

# Effect of a mixed solution of sodium hyaluronate and carboxymethyl cellulose on upper limb dysfunction after total mastectomy: a double-blind, randomized clinical trial

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**Abstract** Restricted shoulder mobility is a major upper limb dysfunction related to lower quality of life and disability after breast cancer surgery. We hypothesized that sodium hyaluronate–carboxymethyl cellulose (HA–CMC) applied to the surface of the pectoralis major muscle after mastectomy would significantly reduce pain and improve range of motion (ROM) of the shoulder in breast cancer patients. We conducted a double-blind, randomized controlled study to evaluate the clinical efficacy and safety of HA–CMC in the prevention of upper limb dysfunction after total mastectomy (TM). A total of 99 women with breast cancer were randomly assigned to one of two groups. In the HA–CMC group ( $n = 50$ ), a mixed HA–CMC was applied to the surface of the pectoralis major and serratus anterior muscle after TM. In the control group ( $n = 49$ ), TM was performed without the use of HA–CMC. The primary outcomes were ROM of the shoulder and motion-related pain assessed using a numeric rating scale measured before surgery (T0) and 3 (T1) and 6 months (T2) after surgery. Secondary outcomes included disabilities of the arm, shoulder, and hand (DASH) and the pectoralis minor length test. Compared with the control group, the HA–CMC group showed greater reductions in postoperative restriction of total shoulder ROM (sum of flexion and horizontal abduction) at 3 months ( $10.20^\circ$ ,  $P = 0.004$ ). Mean pain levels related to flexion and horizontal abduction were significantly lower in the HA–CMC group ( $-1.32$  and  $-0.93$ , respectively,  $P < 0.05$ ). The DASH score was lower ( $-4.94$ ;  $P = 0.057$ ) in the HA–CMC group at T2.

No adverse effect was observed in either group. These results provide evidence that HA–CMC may provide pain relief and improve ROM of the shoulder without causing adverse effects. The effect on pectoralis tightness should be investigated in further studies.

**Keywords** Mastectomy · Upper limb dysfunction · Sodium hyaluronate–carboxymethyl cellulose · Range of motion

## Introduction

Earlier detection and advances in treatment have significantly increased the 5-year breast cancer survival rate [1]. Good survival prospects make quality of life (QOL) an important health issue that warrants research attention [2]. Upper limb dysfunction adversely influences QOL in breast cancer survivors [3]. Pectoralis tightness is the most common form of upper limb dysfunction for up to 6 months after surgery among upper limb dysfunctions categorized based on symptoms and assessments of pain and disabilities [4–6]; moreover, pectoralis tightness is a clinically important complication because it can cause pain and limit motion, making activity and participation difficult [4, 7].

The anterior pectoralis muscle fascia is removed during a muscle-sparing mastectomy [8]. As a result of impaired muscle sheaths and pain-induced contraction after surgery, the pectoralis may become hypertonic and tightened [5]. Pectoralis tightness can alter scapular kinematics. Pectoralis muscle tightness causes the scapula to be pulled into a protracted and depressed position, with adduction contracture in the horizontal plane that may restrict daily living activities [9]. This is a potential mechanism of subacromial impingement or long-term morbidity [10]. Prevention or

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early treatment of pectoralis tightness through stretching exercise [9] may improve long-term functional morbidity [11, 12]. However, exercise starting immediately after surgery could increase the risk of seroma formation and may result in delayed lymphatic drainage [5, 13–16].

There are few effective methods available for preventing pectoralis tightness during this period. Hyaluronan (HA), a naturally occurring component of the extracellular matrix, has received much attention because of its possible application as an adhesion-preventing adjuvant in a variety of surgical procedures [17–20] for cancer patients. An anti-adhesion solution consisting of HA and carboxymethyl cellulose (CMC) was recently developed [21]. This solution reduced capsular contracture after breast implant insertion [22] and attenuated postsurgical adhesion formation in animal models [23].

Given the suggested anti-adhesive mechanisms of HA, we predicted that an agent containing HA–CMC may be effective for preventing or treating upper limb dysfunction after mastectomy. We hypothesized that HA–CMC applied to the surface of the pectoralis major muscle after mastectomy would significantly reduce pain and improve range of motion (ROM) of the shoulder in breast cancer patients. To this end, we conducted a double-blinded randomized controlled clinical trial to examine the effect of a HA derivative solution on upper limb dysfunction and to assess the safety of its application.

## Methods

### Subjects

Between July 2009 and March 2010, a total of 228 women with breast cancer underwent total mastectomy at the authors' institution. Patients who had bilateral or recurrent breast cancer, a history of previous cancer, or who needed palliative surgery, radical mastectomy, immediate reconstruction, or contralateral breast operation for benign disease were excluded. Patients who complained of pain with shoulder motion or had a previous history of upper limb dysfunction were also excluded. The study protocol was approved by the Institutional Review Board, and all participants provided written informed consent. The trial was conducted in accordance with the regulatory standards of the Declaration of Helsinki [24] and has been registered with the Clinical Research Information Service (CRiS), Republic of Korea (KCT0000003).

### Interventions

This was a prospective, randomized, and double-blinded clinical trial. Intraoperatively, patients were randomly assigned to either the HA–CMC group or the control group

using the sealed envelope technique. Randomization to two treatment arms at a ratio of 1:1 was achieved with a stratified randomization procedure and a permuted block size of four using a computer. The stratification factor was a type of axillary surgery [sentinel lymph node biopsy (SLNB) vs. axillary lymph node dissection (ALND)] as this could differently affect shoulder disability. The sequence was concealed in numbered and sealed envelopes until interventions were assigned; envelope seals were broken in the operating theater at the conclusion of the mastectomy and before suturing of the skin. The investigator who generated the allocation sequence was not involved in patient enrollment or patient assignment to a study group. Intervention and evaluation were performed by separate physicians. As a result, the patients and all other people involved, except for the surgeon, were blinded to the type of treatment.

All surgical procedures were performed by the same surgeon (SWK). After the total mastectomy, a HA–CMC gel (Guardix-Sol<sup>®</sup>, 5 g; Hanmi Pharmaceutical, Seoul, Korea) was sprayed onto the surface of the pectoralis major and serratus anterior muscles for patients in the HA–CMC group. In the control group, no treatment was applied following the conclusion of the surgical procedure. All patients in both the groups were given a regular exercise program consisting of neck rotation, neck muscle stretches, pectoralis stretches, side lateral stretches, overhead shoulder stretches, and arm circles as routine care [9]. A physiatrist prescribed one 30-min exercise session provided by experienced physiotherapists. All patients received an informative leaflet on self-care, including general shoulder ROM exercises after surgery.

### Outcome measures

All data were collected prospectively at baseline (T0) and 3 (T1) and 6 months (T2) postoperatively, by a clinical researcher who was blinded to the study. The primary outcome measures were (1) shoulder ROM, measured as the sum of the ROM in forward flexion and horizontal abduction in the affected upper limb using a goniometer based on our clinical experience [4], and (2) motion-related pain assessed using an 11-point numerical rating scale (NRS) [25, 26], where 0 indicates “no pain” and 10 indicates “pain as bad as you can imagine.” All ROMs were measured in a seated position. Horizontal abduction was defined as the maximum degree of scapular retraction in the horizontal plane with 90° of elbow flexion and 90° of shoulder abduction. Clinically meaningful differences in ROM were >10° according to the definition of Thomas-Maclean et al. [27].

Secondary outcome measures were (1) the prevalence of pectoralis tightness [4], (2) the pectoralis minor length test (PMLT) [28], and (3) a validated Korean version of the

disabilities of the arm, shoulder, and hand (DASH) questionnaire [29, 30]. In the absence of definitive diagnostic criteria to rule out pectoralis tightness or to establish the degree of limitation ensuing from this condition, pectoralis tightness was defined as the presence of limitation of forward flexion by more than  $10^\circ$ , with no limitation of external rotation and limited horizontal abduction of more than  $10^\circ$  based on our clinical experience. Shortness of the pectoralis muscle is measured with PMLT, defined by the linear distance from the table to the posterior aspect of the acromion when the subject is in the supine position. As described by Sahrman [31], PMLT is measured using a rigid standard plastic transparent right angle. The base of the protractor was placed on the table, and the vertical side was placed adjacent to the lateral aspect of the acromion without exerting any downward pressure onto the treatment table. The DASH questionnaire was used to measure symptoms and functional status, with a focus on physical function associated with different degrees of upper extremity disability. It consists of 30 items, each with five possible responses. Of these 30 items, 21 ask about the degree of difficulty in performing different physical activities; six ask about symptoms; and three ask about the psychosocial effects of upper extremity problems [29, 30].

#### Postoperative safety assessment

Complications and the duration of drainage after surgery were recorded for each patient, and adverse effects were monitored throughout the study. Drainage was assessed daily from the day of surgery, and drains were removed when the drainage volume fell below 50 mL over a 24-h period. The overall drain output and incidence of symptomatic seroma formation were also measured. A symptomatic seroma, defined as palpable accumulation of fluid under the wound with symptoms, was treated by aspiration or drain insertion [32].

#### Statistical analysis

We estimated that a sample size of 42 per group was needed to achieve 80 % statistical power to detect a mean difference in shoulder ROM of  $10^\circ$  with a standard deviation of  $16.2^\circ$  between treatment groups at a statistical significance level of 0.05 [9]. Baseline demographic and clinical characteristics of the patients in the HA-CMC and control groups were compared using Student's *t* test and  $\chi^2$  test. The primary analysis was based on the intention-to-treat (ITT) principle. For the ITT population, outcome measurements were analyzed using the last observation carried forward (LOCF) method.

Total shoulder ROM, pain related to shoulder ROM, PMLT, and DASH score were included in the analysis,

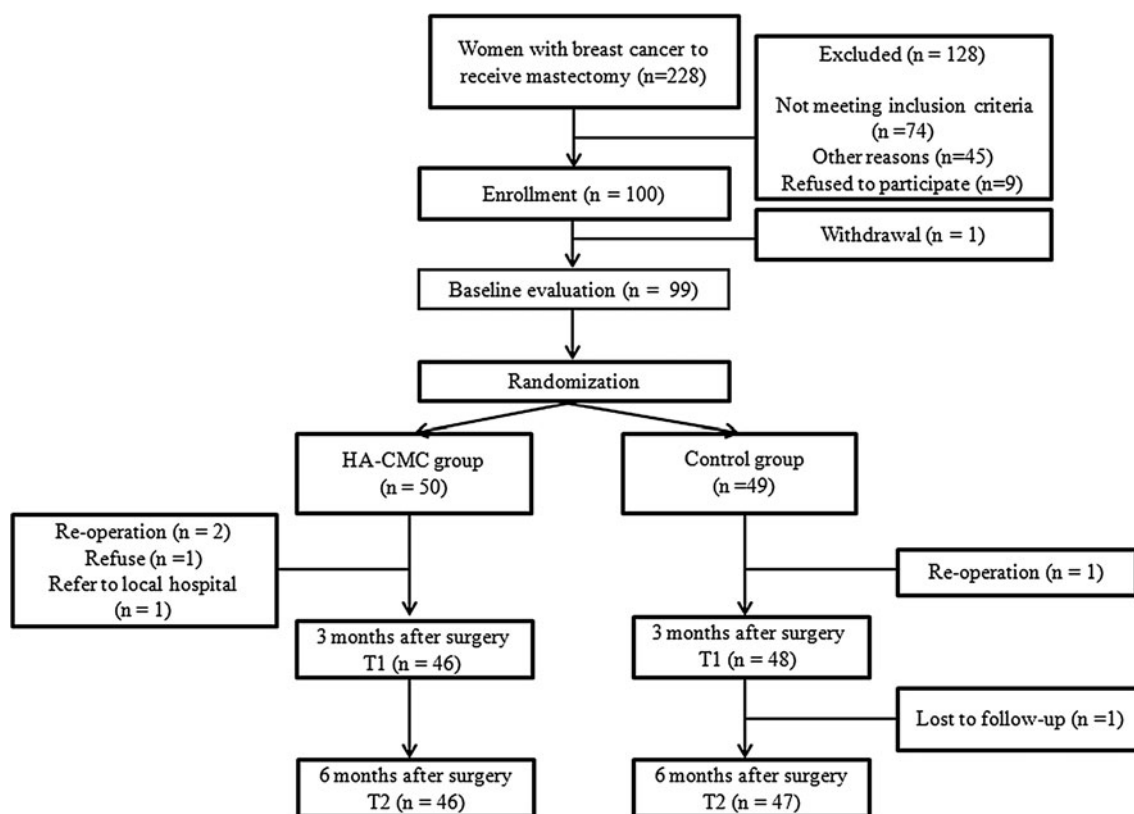
which was conducted using a repeated-measures, mixed-effects model to assess the effect of treatment over time, while accounting for correlations among repeated measures and to adjust the baseline difference in the DASH score over time. Means were modeled as a function of the group assignment and study visit (at baseline and at 3 and 6 months). The model included adjustments for age, body mass index (BMI), radiation therapy, and baseline measures. In addition, robust standard errors were computed. To prevent the assumption of a linear association, time was included in the model as a categorical variable with three categories: T0 (reference), T1, and T2. The control group was used as the reference group, and interactions between treatment and time were included. All data management and statistical analyses were performed using SPSS ver. 17.0 (SPSS, Chicago, IL).

#### Results

Of the 228 women that underwent total mastectomy, 109 satisfied all the inclusion and exclusion criteria, nine refused to participate in the study because of time constraints or unwillingness to visit the clinic. One hundred women were enrolled and one woman changed her mind before baseline evaluation. Participants were randomly assigned to the HA-CMC group ( $n = 50$ ) or control group ( $n = 49$ ) after primary baseline assessment. Five of the 99 participants were lost to follow-up at T1 because of reoperation ( $n = 3$ ), admission to another hospital ( $n = 1$ ), or refusal to undergo follow-up ( $n = 1$ ). One patient in the control group dropped out after the first follow-up session. In total, 46 participants in the HA-CMC group and 47 in the control group completed the follow-up evaluations (Fig. 1). At baseline, no significant differences were detected between the two groups in terms of age, type of axillary surgery, or clinical stage (Table 1).

#### Primary and secondary outcomes

At baseline, the total ROM was comparable in the two groups ( $170.2 \pm 1.6$ , mean  $\pm$  SE in the HA-CMC group and  $172.6 \pm 1.1$  in the control group,  $P = 0.142$  by *t* test). At 3 months, the mean ( $\pm$ SE) adjusted change in the total ROM from baseline was  $-21.5^\circ \pm 2.7^\circ$  in the control group and  $-11.2^\circ \pm 3.5^\circ$  in the HA-CMC group. At 6 months, the mean change in the total ROM from baseline was  $-19.5^\circ \pm 4.9^\circ$  in the control group and  $-13.7^\circ \pm 7.3^\circ$  in the HA-CMC group (Fig. 2; Table 2). Clinically meaningful differences in the mean change were observed at 3 months in the two intervention groups (the mean change in the HA-CMC group minus that in the control



**Fig. 1** Flowchart of recruitment, randomization, and follow-up of the study patients

**Table 1** Baseline characteristics of the subjects

Characteristic	HA-CMC group (N = 50)	Control group (N = 49)
Age (years)	51.1 ± 10.3	48.7 ± 10.5
Right side lesion	23 (46)	25 (51)
T stage		
0–2	24 (48)	22 (44.9)
3–4	26 (52)	27 (55.1)
Axillary surgery		
SLNB	24 (48)	22 (44.9)
ALND	26 (52)	27 (55.1)
Radiation therapy	18 (36)	14 (28.6)
Weight (kg)	58.2 ± 10.4	56.2 ± 8.2
BMI (kg/m <sup>2</sup> )	24.0 ± 4.0	25.2 ± 18.4
Total ROM (°)	170.2 ± 7.9	172.6 ± 7.7
PMLT	2.2 ± 1.2	2.2 ± 1.1
DASH	4.7 ± 9.0	1.7 ± 2.3

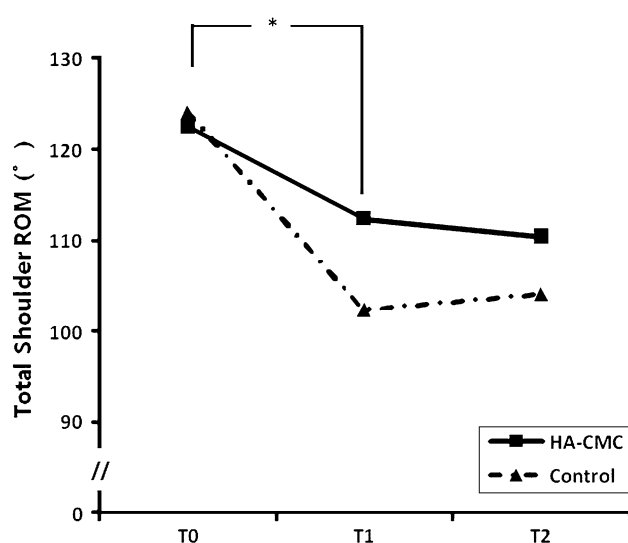
All values are mean ± standard deviation or number (percentage)

SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, PMLT pectoralis minor length test, DASH disabilities of arm, shoulder, and hand

group was 10.1°; 95 % confidence interval [CI] 3.3–16.8;  $P = 0.004$ ). The mean change at 6 months was 5.8° (95 % CI, −8.5–20.1;  $P = 0.424$ ) (Fig. 2).

Pain intensity was similar between the two groups at T0 and changed in a similar manner in both the groups during the follow-up period. Mean increases in pain intensity related to flexion were less in the HA-CMC group than in the control group at T2 ( $0.9 \pm 1.4$  vs.  $2.2 \pm 2.0$ ,  $P = 0.001$ , respectively). Pain related to horizontal abduction increased less in the HA-CMC group as compared with the control group at each follow-up period ( $1.3 \pm 1.4$  vs.  $2.7 \pm 1.9$ ,  $P = 0.001$  at T1;  $1.3 \pm 1.7$  vs.  $2.2 \pm 2.4$ ,  $P = 0.041$  at T2). Patients in the HA-CMC group showed significantly less pain related to flexion ( $-1.32$  point,  $P < 0.001$ ) than those in the control group at T2. The pain related to horizontal abduction in the HA-CMC group was significantly less than in the control group at T1 and T2 ( $-1.34$  point,  $P < 0.001$  at T1;  $-0.93$  point,  $P = 0.034$  at T2) (Table 2).

The prevalence of pectoralis tightness was lower in the HA-CMC group compared with the control group at T1 (30.4 vs. 44.9 %,  $P = 0.079$ ) and T2 (17.4 vs. 31.3 %,  $P = 0.083$ ), but the differences between the groups were not significant. Results of the PMLT were similar between the HA-CMC and control groups at T0, were significantly increased in both the groups at T1 ( $P = 0.304$ ), and were slightly lower in both the groups at T2 ( $P = 0.897$ ). The DASH score was significantly higher in the HA-CMC



**Fig. 2** Effect of HA-CMC on the total shoulder range of motion (ROM). The graphs illustrate the longitudinal effect of HA-CMC on the adjusted mean ROM, with lines representing the HA-CMC (solid) and control (dashed) groups. \* $P = 0.004$ , compared with the control by linear regression using GLMM (Table 2).  $T_0$  before surgery,  $T_1$  3 months after surgery,  $T_2$  6 months after surgery

group than in the control group ( $P = 0.026$ ) at  $T_0$ . The DASH scores were significantly increased at  $T_1$  and  $T_2$  compared to  $T_0$  in both the groups (14.03 score,  $P < 0.001$  at  $T_1$ ; 12.26 score,  $P < 0.001$  at  $T_2$ ) after adjusting for age, BMI, radiation therapy, and baseline DASH score (Table 2). The DASH scores tended to be better in the HA-CMC group than in the control group at  $T_2$  (−4.94 score;  $P = 0.057$ ) with marginal significance.

## Adverse events

The mean drainage duration was  $7.8 \pm 4.0$  days in the HA-CMC group and  $8.0 \pm 3.3$  days in the control group ( $P = 0.828$ ). Overall drain outputs were  $639.0 \pm 684.6$  mL for the HA-CMC group and  $597.4 \pm 486.8$  mL in the control groups ( $P = 0.729$ ). There were no significant differences in the incidence of seroma formation (32.0 vs. 36.7 %,  $P = 0.620$ ), postoperative bleeding (2.0 vs. 4.1 %,  $P = 0.617$ ), and wound infection (4.0 vs. 4.1 %,  $P = 1.000$ ) between the two groups. Over the 6-month follow-up period, no side effects were observed in either group. When the drainage data for each group were analyzed based on the type of axillary surgery, there were no significant differences in terms of drainage duration ( $P = 0.904$ ) or overall output ( $P = 0.743$ ).

## Discussion

The results of this double-blind randomized study indicate that a bioresorbable solution consisting of HA-CMC improved the ROM of the shoulder by attenuating postoperative adhesions. This effect of HA-CMC was still evident at 6 months after surgery without adverse events. To our knowledge, this is the first trial to evaluate the effects of HA on upper limb dysfunction after mastectomy in breast cancer patients.

A mixed HA-CMC solution has been shown to significantly reduce postsurgical adhesion [21, 23]. Sodium HA, an anti-adhesive agent, is a component of the extracellular matrix which is increased in the process of scarless fetal

**Table 2** Generalized estimating equation models of the association between treatment groups and clinical variables, with outcomes at  $T_1$  and  $T_2$

	Total shoulder ROM	Pain related to shoulder motion		PMLT	DASH
		FL	HA		
Treatment (difference from control group)					
HA-CMC	−1.48 (1.43)	0.01 (0.05)	0.01 (0.06)	0.01 (0.11)	0.43 (0.77)
Time (change from T0 in the control group)					
T1	−21.65 (2.76) <sup>a</sup>	1.98 (0.28) <sup>a</sup>	2.65 (0.29) <sup>a</sup>	2.69 (0.21) <sup>a</sup>	14.03 (1.86) <sup>a</sup>
T2	−19.84 (5.06) <sup>a</sup>	2.23 (0.30) <sup>a</sup>	2.19 (0.36) <sup>a</sup>	2.25 (0.21) <sup>a</sup>	12.26 (1.60) <sup>a</sup>
Interaction treatment × time (difference from control group)					
T1	10.20 (3.49) <sup>a</sup>	−0.41 (0.37)	−1.34 (0.36) <sup>a</sup>	−0.06 (0.31)	−0.20 (2.96)
T2	6.15 (7.36)	−1.32 (0.37) <sup>a</sup>	−0.93 (0.44) <sup>a</sup>	0.32 (0.29)	−4.94 (2.59) <sup>b</sup>

Values are beta coefficient (standard error) from a generalized estimating equation model (adjusted for age, BMI, radiation therapy, and baseline measures) predicting  $T_1$  and  $T_2$  outcomes

FL shoulder flexion, AB shoulder abduction, IR internal rotation, ER external rotation, HA horizontal abduction, PMLT pectoralis minor length test, DASH disabilities of arm, shoulder, and hand, BMI body mass index, RT radiation therapy,  $T_1$  3 months after surgery,  $T_2$  6 months after surgery

<sup>a</sup>  $P < 0.05$ , <sup>b</sup>  $0.05 < P < 0.1$



wound healing [33]. The efficacy of HA in abdominal and gynecological surgery has been widely reported [19, 20]. In shoulder disorders, a few studies have shown that HA decreases peritendinous adhesions after surgery in animal models [17, 34, 35] and reduces shoulder stiffness when used as a non-surgical therapy [36, 37]. In vivo subacromial injection of an anti-adhesive agent after arthroscopic rotator cuff repair produced faster recovery from postoperative shoulder stiffness [38].

In this study, the mean flexion ROM and mean abduction ROM were 152.0° and 145.8° in the control group at 3 months after surgery. Previous studies reported shoulder flexion limitations with means of 143° [39], 152° [40], and 163° [41]. Normative data for average shoulder flexion and abduction in healthy females were 176° and 187°, respectively [42]. Therefore, flexion and abduction ROM values in breast cancer survivors are approximately 24° and 42° less than the respective values in healthy women. In our study, an anti-adhesive agent after mastectomy tended to reduce the limitation of total ROM in forward flexion and horizontal abduction, with a 10.1° difference. These differences were clinically significant [27].

Spraying an anti-adhesive agent on the pectoralis muscles significantly relieved the pain related to shoulder flexion, abduction, and horizontal abduction. The primary actions of the entire pectoralis muscle are adduction, internal rotation, and flexion of the shoulder [43, 44]. A loss of muscle flexibility induces motion-related pain [5]. Regional or localized pain is the most frequent impairment after breast cancer treatment, with an incidence of 20–65 % [45], showing a strong relationship with disability and reduced QOL [46]. In addition, the presence of pain before and soon after surgery is a major predictor of chronic pain after breast surgery [47]. Therefore, intervention to reduce pain intensity is clinically important. There is increasing evidence that postmastectomy pain is related to not only nerve injury but also myofascial tissue [48]. Studies have reported that myofascial dysfunction is common in the pectoralis major as a result of muscle trauma after transaxillary surgery [49]. According to the considerations for chronic pain clinical trials as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [50], raw score changes of approximately 1 point on a 10-point NRS for pain intensity represents not very important decreases. Farrar et al. [51] found that a decrease of  $\geq 1.7$  points was required to distinguish between patients who rated their improvement in pain as “much improved” or better and those who rated their change as “minimally improved” at best. Therefore, the decreases in pain intensity of  $<1.7$  points observed in this study represent clinically minimal or small changes [52, 53].

In this study, the patients in the HA–CMC group had less disability and a lower incidence of pectoralis tightness than the control group, but the difference was not significant. Pectoralis tightness and pain from the adhesion can be relieved or prevented by stretching exercises [41, 54, 55]. We provided all participants with information on self-care, including shoulder and pectoralis stretching exercises, as a part of routine care during the follow-up period. However, exercise programs that start on the first few days after surgery have been associated with an increased risk of seroma formation [52–55]. Previous studies indicate that a short period of immobilization may be beneficial, but it should be limited to the first few days after surgery [56]. The application of HA–CMC may prevent early postoperative adhesion during this painful period [38].

There were several methodological limitations in this study. First, it assessed the outcomes after medium-term follow-up. To determine the long-term effects, additional follow-up examinations are needed. Second, all patients in both the groups were given information on stretching exercises, and there was no control group with restricted passive motion, making it impossible to determine whether HA–CMC was effective without exercise after a mastectomy. Third, changes during the early postoperative period should be assessed, as HA–CMC is effective for 2 weeks. Data for 2 weeks or 1-month postsurgery may be helpful for assessing the immediate effectiveness of anti-adhesive agents.

## Conclusion

The application of HA–CMC on the pectoralis muscles after a mastectomy improved the ROM of the shoulder by attenuating postoperative adhesions with no adverse effects. Its effectiveness in preventing pectoralis tightness and upper limb dysfunction should be evaluated in future studies.

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## References

1. Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, Thun M (2006) Trends in breast cancer by race and ethnicity: update 2006. *CA Cancer J Clin* 56:168–183
2. Hayes SC, Rye S, Battistutta D, DiSipio T, Newman B (2010) Upper-body morbidity following breast cancer treatment is common, may persist longer-term and adversely influences quality of life. *Health Qual Life Outcomes* 8:92
3. Kwan W, Jackson J, Weir LM, Dingee C, McGregor G, Olivotto IA (2002) Chronic arm morbidity after curative breast cancer

- treatment: prevalence and impact on quality of life. *J Clin Oncol* 20:4242–4248
4. Yang EJ, Park WB, Seo KS, Kim SW, Heo CY, Lim JY (2010) Longitudinal change of treatment-related upper limb dysfunction and its impact on late dysfunction in breast cancer survivors: a prospective cohort study. *J Surg Oncol* 101:84–91
  5. Chevillet AL, Tchou J (2007) Barriers to rehabilitation following surgery for primary breast cancer. *J Surg Oncol* 95:409–418
  6. Stubblefield MD, Custodio CM (2006) Upper-extremity pain disorders in breast cancer. *Arch Phys Med Rehabil* 87:S96–S99 (quiz S100–S101)
  7. Karki A, Simonen R, Malkia E, Selfe J (2005) Impairments, activity limitations and participation restrictions 6 and 12 months after breast cancer operation. *J Rehabil Med* 37:180–188
  8. Silen W, Matory W, Love S (1996) *Atlas of techniques in breast surgery*. Lippencott-Raven, New York
  9. Lee SA, Kang JY, Kim YD, An AR, Kim SW, Kim YS, Lim JY (2010) Effects of a scapula-oriented shoulder exercise programme on upper limb dysfunction in breast cancer survivors: a randomized controlled pilot trial. *Clin Rehabil* 24:600–613
  10. Shamley D, Srinaganathan R, Oskrochi R, Lascrain-Aguirrebena I, Sugden E (2009) Three-dimensional scapulothoracic motion following treatment for breast cancer. *Breast Cancer Res Treat* 118:315–322
  11. Reigle BS (2006) The prevention of disablement: a framework for the breast cancer trajectory. *Rehabil Nurs* 31:174–179
  12. Caban ME, Freeman JL, Zhang DD, Jansen C, Ostir G, Hatch SS, Goodwin JS (2006) The relationship between depressive symptoms and shoulder mobility among older women: assessment at one year after breast cancer diagnosis. *Clin Rehabil* 20:513–522
  13. Agrawal A, Ayantunde AA, Cheung KL (2006) Concepts of seroma formation and prevention in breast cancer surgery. *ANZ J Surg* 76:1088–1095
  14. Chen SC, Chen MF (1999) Timing of shoulder exercise after modified radical mastectomy: a prospective study. *Changgeng Yi Xue Za Zhi* 22:37–43
  15. Lotze MT, Duncan MA, Gerber LH, Woltering EA, Rosenberg SA (1981) Early versus delayed shoulder motion following axillary dissection: a randomized prospective study. *Ann Surg* 193:288–295
  16. Shamley DR, Barker K, Simonite V, Beardshaw A (2005) Delayed versus immediate exercises following surgery for breast cancer: a systematic review. *Breast Cancer Res Treat* 90:263–271
  17. Hagberg L, Gerdin B (1992) Sodium hyaluronate as an adjunct in adhesion prevention after flexor tendon surgery in rabbits. *J Hand Surg Am* 17:935–941
  18. Tuncay I, Ozbek H, Atik B, Ozen S, Akpinar F (2002) Effects of hyaluronic acid on postoperative adhesion of tendo calcaneus surgery: an experimental study in rats. *J Foot Ankle Surg* 41:104–108
  19. Fujii S, Shimada H, Ike H, Kunisaki C, Ohki S, Ichikawa Y, Ohta M, Yamagishi S, Osada S (2009) Reduction of postoperative abdominal adhesion and ileus by a bioresorbable membrane. *Hepatogastroenterology* 56:725–728
  20. Mais V, Bracco GL, Litta P, Gargiulo T, Melis GB (2006) Reduction of postoperative adhesions with an auto-crosslinked hyaluronan gel in gynaecological laparoscopic surgery: a blinded, controlled, randomized, multicentre study. *Hum Reprod* 21:1248–1254
  21. Kim JH, Lee JH, Yoon JH, Chang JH, Bae JH, Kim KS (2007) Antiadhesive effect of the mixed solution of sodium hyaluronate and sodium carboxymethylcellulose after endoscopic sinus surgery. *Am J Rhinol* 21:95–99
  22. Lew DH, Yoon JH, Hong JW, Tark KC (2010) Efficacy of anti-adhesion barrier solution on periimplant capsule formation in a white rat model. *Ann Plast Surg* 65:254–258
  23. Park JS, Cha SJ, Kim BG, Choi YS, Kwon GY, Kang H, An SS (2011) An assessment of the effects of a hyaluronan-based solution on reduction of postsurgical adhesion formation in rats: a comparative study of hyaluronan-based solution and two film barriers. *J Surg Res* 168:49–55
  24. (2000) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 284:3043–3045
  25. Gagliese L, Weizblit N, Ellis W, Chan VW (2005) The measurement of postoperative pain: a comparison of intensity scales in younger and older surgical patients. *Pain* 117:412–420
  26. Komiyama O, De Laat A (2005) Tactile and pain thresholds in the intra- and extra-oral regions of symptom-free subjects. *Pain* 115:308–315
  27. Thomas-Maclean RL, Hack T, Kwan W, Towers A, Miedema B, Tilley A (2008) Arm morbidity and disability after breast cancer: new directions for care. *Oncol Nurs Forum* 35:65–71
  28. Lewis JS, Valentine RE (2007) The pectoralis minor length test: a study of the intra-rater reliability and diagnostic accuracy in subjects with and without shoulder symptoms. *BMC Musculoskelet Disord* 8:64
  29. Hudak PL, Amadio PC, Bombardier C (1996) Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). *Am J Ind Med* 29:602–608
  30. Lee JY, Lim JY, Oh JH, Ko YM (2008) Cross-cultural adaptation and clinical evaluation of a Korean version of the disabilities of arm, shoulder, and hand outcome questionnaire (K-DASH). *J Shoulder Elbow Surg* 17:570–574
  31. Sahrmann S (2002) *Diagnosis and treatment of movement impairment syndromes*. Mosby, London
  32. Ko E, Han W, Cho J, Lee JW, Kang SY, Kim EK, Hwang KT, Noh DY (2009) Fibrin glue reduces the duration of lymphatic drainage after lumpectomy and level II or III axillary lymph node dissection for breast cancer: a prospective randomized trial. *J Korean Med Sci* 24:92–96
  33. Schimizzi AL, Massie JB, Murphy M, Perry A, Kim CW, Garfin SR, Akesson WH (2006) High-molecular-weight hyaluronan inhibits macrophage proliferation and cytokine release in the early wound of a preclinical postlaminectomy rat model. *Spine J* 6:550–556
  34. Liu Y, Skardal A, Shu XZ, Prestwich GD (2008) Prevention of peritendinous adhesions using a hyaluronan-derived hydrogel film following partial-thickness flexor tendon injury. *J Orthop Res* 26:562–569
  35. Menderes A, Mola F, Tayfur V, Vayvada H, Barutcu A (2004) Prevention of peritendinous adhesions following flexor tendon injury with SEPRAFILM. *Ann Plast Surg* 53:560–564
  36. Shibata Y, Midorikawa K, Emoto G, Naito M (2001) Clinical evaluation of sodium hyaluronate for the treatment of patients with rotator cuff tear. *J Shoulder Elbow Surg* 10:209–216
  37. Moskowitz RW, Blaine TA (2005) An overview of treatment options for persistent shoulder pain. *Am J Orthop (Belle Mead NJ)* 34:10–15
  38. Oh CH, Oh JH, Kim SH, Cho JH, Yoon JP, Kim JY (2011) Effectiveness of subacromial anti-adhesive agent injection after arthroscopic rotator cuff repair: prospective randomized comparison study. *Clin Orthop Surg* 3:55–61
  39. Hayes S, Battistutta D, Newman B (2005) Objective and subjective upper body function six months following diagnosis of breast cancer. *Breast Cancer Res Treat* 94:1–10
  40. Kaya T, Karatepe AG, Gunaydn R, Yetis H, Uslu A (2010) Disability and health-related quality of life after breast cancer surgery: relation to impairments. *South Med J* 103:37–41
  41. Cinar N, Seckin U, Keskin D, Bodur H, Bozkurt B, Cengiz O (2008) The effectiveness of early rehabilitation in patients with modified radical mastectomy. *Cancer Nurs* 31:160–165

42. Barnes CJ, Van Steyn SJ, Fischer RA (2001) The effects of age, sex, and shoulder dominance on range of motion of the shoulder. *J Shoulder Elbow Surg* 10:242–246
43. Connell DA, Potter HG, Sherman MF, Wickiewicz TL (1999) Injuries of the pectoralis major muscle: evaluation with MR imaging. *Radiology* 210:785–791
44. Petilon J, Carr DR, Sekiya JK, Unger DV (2005) Pectoralis major muscle injuries: evaluation and management. *J Am Acad Orthop Surg* 13:59–68
45. Randal J (1998) Post-mastectomy pain found to be common: treatment options sparse, but growing. *J Natl Cancer Inst* 90:731–732
46. Rietman JS, Dijkstra PU, Debreczeni R, Geertzen JH, Robinson DP, De Vries J (2004) Impairments, disabilities and health related quality of life after treatment for breast cancer: a follow-up study 2.7 years after surgery. *Disabil Rehabil* 26:78–84
47. Perkins FM, Kehlet H (2000) Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* 93:1123–1133
48. Kudel I, Edwards RR, Kozachik S, Block BM, Agarwal S, Heinberg LJ, Haythornthwaite J, Raja SN (2007) Predictors and consequences of multiple persistent postmastectomy pains. *J Pain Symptom Manage* 34:619–627
49. Cummings M (2003) Myofascial pain from pectoralis major following trans-axillary surgery. *Acupunct Med* 21:105–107
50. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S (2008) Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 9:105–121
51. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM (2001) Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 94:149–158
52. Bird SB, Dickson EW (2001) Clinically significant changes in pain along the visual analog scale. *Ann Emerg Med* 38:639–643
53. Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB (2003) What decline in pain intensity is meaningful to patients with acute pain? *Pain* 105:151–157
54. Box RC, Reul-Hirche HM, Bullock-Saxton JE, Furnival CM (2002) Shoulder movement after breast cancer surgery: results of a randomised controlled study of postoperative physiotherapy. *Breast Cancer Res Treat* 75:35–50
55. Morimoto T, Tamura A, Ichihara T, Minakawa T, Kuwamura Y, Miki Y, Sasa M (2003) Evaluation of a new rehabilitation program for postoperative patients with breast cancer. *Nurs Health Sci* 5:275–282
56. Jarvinen TA, Jarvinen TL, Kaariainen M, Kalimo H, Jarvinen M (2005) Muscle injuries: biology and treatment. *Am J Sports Med* 33:745–764