Effect of the mixed solution of sodium hyaluronate and carboxymethylcellulose on upper limb dysfunction after total mastectomy: a randomized double-blind clinical trial

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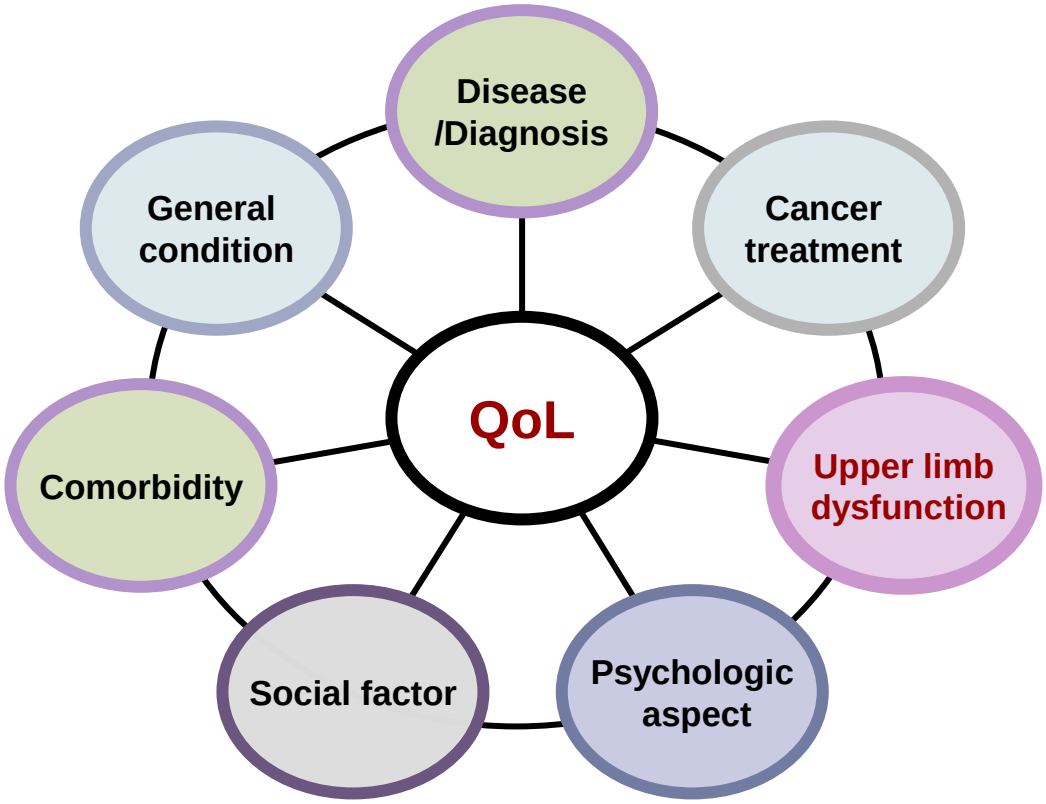
The trial is registered with the Clinical Research Information Service (**CRiS**), Republic of Korea: KCT0000003.

Quality of Life for Breast Cancer Survivors

- Increases in life expectancy for women with breast cancer
  the need for improved quality of life (QOL)
- Upper limb dysfunction (ULD) remains one significant complication after treatment (Satariano et al., 1996)



Engel J et al, Acta Oncologica, 2003

Upper limb dysfunctions

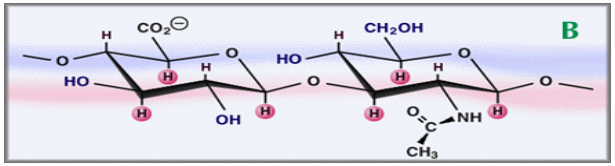
Common types of ULD after breast cancer surgery

Pectoralis tightness

- The most common disorder at early and intermediate periods after surgery
  - Pectorals hypertonic through contraction after surgery
  - Thoracic flexion and scapular protraction could aggravate muscle shortening
- Limitation of flexion, horizontal abduction→ ADL ↓
- Late ULD such as RCD appeared to be associated with the pectoral tightness at earlier times

Hyaluronate-carboxymethylcellulose

- Seprafilm is adhesion barrier bioresorbable **membrane** consisted of haylunonate (HA) and carboxymethyl cellulose (CMC)
- Antiadhesive barrier solution (AABS)
  - Sodium hyaluronate carboxymethyl cellulose (HA-CMC) in **liquid form**
  - Applied more readily than the solid film type



- Intraabdominal adhesions in abdominal and pelvic surgery

(Fujii et al., Hepatogastroenterology, 2009)

- Rotator cuff repair (Oh et al,, Clinics in Orthopedic Surgery 2011)
- After a breast reconstruction using breast implant (Lew et al., Ann Plast Surg 2010)

- However, there are no reports on the anti-adhesive effect of HA after mastectomy in vivo

Objectives

- We evaluated the clinical efficacy and safety of the HA-CMC for prevention of upper limb dysfunction after total mastectomy (TM).

Design

- A prospective randomized, double-blind clinical trial of intramuscular HA-CMC group versus Control group

Subjects and Methods

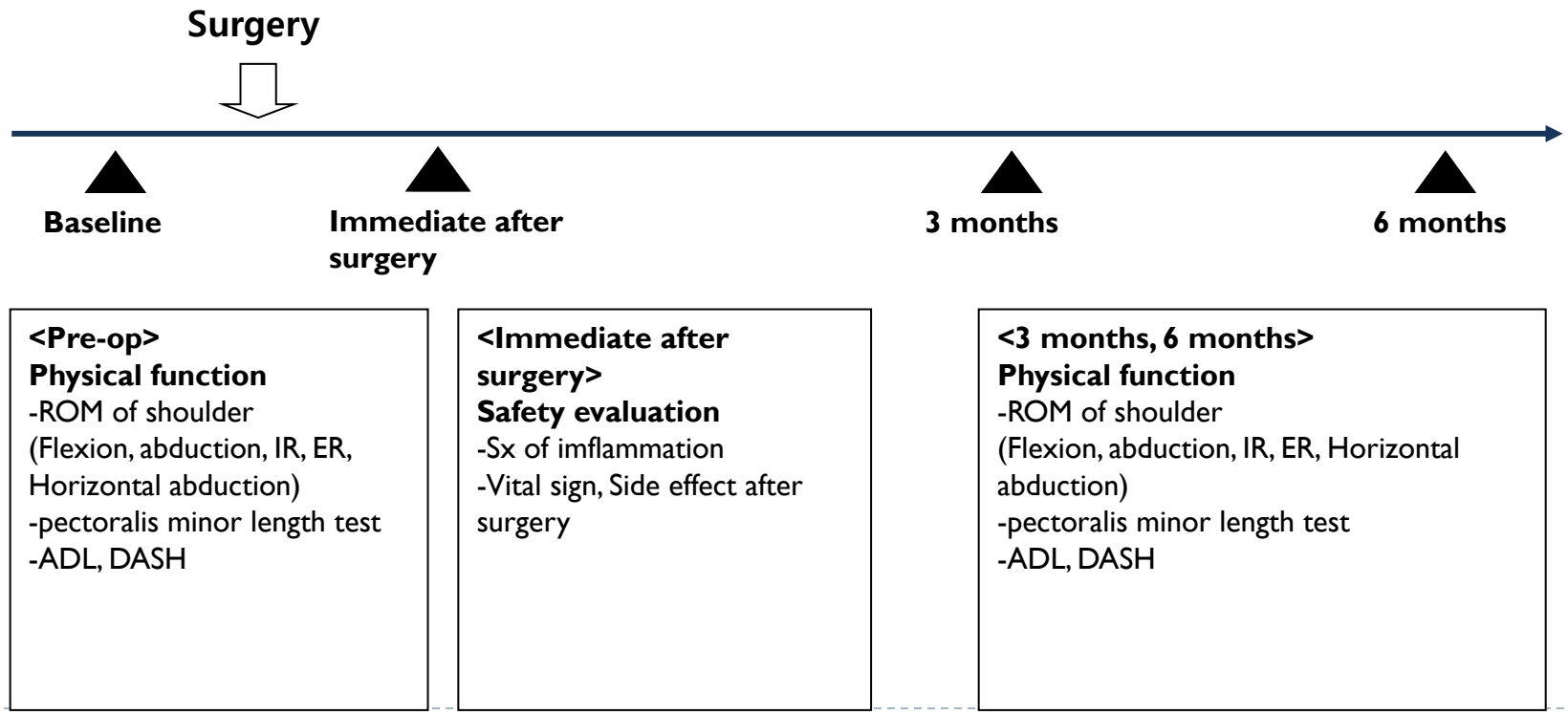
- Between January 2009 and 2010, women with breast cancer who underwent mastectomy in SNUBH
- Inclusion criteria
  - pathologic classification
  - axillary surgery (SLNB, AD)
  - Radiation treatment
- Exclusion
  - Previous history of upper limb dysfunction
  - Severe shoulder disability

Treatment Procedure

- Randomization
  - by the computerized stratified block randomization procedure
  - allocated by means of 2 levels of 2 strata
    - stratum 1: cancer T stage 1,2 or 3,4,
    - stratum 2: SLNB and AD
- In HA-CMC group
  - the mixed solution of HA-CMC was applied on the surface of pectoralis major muscle after TM
- In control group
  - the standard fashion without the use of HA-CMC

Experimental Design

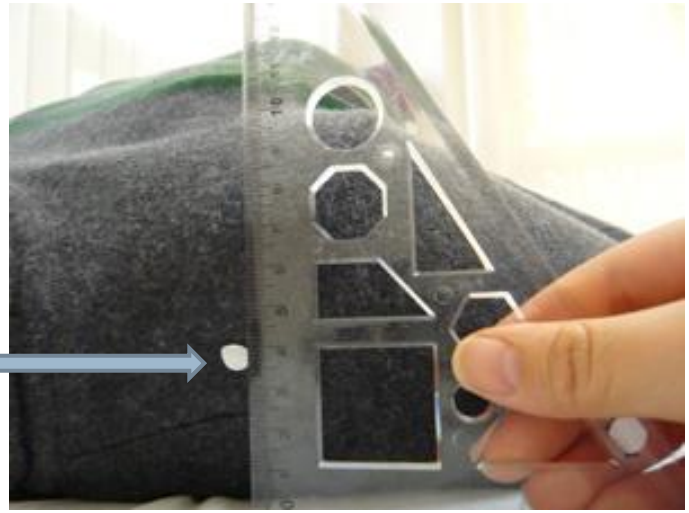
- A prospective, randomized controlled trial with blinded assessments before surgery (T0) and 3 (T1), 6 months (T2) after surgery



Outcome Measurement

- Primary outcome:
  - The range of motion (ROM) of shoulder
  - Forward flexion and horizontal abduction
  - Measured using a goniometer with the scapula in a fixed position
- Secondary outcome:
  - Motion related pain by visual analogue scale (VAS) score
  - Pectoralis minor length test (PMLT)
  - Disabilities of arm, shoulder and hand (DASH)

The pectoralis minor length test



A shortened **pectoralis muscle**

The linear distance from the treatment table to the **posterior aspect of the acromion**

>2.6cm : Pectoralis tightness

Lewis JS et al., 2007

Disabilities of arm, shoulder and hand (DASH)

- To measure the functional status and symptoms
- associated with different degrees and levels of upper-extremity disability
- 30 items

손,팔,어깨의 장애 평가 (DASH)

이 설문지는 당신의 증상 및 특정 동작을 수행하는 능력에 관한 질문들입니다.
당신의 지난 주 상태를 기준으로, 해당되는 번호에 동그라미(○)하여 모든 질문에 답변해 주시기 바랍니다.
만약 지난 주 동안 질문한 동작을 할 기회가 없었다면, 당신의 상태에 가장 가까운 답변에 표시해 주시기 바랍니다.
어느쪽 손이나 팔을 쓰는지는 중요하지 않습니다.
어떻게 동작을 수행하는지에 관계 없이 당신의 수행 능력을 기준으로 답변해 주시기 바랍니다.
1~30 문항에서 1~5 숫자를 체크해주시면 됩니다. 21 문항도 꼭 기입해주십시오.
(숫자가 클수록 수행하기 어려움 또는 통증이 심함을 의미합니다.)
일/직업 칸, 스포츠/악기 칸은 해당하시는 분만 기입해 주시면 됩니다.
(일에는 가사일도 포함됩니다.) 선택 사항이지만 되도록 기입해 주시길 부탁드립니다.
지난 주의 상태를 기준으로 해당하는 번호에 동그라미(○)하여 당신의 동작 수행 능력을 평가하여 주시기 바랍니다.

	어려움이 없음	약간 어려움	중간 정도 어려움	아주 어려움	전혀 할 수 없음
1. 밀폐된 용기나 새 단지 뚜껑열기	1	2	3	4	5
2. 글씨 쓰기	1	2	3	4	5
3. 열쇠 돌려 문 열기	1	2	3	4	5
4. 식사 준비하기	1	2	3	4	5
5. 무거운 문을 밀어서 열기	1	2	3	4	5
6. 머리보다 높은 선반에 물건 놓기	1	2	3	4	5
7. 힘든 집안일하기(벽청소, 바닥청소 등)	1	2	3	4	5
8. 정원 가꾸기 (실내 포함)	1	2	3	4	5
9. 잠자리 준비하기 (이부자리 갈기)	1	2	3	4	5
10. 쇼핑백이나 서류가방 들고 가기	1	2	3	4	5
11. 무거운 물건 나르기(5kg 이상)	1	2	3	4	5
12. 머리 보다 높은 곳의 전등 교체하기	1	2	3	4	5
13. 머리감기 또는 머리말리기	1	2	3	4	5
14. 등 닦기(샤워할 때)	1	2	3	4	5
15. 스웨터를 머리부터 뒤집어 써 입기	1	2	3	4	5
16. 칼로 음식 자르기	1	2	3	4	5
17. 힘들지 않은 여가활동(카드놀이, 뜨개질 등)	1	2	3	4	5
18. 팔, 어깨, 손에 어느 정도의 힘이나 충격이 가는 여가활동 (골프, 망치질, 테니스 등)	1	2	3	4	5
19. 팔을 자유롭게 움직이는 여가활동(원반던지기, 배드민턴 등)	1	2	3	4	5
20. 교통수단 이용하기 (자가 운전)	1	2	3	4	5
21. 성 관계 갖기	1	2	3	4	5

	전혀 없었음	약간 있었음	중간 정도 있었음	상당히 있었음	극히 지장 받았음
22.**지난 주 동안** 당신의 팔, 어깨, 손의 문제로 인하여 가족,친구,이웃 또는 다른 모임과의 사회 활동에 어느 정도 지장이 있었습니까?	1	2	3	4	5

	전혀 제한 받지 않았음	약간 제한 받았음	중간 정도 제한받았음	매우 제한 받았음	할 수 없었음
23.**지난 주 동안** 당신의 팔, 어깨, 손의 문제로 인하여 일이나 일상 활동에 어느 정도 제한을 받았습니까?	1	2	3	4	5

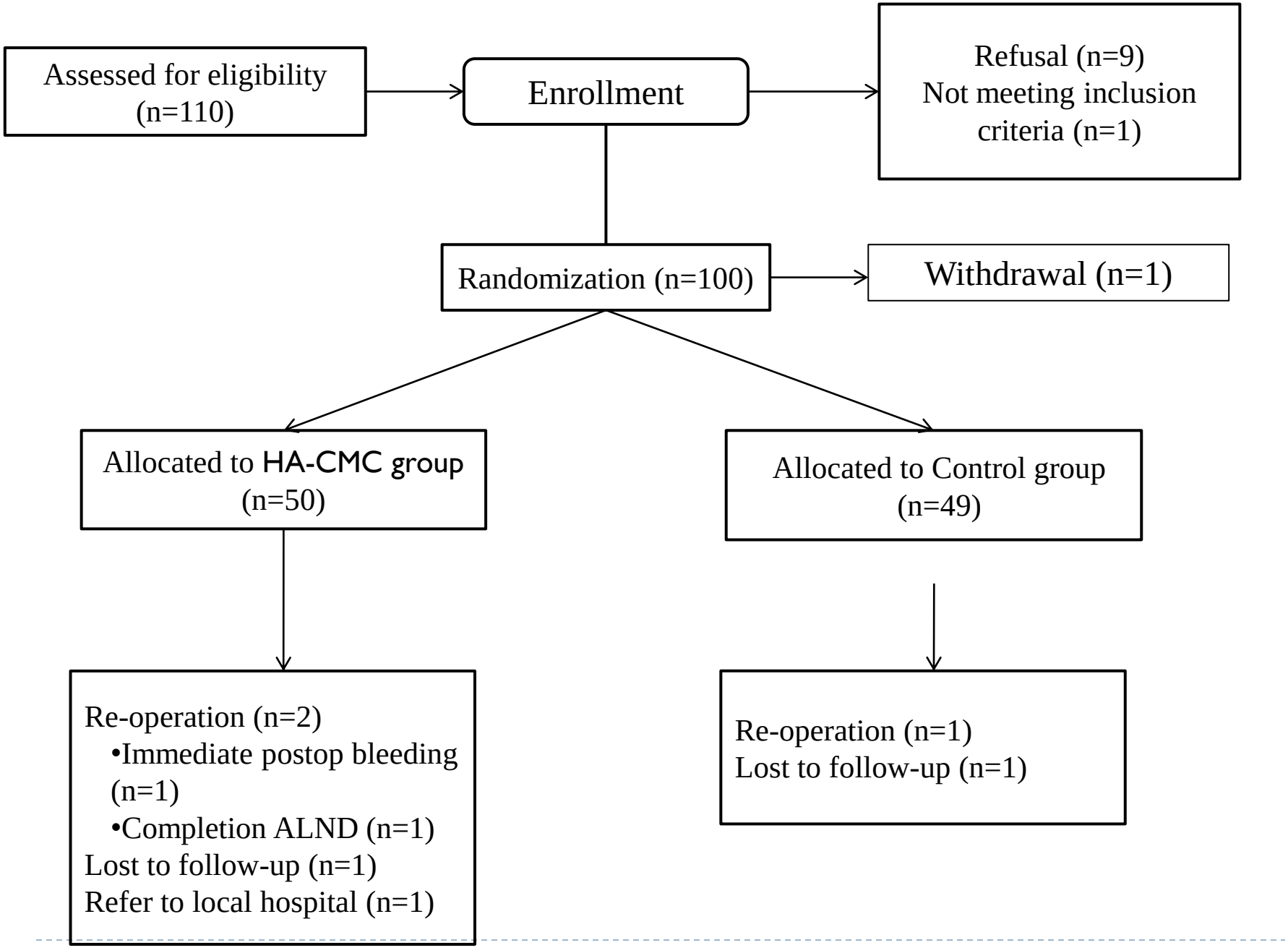
지난 주의 상태를 기준으로 해당하는 번호에 동그라미(○)하여 다음 증상들의 정도를 평가하여 주시기 바랍니다.

	없음	약간 느낌	중간 정도 느낌	상당히 느낌	극심하게 느낌
24. 팔, 어깨, 손의 통증	1	2	3	4	5
25. 특정한 동작이나 행동을 할 때 발생하는 팔,어깨,손의 통증	1	2	3	4	5
26. 팔, 어깨, 손의 저린감	1	2	3	4	5
27. 팔, 어깨, 손의 근력 약화	1	2	3	4	5
28. 팔, 어깨, 손의 뻣뻣함	1	2	3	4	5

Statistical Analysis

- Baseline demographic and clinical characteristics were compared between HA-CMC group and control group with the use of a Student's *t*-test.
- The primary analyses focused on the ROM of shoulder in each group and analysis of this was performed with the use of mixed-effects linear models to obtain adjusted means and standard errors.
- Two-sided P-values of less than 0.05 were considered to indicate statistical significance. All data management and statistical analysis were performed using SPSS version 17.0 (SPSS Inc., Chicago,IL).

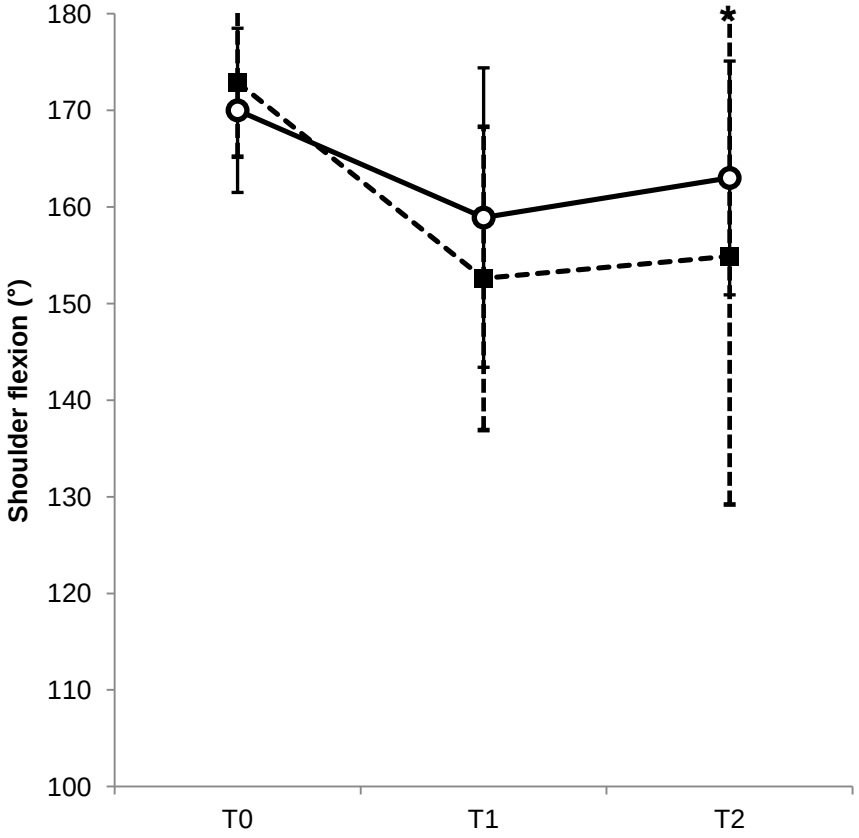
Results


Assessed for eligibility (n=110)
Enrollment
Refusal (n=9)
Not meeting inclusion criteria (n=1)
Randomization (n=100)
Withdrawal (n=1)
Allocated to HA-CMC group (n=50)
Allocated to Control group (n=49)
Re-operation (n=2)
•Immediate postop bleeding (n=1)
•Completion ALND (n=1)
Lost to follow-up (n=1)
Refer to local hospital (n=1)
Re-operation (n=1)
Lost to follow-up (n=1)

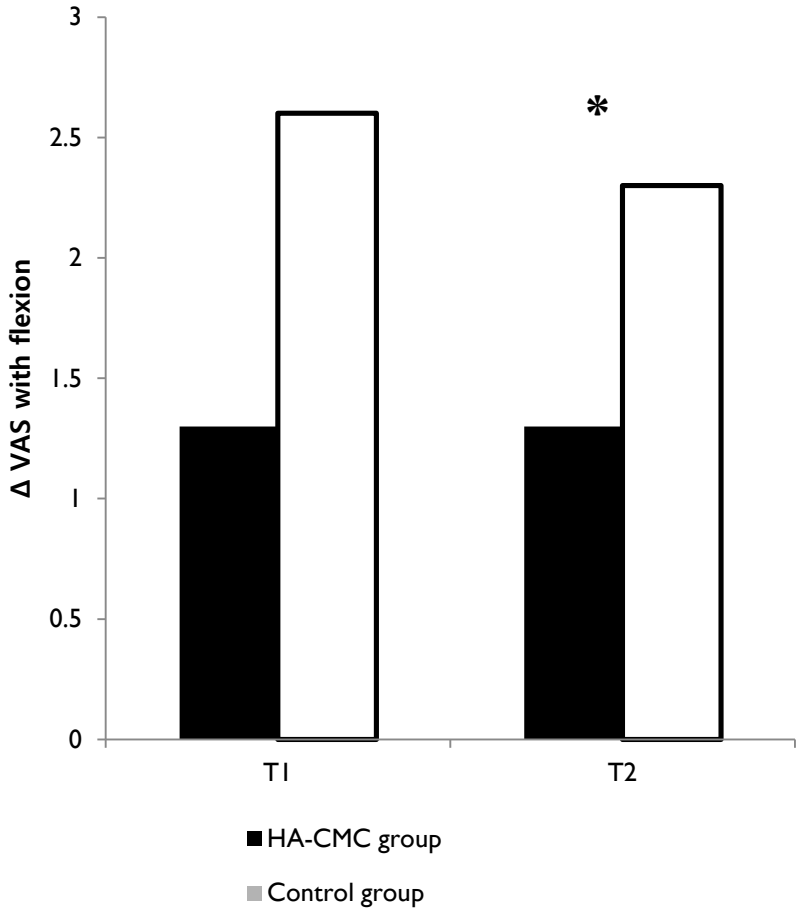
Baseline characteristics of subjects

	HA-CMC group (n=50)	Control group (n=49)	P
Age, years	51.1 ± 10.3	48.7 ± 10.5	0.254
Right-side lesion (%)	23(46%)	25(51%)	0.383
T stage			
0	2 (4%)	4 (8.2%)	0.909
1	24(48%)	21 (42.9%)	
2	20(40%)	20 (40.8%)	
3	3(6%)	3 (6.1%)	
4	1(2%)	1 (2.0%)	
Axillary Surgery			
SLNB	24 (48%)	22 (44.9%)	0.457
ALND	26 (52%)	27 (55.1%)	
Weight	58.2 ± 10.4	56.2 ± 8.2	0.281
Hight	155.6 ± 5.7	155.6 ± 14.1	1
BMI	24.0 ± 4.0	25.2 ± 18.4	0.681

Comparison of shoulder flexion between HA-CMC and control group

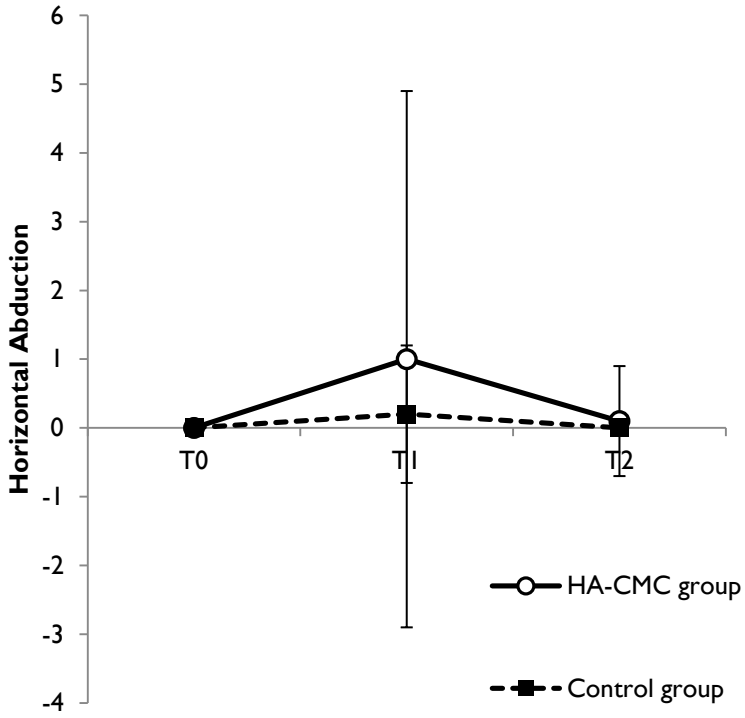


ROM of shoulder flexion

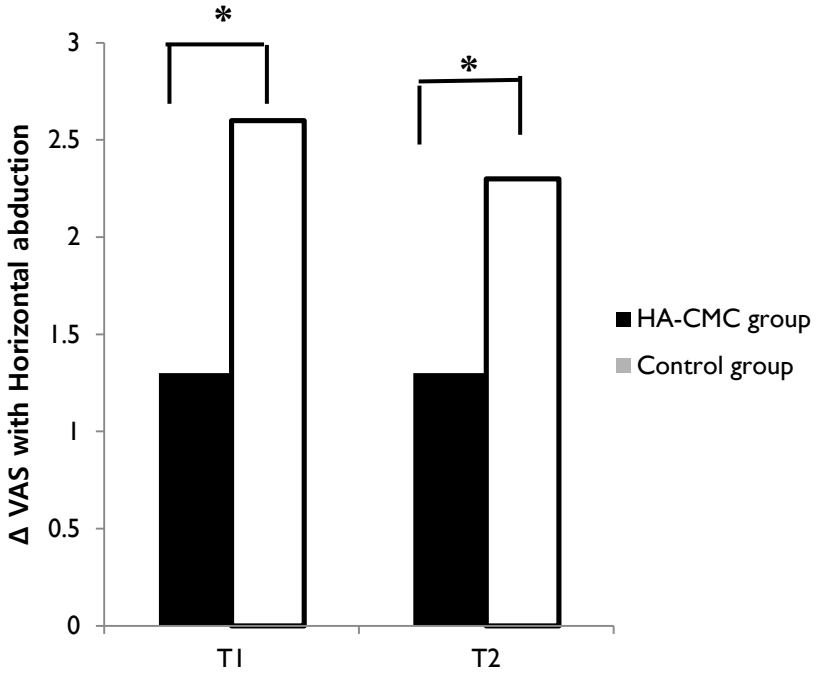


Pain (VAS) related with the motion

Comparison of Horizontal abduction between HA-CMC and control group



ROM of Horizontal Abduction



Pain (VAS) related with the motion

Generalized Linear Mixed Models of the association between Treatment groups with Upper limb dysfunction at each time point

	Shoulder Flexion			PMLT			DASH		
	β	SE	P	β	SE	P	β	SE	P
Intercept	182.63	4.71	<0.001	1.38	0.45	0.002	-7.91	4.43	0.075
Age	-0.2	0.09	0.039	0.02	0.01	0.077	0.19	0.09	0.031
Treatment (differences at baseline)									
Control group	ref.		ref.	ref.		ref.	ref.		ref.
HA-CMC group	-2.44	1.64	0.136	-0.02	0.22	0.94	2.54	1.2	0.035
Interaction control X time (change from T0)									
T0	ref.		ref.	ref.		ref.	ref.		ref.
T1	**-20.32**	**2.43**	**<0.001**	**2.64**	**0.21**	**<0.001**	**13.9**	**1.86**	**<0.001**
T2	**-17.98**	**3.87**	**<0.001**	**2.35**	**0.23**	**<0.001**	**12.23**	**1.66**	**<0.001**
Interaction HA-CMC X time (difference from control)									
T0	ref.		ref.	ref.		ref.	ref.		ref.
T1	**9.15**	**3.28**	**0.005**	0.02	0.32	0.948	-0.09	3.02	0.976
T2	**10.78**	**4.27**	**0.012**	0.37	0.33	0.262	-5.4	2.8	0.054

Time was included in the model as a categorical variable with four categories so as not to assume a linear association: T0 (reference), T1, and T2.
Interaction variables between each treatment group and time were included: for interaction with control group, the coefficients refer to the changes from
baseline; and for the HA-CMC group, the coefficients refer to the difference from the control group (reference group) on the changes from baseline

Adverse Side Effects

- No adverse side effects reported in both groups.

Conclusion

- These results provide evidence that HA-CMC is effective on upper limb dysfunction in patients undergoing TM by attenuating postoperative adhesion.

Acknowledgment

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