VII).

Discussion

The most important findings of this study were (1) the mean changes in SPADI scores, active and passive ROM, and functional scores (ASES, Constant, and DASH score) in the CS with HA group were superior to those of the saline and HA groups after 1 month. Compared to the CS group, there was no significant difference, but the CS with HA group showed greater changes. (2) The mean change in pain at rest and at night and worst and average scores from 1 day to 1 month after injection in the CS with HA groups was superior to those of the saline and HA groups. The CS group and the HA group were not significantly different compared to the saline group. (3) There was no significant difference between the HA group and the saline group in any outcome measure in patients with AC. Thus, in treatment of AC, the simultaneous injection of CS with HA may be faster and more effective for improving pain and function than a single injection of CS or HA.

To the best of our knowledge, only one study has been conducted on simultaneous injections of CS and HA for AC.[33] In that study, simultaneous injections of CS with HA and injections of CS alone were compared without control group, and the simultaneous injections of CS with HA showed superior results for improving ROM six months after injection compared to the injections of CS alone. Unlike that study, our study used saline as the positive control, used a homogenous patient group by limiting the symptom duration to less than one year, and injected the same dose only once in the groups. Through this, it was possible to evaluate the actual treatment effect of each group compared to the saline positive control as well as to compare the simultaneous injection of CS with HA to single injections of CS or HA. As a result, in our study, all groups showed improvement in pain and function, and there was no significant difference between the groups after 3 and 6 months. This difference in the results of the previous study and our study may be because the previous study performed monthly injections for 6 months, but our study administered only single injections. Furthermore, our study compared saline injections and each injection regimen from 1 day after injection, so the objective effect of each drug regimen could be determined from an early follow-up period. Almost all previous studies on CS or HA injections evaluated the effects one month or later after injection.[10,34,40] Our study showed that the mean changes in SPADI scores and active FF, active IR, and Constant scores in the CS group and the CS with HA group were superior to those in the saline group, and in passive ABD, the CS with HA group was superior to the CS group after a month. Furthermore, the CS with HA group showed significantly better SPADI scores and passive IR, ASES, and DASH scores than the saline group 1 week after injection and showed greater changes than the CS group. As new findings that have not been found in previous studies, our results suggest that the simultaneous injection of CS and HA can have a greater effect from 1 week after injection, which is an earlier response than previously reported. A previous in vivo study reported that the combination of CS and HA increased the concentration of CS faster.[5] We think the fast effect of the simultaneous injection of CS and HA in our study might have resulted from this synergistic phenomenon. Taken together, the simultaneous injection of CS and HA is the fastest and most effective method for the functional recovery of patients with AC, and an injection of CS alone was also effective for functional recovery but was slower and less effective than the simultaneous injection of CS and HA.

The pain of AC is more severe at night, and many patients feel uncomfortable sleeping on the affected side.[27] In previous studies, CS was reported to show improvement in pain early after injection.[7,10,34,40] In our study, for all pain except pain on motion, only the simultaneous injection of CS with HA showed a significant effect from 1 day to 1 month compared to the saline group, resulting in rapid pain improvement. The injection of CS alone had no statistically significant effect compared to the saline group but showed a tendency to rapidly decrease all types of pain from one day after injection. In contrast, night pain one day after injection increased in the saline and HA groups compared to before injection. At 3 and 6 months after injection, pain improved in all groups, but the effect was experienced more quickly in the CS group and the CS with HA group. Furthermore, the average pain scores in the CS with HA group were superior to those in the CS group at 1 day, 1 week, and 1 month after injection. Thus, the results of our study showed that the intraarticular injection of CS had an excellent effect in improving the quality of sleep, ROM, and function by rapidly alleviating pain in patients with AC, and this action had a synergistic effect when simultaneously injected with HA.

Compared to other groups including the saline group, the injection of HA alone did not show a significant difference in any outcome measures at any follow-up period and did not have a rapid effect on pain improvement. Rather, at follow-up up to 3 months, the injection of CS alone was superior to the injection of HA alone for rapid pain relief and improvement in ROM. Thus, the efficacy of HA alone may be inferior. Some previous studies reported the positive effects of HA for painful shoulder disease three months after injection.[9,15,21,23] However, because the patient experiences three painful events, the injection of HA is thought to be inefficient compared to an injection of CS. In addition, considering the previous studies that showed improvement in pain and function by any treatment after 6 weeks, 3 months may be inappropriate for evaluating the effects of the injection.[10,34] One of the reasons for recommending an injection of HA was the concern about systemic side effects caused by CS. However, as the shoulder joint has a less vascularized small synovial surface, and pathological changes in fibrosis and adhesion prevent systemic steroid absorption, the systemic spillover of CS is minimal.[12,32]

The clinical usefulness of HA injections has been demonstrated by their safe and efficient use for knee osteoarthritis, and the onset of therapeutic effect has been reported to be delayed between 2 and 5 weeks of injection.[16,19] In contrast, CS was reported to show maximum pain relief between 1 and 2 weeks in treating osteoarthritis of the knee.[8] Both drugs improve synovial fluid quality and relieve clinical symptoms by anti-inflammatory effects. However this effect was rapid but short for CS and delayed but prolonged for HA.[2] Many studies on the simultaneous injection of CS and HA have been conducted in treating osteoarthritis of the knee.[11,29,30,35,42] According to these studies, CS depolymerizes superoxide anion generated by inflammatory cells, and HA protects joints from the harmful effects of CS when injected together. Thus, it has synergistic effects and shows excellent clinical results. Furthermore, the simultaneous injection of CS and HA was advantageous in increasing the concentration of CS rapidly and maintaining a sustainable concentration longer.[5] In the treatment of AC, the effective execution of ROM exercises through rapid pain relief is important. Therefore, a simultaneous intra-articular injection of CS and HA, which brings rapid pain relief and functional improvement, is suggested to be a more effective treatment than HA which requires three injections and shows delayed onset.

This study had several limitations. As a single-center study, the number of subjects was small. Although the sample size was determined through power analysis, it was determined that such a small sample size affected the outcome measures, which found no significant difference between the groups despite the obvious differences in mean changes. The routine regimen is to inject HA three times a week for intra-articular injections, but only a single injection of HA was performed to evaluate the efficacy of a single drug. Contrary to the study of Hannafin and Chiaia in which AC was divided into 4 stages according to arthroscopic findings and clinical examination,[13] we selected patients in the freezing stage only by clinical examination. However, there was no difference in symptom duration between the 4 groups, so the comparison of the efficacy of drugs seems reasonable.

Conclusion

In the treatment of AC, the simultaneous injection of CS and HA was more effective for improving SPADI score at one month after injection than a single injection of HA and was not inferior to a single injection of CS. Thus, the simultaneous injection of CS and HA can be recommended for the effective and safe treatment of AC.

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Supplementary data

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References

1. Arslan S, Celiker R. Comparison of the efficacy of local corticosteroid injection and physical therapy for the treatment of adhesive capsulitis. Rheumatol Int 2001;21:20-3.
2. Ayral X. Injections in the treatment of osteoarthritis. Best Pract Res Clin Rheumatol 2001;15:609-26.
3. Binder A, Hazleman BL, Parr G, Roberts S. A controlled study of oral prednisolone in frozen shoulder. Br J Rheumatol 1986;25:288-92.
4. Blanchard V, Barr S, Cerisola FL. The effectiveness of corticosteroid injections compared with physiotherapeutic interventions for adhesive capsulitis: a systematic review. Physiotherapy 2010;96:95-107. https://doi.org/10.1016/j.physio.2009.09.003.
5. Borden RC, Saunders JE, Berryhill WE, Krempl GA, Thompson DM, Queimado L. Hyaluronic acid hydrogel sustains the delivery of dexamethasone across the round window membrane. Audiol Neurootol 2011;16:1-11. https://doi.org/10.1159/000313506.
6. Brown H, Prescott R. Applied mixed models in medicine, 2nd edition. Biometrics 2007;63:626-7. https://doi.org/10.1111/j.1541-0420.2006.00787_3.x.
7. Bulgen DY, Binder AI, Hazleman BL, Dutton J, Roberts S. Frozen shoulder: prospective clinical study with an evaluation of three treatment regimens. Ann Rheum Dis 1984;43:353-60.
8. Caborn D, Rush J, Lanzer W, Parenti D, Murray C. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. J Rheumatol 2004;31:333-43.
9. Calis M, Demir H, Ulker S, Kirnap M, Duygulu F, Calis HT. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? Rheumatol Int 2006;26:536-40. https://doi.org/10.1007/s00296-005-0022-2.
10. Carette S, Moffet H, Tardif J, Bessette L, Morin F, Fremont P, et al. Intraarticular corticosteroids, supervised physiotherapy, or a combination of the two in the treatment of adhesive capsulitis of the shoulder: a placebo-controlled trial. Arthritis Rheum 2003;48:829-38. https://doi.org/10.1002/art.10954.
11. Grecomoro G, Piccione F, Letizia G. Therapeutic synergism between hyaluronic acid and dexamethasone in the intra-articular treatment of osteoarthritis of the knee: a preliminary open study. Curr Med Res Opin 1992;13:49-55.
12. Habib GS, Abu-Ahmad R. Lack of effect of corticosteroid injection at the shoulder joint on blood glucose levels in diabetic patients. Clin Rheumatol 2007;26:566-8. https://doi.org/10.1007/s10067-006-0353-8.
13. Hannafin JA, Chiaia TA. Adhesive capsulitis. A treatment approach. Clin Orthop Relat Res 2000:95-109.
14. Harris JD, Griesser MJ, Copelan A, Jones GL. Treatment of adhesive capsulitis with intra-articular hyaluronate: a systematic review. Int J Shoulder Surg 2011;5:31-7. https://doi.org/10.4103/0973-6042.83194.
15. Itokazu M, Matsunaga T. Clinical evaluation of high-molecular-weight sodium hyaluronate for the treatment of patients with periarthritis of the shoulder. Clin Ther 1995;17:946-55.
16. Iwata H. Pharmacologic and clinical aspects of intraarticular injection of hyaluronate. Clin Orthop Relat Res 1993:285-91.
17. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci (Lond) 1998;94:557-72.
18. Jo CH, Shin YH, Shin JS. Accuracy of intra-articular injection of the glenohumeral joint: a modified anterior approach. Arthroscopy 2011;27:1329-34. https://doi.org/10.1016/j.arthro.2011.06.011.
19. Jones AC, Pattrick M, Doherty S, Doherty M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. Osteoarthritis Cartilage 1995;3:269-73.
20. Kim D-H, Song K-S, Min B-W, Bae K-C, Lim Y-J, Cho C-H. Early clinical outcomes of manipulation under anesthesia for refractory adhesive capsulitis: comparison with arthroscopic capsular release. Clin Orthop Surg 2020;12:217-23. https://doi.org/10.4055/cios19027.
21. Leardini G, Perbellini A, Franceschini M, Mattara L. Intra-articular injections of hyaluronic acid in the treatment of painful shoulder. Clin Ther 1988;10:521-6.
22. Lee HJ, Lim KB, Kim DY, Lee KT. Randomized controlled trial for efficacy of intra-articular injection for adhesive capsulitis: ultrasonography-guided versus

blind technique. Arch Phys Med Rehabil 2009;90:1997-2002. https://doi.org/10.1016/j.apmr.2009.07.025.
23. Lim TK, Koh KH, Shon MS, Lee SW, Park YE, Yoo JC. Intra-articular injection of hyaluronate versus corticosteroid in adhesive capsulitis. Orthopedics 2014;37:e860-5. https://doi.org/10.3928/01477447-20140924-51.
24. Lorbach O, Kieb M, Scherf C, Seil R, Kohn D, Pape D. Good results after fluoroscopic-guided intra-articular injections in the treatment of adhesive capsulitis of the shoulder. Knee Surg Sports Traumatol Arthrosc 2010;18:1435-41. https://doi.org/10.1007/s00167-009-1030-7.
25. Munro C, Barker SL, Kumar K. Arthroscopic capsular release for frozen shoulder—time to thaw the delay? Surg Sci 2013;04:22-4. https://doi.org/10.4236/ss.2013.49A004.
26. Neviaser AS, Hannafin JA. Adhesive capsulitis: a review of current treatment. Am J Sports Med 2010;38:2346-56. https://doi.org/10.1177/0363546509348048.
27. Neviaser AS, Neviaser RJ. Adhesive capsulitis of the shoulder. J Am Acad Orthop Surg 2011;19:536-42. https://doi.org/10.5435/00124635-201109000-00004.
28. O'Kane JW, Jackins S, Sidles JA, Smith KL, Matsen FA 3rd. Simple home program for frozen shoulder to improve patients' assessment of shoulder function and health status. J Am Board Fam Pract 1999;12:270-7.
29. Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int 2006;26:314-9. https://doi.org/10.1007/s00296-005-0584-z.
30. Petrella RJ, Emans PJ, Alleyne J, Dellaert F, Gill DP, Maroney M. Safety and performance of Hydros and Hydros-TA for knee osteoarthritis: a prospective, multicenter, randomized, double-blind feasibility trial. BMC Musculoskelet Disord 2015;16:57. https://doi.org/10.1186/s12891-015-0513-6.
31. Rangan A, Hanchard N, McDaid C. What is the most effective treatment for frozen shoulder? BMJ 2016;354:i4162. https://doi.org/10.1136/bmj.i4162.
32. Roh YH, Yi SR, Noh JH, Lee SY, Oh JH, Gong HS, et al. Intra-articular corticosteroid injection in diabetic patients with adhesive capsulitis: a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc 2012;20:1947-52. https://doi.org/10.1007/s00167-011-1776-6.
33. Rovetta G, Monteforte P. Intraarticular injection of sodium hyaluronate plus steroid versus steroid in adhesive capsulitis of the shoulder. Int J Tissue React 1998;20:125-30.
34. Ryans I, Montgomery A, Galway R, Kernohan WG, McKane R. A randomized controlled trial of intra-articular triamcinolone and/or physiotherapy in shoulder capsulitis. Rheumatology (Oxford) 2005;44:529-35. https://doi.org/10.1093/rheumatology/keh535.
35. Schaefer EC, Stewart AA, Durgam SS, Byron CR, Stewart MC. Effects of sodium hyaluronate and triamcinolone acetonide on glucosaminoglycan metabolism in equine articular chondrocytes treated with interleukin-1. Am J Vet Res 2009;70:1494-501. https://doi.org/10.2460/ajvr.70.12.1494.
36. Shaffer B, Tibone JE, Kerlan RK. Frozen shoulder. A long-term follow-up. J Bone Joint Surg Am 1992;74:738-46.
37. Shah N, Lewis M. Shoulder adhesive capsulitis: systematic review of randomised trials using multiple corticosteroid injections. Br J Gen Pract 2007;57:662-7.
38. Tveita EK, Tariq R, Sesseng S, Juel NG, Bautz-Holter E. Hydrodilatation, corticosteroids and adhesive capsulitis: a randomized controlled trial. BMC Musculoskelet Disord 2008;9:53. https://doi.org/10.1186/1471-2474-9-53.
39. van den Hout WB, Vermeulen HM, Rozing PM, Vliet Vlieland TPM. Impact of adhesive capsulitis and economic evaluation of high-grade and low-grade mobilisation techniques. Aust J Physiother 2005;51:141-9. https://doi.org/10.1016/s0004-9514(05)70020-9.
40. van der Windt DA, Koes BW, Devillé W, Boeke AJ, de Jong BA, Bouter LM. Effectiveness of corticosteroid injections versus physiotherapy for treatment of painful stiff shoulder in primary care: randomised trial. Bmj 1998;317:1292-6.
41. van der Windt DA, Thomas E, Pope DP, de Winter AF, Macfarlane GJ, Bouter LM, et al. Occupational risk factors for shoulder pain: a systematic review. Occup Environ Med 2000;57:433-42.
42. Vento R, Torregrossa MV, Guiliano M, Grecomoro G, Piccione F. Effects of dexamethasone on human synovial fibroblast-like cells, from osteoarthritic joints, in culture. Life Sci 1990;47:2199-205.
43. Yoo JC, Koh KH, Shon MS, Bae KH, Lim TK. Clinical outcome after arthroscopic capsular release for adhesive capsulitis of the shoulder. Clin Shoulder Elbow 2018;21:127-33. https://doi.org/10.5397/cise.2018.21.3.127.
44. Yoon SH, Lee HY, Lee HJ, Kwack KS. Optimal dose of intra-articular corticosteroids for adhesive capsulitis: a randomized, triple-blind, placebo-controlled trial. Am J Sports Med 2013;41:1133-9. https://doi.org/10.1177/0363546513480475.