The effectiveness of botulinum toxin A for treatment of upper limb impairments and dysfunctions in breast cancer survivors: a randomized controlled trial

Botox for upper limb dysfunctions after breast cancer treatment.

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Conflict of interest

This study was funded by the MSD OncoAward. The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. We had no support from any organisation for the submitted work; no financial relationships with any organisation that might had an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. We had full control of all primary data and we agree to allow the journal to review the data if requested. The authors have no further conflicts of interest.

Abstract

Objective: To examine the effectiveness of a single Botulinum Toxin A (BTX-A) infiltration in the pectoralis major muscle, in addition to a standard physical therapy (PT) program on upper limb impairments and dysfunctions after breast cancer treatment.

Methods: Fifty breast cancer patients with persistent pain 3 months after finishing treatment participated in a double-blinded randomized controlled trial. The intervention group received a single BTX-A infiltration. The control group received a placebo (saline) infiltration. Within one week after the infiltration, all patients attended an individual PT program (12 sessions) during the first 3 months. Outcome parameters were active shoulder range of motion, upper limb strength, scapular statics and shoulder function. Measures were taken before the intervention, at 1, 3 (i.e. after the intervention) and 6 months follow-up.

Results: No differences between groups were found for all outcome parameters over the course of 6 months. However, overall beneficial effects of the PT for active forward flexion shoulder range of motion and shoulder function were found in both groups.

Conclusion: A single Botulinum Toxin A (BTX-A) infiltration in the pectoralis major muscle, in addition to a PT program cannot be recommended to treat upper limb impairments and dysfunctions after breast cancer treatment.

Keywords: breast neoplasms, Botulinum Toxins, pectoralis muscles, shoulder function, physical therapy modalities

Introduction

Of all cancers worldwide, breast cancer is the second most commonly diagnosed cancer.(Torre et al., 2015) Improvements in the multimodal treatment approach (e.g. surgery, radiotherapy, chemotherapy, hormone therapy) has led to increasing survival rates of breast cancer. However, many survivors suffer from a wide range of side effects after treatment, including upper limb impairments.(Hidding et al., 2014) Most frequent reported impairments include pain, decreased shoulder mobility, decreased upper limb strength and lymphedema. (Ebaugh et al., 2011, Hidding et al., 2014) Additionally, altered postures and upper limb kinematics have been considered relevant impairments after breast cancer treatment as well.(Shamley et al., 2012, Shamley et al., 2009, Shamley et al., 2007, Crosbie et al., 2010, Brookham et al., 2018) These impairments, may last for years after the treatment of breast cancer. (Stubblefield and Keole, 2014) Moreover, they may have a negative impact on overall functioning and quality of life.(Rietman et al., 2003, Rietman et al., 2006, Hidding et al., 2014, Nesvold et al., 2010)

For this reason, it is important to treat the underlying cause of these upper limb impairments and consequent dysfunctions in patients after breast cancer treatment. The onset of upper limb impairments can be explained by changes in the pectoral muscles after treatment for breast cancer, among others.(Stubblefield and Keole, 2013, Hidding et al., 2014, De Groef et al., 2015, Lee et al., 2016) Several studies describe an increased muscle tone and shortening of the pectoralis major muscle after breast cancer treatment. (Shamley et al., 2009) (Hage et al., 2014) Both tissue removal during surgery and post-radiotherapy fibrosis may enhance this. Additionally, patients have the tendency to adapt an altered kyphotic posture and shoulder protraction because of pain, fear of movement and/or protection of the surgical side.(Stubblefield and Keole, 2013, Crosbie et al., 2010, Shamley et al., 2009, Shamley et al., 2007, Glowacka et al., 2017) These hypertonic and shortened pectoral muscles may thus contribute to impairments such as pain, decreased mobility and strength at the upper limb region.(Stubblefield and Keole, 2013)

Currently, there is evidence for the combination of certain physical therapy modalities such as passive mobilizations, stretching, myofascial therapy and specific exercises for treatment of pain and impaired shoulder mobility after breast cancer.(De Groef et al., 2015, McNeely et al., 2010, De Groef et al., 2017d) Unfortunately, many patients still experience upper limb impairments. Therefore, additional treatment modalities are warranted.

Botulinum Toxin A (BTX-A) is a neurotoxin that blocks acetylcholine and thereby inhibits muscle spasms and the transmission of pain information to the central nervous system. (Hayes et al., 2012, Crosbie et al., 2010) BTX-A is a commonly used therapy in other populations than the breast cancer population for the treatment of hypertonic muscles and pain. In hemiplegic survivors of stroke, a positive effect was found on shoulder pain and spasticity after a BTX-A infiltration into the pectoralis major and

teres major muscle.(Marciniak et al., 2012) Other studies found beneficial effects on upper limb kinematics in children with hemiplegic Cerebral Palsy (Fitoussi et al., 2011) and with obstetrical brachial plexus palsy. (Arad et al., 2013)

In the breast cancer population, BTX-A is used for other indications than upper limb impairments. First of all, a number of studies have investigated the effect of BTX-A on postsurgical pain and reduced shoulder mobility caused by subpectoral tissue expanders and breast implants. Beneficial effects of BTX-A compared to a placebo infiltration were found for postoperative pain, the use of narcotics and the volume of expansion per session. (Gabriel et al., 2015, Layeeque et al., 2004, Winocour et al., 2014, Figus et al., 2009) Second, our own research revealed that a single BTX-A infiltration in combination with an individual physical therapy program significantly decreased pain intensity at the upper limb in breast cancer survivors up to 6 months after the infiltration. However, the effect size was not clinically relevant.(De Groef et al., 2018)

To our knowledge, no studies have investigated the effect of BTX-A on upper limb impairments and dysfunctions in the overall breast cancer patients. Therefore, the aim of the present study is to investigate the added value of a single BTX-A infiltration in the major pectoralis muscle to the current evidence based physical therapy modalities for treatment of upper limb impairments after breast cancer treatment. These impairments include restricted shoulder mobility, decreased upper limb strength, altered posture and kinematics and upper limb dysfunctions itself.

Methods

This study was approved by the Ethical Committee of the University Hospitals Leuven (ref number: s57283). All participants gave written informed consent before data collection began. The trial has been registered at the Dutch Trial Registry (NTR4944). The current manuscript reports results on the secondary outcome measurements of this trial. Results on the primary outcome (i.e. upper limb pain) are reported elsewhere.(De Groef et al., 2018)

Participants

Patients were recruited at the Multidisciplinary Breast Centre and the Department of Physical Medicine and Rehabilitation of the University Hospitals in Leuven between February 2015 and July 2016. Inclusion criteria were (1) women treated for a primary breast cancer with sentinel lymph node biopsy or axillary clearance and/or mastectomy (with immediate reconstruction) or breast conserving surgery; (2) radiation therapy was terminated at least three months ago; (3) more than 3 months of pain at the pectoral region (i.e. minimum pain intensity during the past week during activities > 0/100 on the Visual Analogue Scale). Patients were excluded if (1) they were not able to visit the hospital for the therapeutic sessions and assessments the entire duration of the study; (2) presence of current episodes of cancer or metastasis and (3) patients with breast reconstruction with a tissue expander.

Procedure

The study is a double-blinded (patients and assessors) randomized controlled trial. At the start of the study, patients were randomized into the intervention group (receiving a BTX-A injection in the pectoralis major muscle) and the control group (receiving a saline solution infiltration in the pectoralis major muscle). A 4-size permuted block randomization was used. The allocation to the groups was concealed to the physical therapists, patients and assessors. The random allocation sequence was computer-generated and with a 1:1 ratio. An independent person, not involved in recruitment or treatments carried out the randomization. The sequence of randomization was determined by the patient's identification number, which she received after inclusion in the study.

Interventions

Patients in the intervention group received an intramuscular BTX-A (100 units, Allergan Botox) infiltration in the pectoralis major muscle at the operated side. Patients in the control group received an intramuscular infiltration of 50 ml saline (Mini-Plasco 20 ml B. Braun NaCl 0.9%). Injections were evenly spread over the muscle belly, including the clavicular and sternal part. Injections were given after baseline assessment and before the first physical therapy session by one orthopedic surgeon (PD)

Within one week after the infiltration, both groups started with a standard physical therapy program that lasted 3 months. The sessions were individual, lasted 30 minutes and consisted of different physical therapy modalities including: (1) passive mobilizations of the shoulder to improve passive and active

shoulder ROM; (2) stretching of pectoral muscles to improve muscle flexibility and passive and active shoulder ROM; (3) scar tissue massage to improve flexibility of the scar(s) and (4) exercise schemes to improve muscle flexibility, endurance and strength, scapula-thoracic control and active shoulder ROM. This individual physical therapy program was followed by a 3 months' home program. The home program consisted of mobilizing and stretching exercises, performed twice a day at home to maintain flexibility of the pectoral muscles. Also, postural and stabilizing exercises were given to obtain an adequate posture and prevent protraction of the shoulder.

The physical therapy sessions were performed by three manual therapists (ADG, NV, SDG). All therapists were Masters in Rehabilitation Sciences, two with 6 years and one with 2 years of clinical experience. At several times during the study, training sessions were organized for all therapists to ensure standardization and similarity of the treatment sessions.

Outcomes

All patients were evaluated before the infiltration (= baseline assessment), 1 month after baseline, at the end of the intervention (after 3 months) and at 6 months follow-up at the Department of Physical Medicine and Rehabilitation of the University Hospitals in Leuven. Two blinded assessors (ADG, RVH) performed the measurements. Both assessors were experienced in performing the assessment from a previous clinical trial in the same setting.(De Groef et al., 2017a, De Groef et al., 2017c, De Groef et al., 2017d) The outcomes of interest were shoulder mobility, upper limb strength, scapular statics and kinematics and shoulder function. Details on the outcome parameters and the measurement methods are given in Table 1.

Sample size calculation

Sample size calculation was performed for the primary outcome 'pain intensity at the upper limb region' of which results are published elsewhere.(De Groef et al., 2018) The current study analyzed secondary outcome parameters of this larger randomized trial.

Statistical analyses

Data were analyzed according to the intention to treat principle. First, overall treatment effects (i.e. change over time) were analyzed by a multivariate linear model for repeated (longitudinal) measurements, using an unstructured covariance matrix. The primary endpoint of the trial was change in upper limb function 3 months after baseline. Additionally, short term (1 month) and long term (6 months) effects were analyzed. The effect size for continuous outcomes is given by the difference in mean change and its 95% Confidence Interval (CI). Second, the fisher exact test was used to compare point prevalence rates at different points in time. For binary outcomes, relative risk reduction (%) and

its 95% CI is given as measures of effect size. Statistical significance was taken as $p < 0.05$. All data were analyzed with SPSS 25.0 (IBM Corp. Released 2018. Armonk, NY: IBM Corp).

Results

A total of fifty patients were included in the current study (see Figure 1). Twenty-five patients were randomized into the intervention group (receiving a BTX-A infiltration), twenty-five patients were subjected to the control group (receiving a placebo infiltration). The patient characteristics are shown in Table 2.

The results for the different outcome parameters are given in Table 3. The first outcome parameter of interest was **shoulder mobility**. For both active forward and abduction range of motion (ROM), no significant difference between groups in change over time were found. However, as illustrated by the decrease in the point prevalence rates of impaired shoulder mobility, an improvement in shoulder mobility was found in both groups. In particular for forward flexion, a decrease in the prevalence rate of impairments of 40% to 20% and 56% to 36% in the intervention and control group, respectively, was found.

The second outcome parameter of interest was **upper limb strength**. Both change in handgrip strength itself and prevalence rates of impaired handgrip strength at different points in time did not significantly differ between groups. Remarkably, only few patients had an actual impaired handgrip strength according to the definition of Kim et al (Table 1).(Kim et al., 2014)

For **shoulder statics and kinematics**, the acromion-table index, pectoralis minor index and scapular upward rotation were considered. Overall, no significant differences in changes over time were found for any outcome parameter. Only for scapular upward rotation at maximal scaption range motion (> 135°) of the upper limb a significant difference in change between groups from baseline to 3 months has been found (mean difference in change of 9 degrees with 95% CI (0 to 9)). However, the clinical relevance of this result is questionable.

At last, self-reported **shoulder function** was considered. No significant differences in changes were found from baseline up to 6 months between groups. However, a slight decrease in both groups was noted for self-reported shoulder function. For the prevalence rate of impaired shoulder function at 1 month, a trend to a significant difference between both groups was found in favor of the intervention group (74% versus 96%, p=0.096).

Discussion

The present study investigated the effectiveness of a single BTX-A infiltration in the pectoralis major muscle, in addition to a standard physical therapy program, on shoulder mobility, upper limb strength, shoulder posture and kinematics and shoulder function in women after breast cancer treatment. No significant differences were found between groups in change of the outcome parameters over time. However, improvements of shoulder mobility and shoulder function were found in both groups indicating the possible beneficial effects of the standard physical therapy program itself.

This is the first randomized controlled trial investigating the effectiveness of BTX-A on upper limb impairments and dysfunctions after breast cancer. Despite the beneficial effects on pain intensity reported in a previous study (De Groef et al., 2018), no significant nor clinically relevant differences were found between groups. For the first outcome parameter '**shoulder mobility'** improvements in both groups were found, in particular for forward flexion ROM. This result may indicate the beneficial effects of the standard physical therapy program itself. However, changes are not clinically relevant (i.e. improvement of more than 15 degrees) and smaller than in other studies with a similar physical therapy program.(De Groef et al., 2017a) Despite the long time after surgery (i.e. 1.8 and 2.2 years post-surgery in the intervention and control group, respectively), it cannot be ruled out that these improvements are attributed to natural recovery of upper limb function after breast cancer.

The second outcome parameter of interest was **upper limb strength**, measured by handgrip strength. Remarkably, according to the definition of an interlimb difference of 6.5 kg, only few patients had an impairment in upper limb strength.(Kim et al., 2014) Cautions is warranted for the interpretation of the results since hand dominance and preoperative handgrip strength were not taking into account. Handgrip strength has been proposed as a measure of function in breast cancer survivors because of the good relationship with shoulder pain and passive shoulder flexion.(Cantarero-Villanueva et al., 2012) However, this could not be confirmed in the present study since all patients had pain (i.e. inclusion criteria) and up to 100% reported upper limb dysfunctions. Moreover, the mean value for handgrip strength of the present study population was comparable with the 25th percentile of healthy aged-matched women.(Dodds et al., 2014) This indicates that there indeed may not have been a large impairment at baseline and no window of opportunity for improvement for upper limb strength.

Third, **shoulder posture and kinematics** were measured by three variables. Only one significant result was found for scapular upward rotation at maximal scaption of the upper limb. The clinical relevance of this result is however questionable. First, only a small number of participants reached a scaption ROM more than 135 degrees resulting in a small group for the analyses (Table 3). Second, measurement of scapular upward rotation with two inclinometers as performed in the present study only showed acceptable inter-rater reliability in the resting position.(De Groef et al., 2017b) Third, scapular

movements are inherently variable and no clear relationship between scapular statics and dynamics on the one hand and pain and upper limb dysfunctions on the other hand has been found yet.(Ratcliffe et al., 2014)

At last **shoulder function** was evaluated by a self-reported measure, namely the DASH questionnaire. The results showed no significant differences between groups and improvements in the DASH score are rather small, not reaching the minimal clinically important difference of the DASH questionnaire. On the contrary, a borderline significant difference between groups was found for the prevalence rate of patients with upper limb dysfunctions after 1 month. Possibly, BTX-A may have caused reduced muscle tone of the pectoral muscle so that patients in the intervention group had an improvement in e.g. shoulder mobility and consequent gain in shoulder function.

It could be argued that the BTX-A infiltration has a negative effect on upper limb biomechanics since a paralysis of the major pectoral muscle is induced. However, it is reassuring that this cannot be confirmed in the present study. Despite no significant difference between groups for any outcome, both groups improved with even slightly larger improvements in the intervention group indicating no harmful effects of BTX-A. However, the main function of the pectoralis major muscle, i.e. adduction of the upper limb, was not assessed.

The present study reports secondary outcome parameters of a larger clinical trial. The primary outcome parameter was pain in the breast region measured with the VAS. No difference was found in changes of pain intensity at the primary endpoint (i.e. after 3 months) (mean difference of 3/100; 95% CI 13 to 19). However, from baseline up to 6 months, a significant difference in upper limb pain was seen between groups in favor of the intervention group (mean difference of 16/100; 95% CI 1 to 31). More details of this primary outcome and other pain-related secondary outcome parameters are mentioned elsewhere. (De Groef et al., 2018) The present study indicates that the beneficial effects on pain are not translated into improvements of upper limb impairments and function. Given the complex nature of upper limb problems after breast cancer, other mechanisms can contribute to the upper limb impairments such as myofascial dysfunctions, Axillary Web Syndrome, scar tissue, nerve damage and lymphedema.(Stubblefield and Keole, 2013, De Groef et al., 2015) The fact that these other causes were not taken into account could explain the limited results of the present study. Moreover, the present study was designed and powered to detect beneficial effects of BTX-A on pain. Given the working mechanism of BTX-A this made most sense. BTX-A is a neurotoxin that blocks acetylcholine and thereby inhibits muscle spasms and the transmission of pain information to the central nervous system.(Dutta et al., 2016, Nigam and Nigam, 2010) However, it may be interesting to investigate whether pain reduction acts as a moderating factor for the treatment effect of BTX-A on upper limb impairments and function. Possibly, BTX-A has no direct effect on upper limb function but through a reduction in pain, maladaptive postures and movement patterns may improve resulting in better shoulder ROM, alignment,

kinematics and general shoulder function. On the other hand, a reduction in pain may not guarantee an improvement in upper limb function. As described above, both pain and upper limb impairments are complex phenomenon that may interact with each other and many other (biopsychosocial) factors.

Strength and limitations

The study has several **strengths**. First, a sample size calculation was performed before the start of the study, giving it more power. However, this was only done for the primary outcome parameter (pain intensity). Second, the randomization was concealed and both assessors and patients were blinded. Furthermore, despite of the missing data of two participants at one assessment point, there were no drop-outs. Fourth, both patients in the control group and the intervention group were treated by the same therapists, which ensured that their treatment programme was very similar.

Some study **limitations** should be addressed as well**.** First, because multiple testing was carried out, the risk of false positive findings is high. Second, we have to mention the lack of follow-up during the home exercise programme. Consequently, this means that the adherence of the patients to the home exercise programme is not known. This could bias the outcomes at 6 months follow-up. Third, the aim of the present study was to investigate effects of BTX-A on upper limb impairements. However, no inclusion criteria for this purpose and no direct measure of major pectoral muscle function was used since it was only a secondary aim of the full research project. Consequently, side effects of the paralysis of the pectoral muscles could not be investigated in detail.

Clinical implications

As described above, no clinically relevant results were found. The only meaningful results are decrease in the prevalence rate of impaired forward flexion mobility with 20% in both groups and prevalence rate of upper limb dysfunctions with 16% in the intervention group only after 6 months. As indicated in previous studies, pain and upper limb impairments are complex and difficult to treat.(De Groef et al., 2018, De Groef et al., 2015, De Groef et al., 2017a, De Groef et al., 2017c, De Groef et al., 2017d) Similar as in these previous studies it appears that a certain subgroup of patients responds well to the intervention while others do only partly or not at all. An individually tailored approach is needed to increase effectiveness of the applied physical therapy modalities and other interventions such as BTX-A. In light of the present study, it is crucial to identify hypertonia and/or shortening of the major pectoral muscle as the primary cause of the upper limb impairments in each specific patient. Furthermore, the required dose of BTX-A to ensure a treatment effect should be investigated further and tailored to the specific needs of the patient. This individually tailored approach should be investigated in well-powered randomized controlled trials. Such studies are necessary to further unravel the mechanisms of (persistent) pain and upper limb impairments after breast cancer treatment. Additionally, besides clinical outcome measures, it is recommended to evaluate patient reported outcome parameters such as self-

perceived improvement.

Conclusions

A single BTX-A infiltration in the pectoralis major muscle in addition to a standard physical therapy program cannot be recommended at this stage to improve upper limb impairments and dysfunctions after breast cancer treatment.

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Table 1: Overview of the outcome parameters and measurement method

Outcome parameter	Measurement methods
Shoulder range of motion	
Active forward flexion and abduction ROM (°)	ROM (°) measured with an inclinometer in sitting position (Valentine and Lewis, 2006)
Point prevalence of impaired shoulder ROM (%)	Interlimb difference of $\geq$ 15° measured with inclinometer in the sitting position (Tengrup et al., 2000)
Upper limb strength	
Upper limb strength (kg)	Handgrip strength (kg) measured with the Jamar Handheld dynamometer (Kim et al., 2014)
Point prevalence of impaired upper limb strength (%)	Difference of $\geq$ 6.5 kg between sides, measured with the Jamar Handheld dynamometer (Kim et al., 2014)
Scapular statics and kinematics	
Forward shoulder position (% of body length)	1) **Acromion-Table Index (ATI):** the subject was in a supine position and was asked to adopt a natural relaxed position. The distance between the most posterior border of the acromion and the table was measured and 2) **Pectoralis Minor Index (PMI**): The resting muscle length of the pectoralis minor was measured between the caudal edge of the 4th rib and the inferomedial aspect of the coracoid process with a sliding caliper. Both measurements were performed with a sliding caliper (Hogetex, 0 to 300 mm) and normalized to body length (De Groef et al., 2017b)
Scapular upward rotation (°)	One gravity inclinometer was velcro taped perpendicular to the humeral shaft, just below the deltoid tuberosity. The second inclinometer was

	aligned manually along the scapular spine. The subject was asked to perform one arm abduction movement in the scapular plane, i.e. scaption (30° anterior to the coronal plane) with full elbow extension, neutral wrist flexion/extension and with the thumb leading. The movement was guided by the raters' instructions. The subject was asked to stop at 45°, 90°, 135° and at their maximum achievable arm movement. The degree of scapular upward rotation was noted at each available scaption position.(De Groef et al., 2017b)
Shoulder function	
Shoulder function (%) Point prevalence of impaired shoulder function (%)	DASH questionnaire (Angst et al., 2011) DASH score of > 15%(Angst et al., 2011)

ROM =range of motion; ATI=Acromion-Table Index; PMI=Pectoralis Minor Index; DASH=Disability of arm, shoulder and hand questionnaire

Table 2: Characteristics of patients according to treatment allocation. Figures are numbers (percentage) of patients unless specified otherwise.

	Intervention group (N=25)	Control group (N=25)
Mean (SD) age (years)	53.4 (10.0)	56.6 (10.0)
Mean (SD) BMI	24.8 (3.6)	28.1 (5.0)
Mean (SD) time since surgery (years)	1.8 (1.6)	2.2 (2.3)
Mean (SD) number of standard physical therapy sessions	13 (1)	12 (1)
Type of breast surgery		
Mastectomy	12 (48%)	17 (68%)
Breast conserving	10 (40%)	6 (24%)
Mastectomy with immediate reconstruction	3 (12%)	2 (8%)
Level of axillary surgery		
Sentinel Lymph Node biopsy	8 (32%)	6 (24%)
I-II	10 (40%)	10 (40%)
I-III	7 (28%)	9 (36%)
Tumor Size		
pT0	0 (0%)	1 (4%)
pT1	9 (36%)	8 (32%)
pT2	12 (48%)	10 (40%)
pT3	4 (16%)	6 (24%)
Lymph node stage		
pN0	9 (36%)	9 (36%)
pN1	12 (48%)	9 (36%)

pN2	2 (8%)	5 (20%)
pN3	2 (8%)	2 (8%)
Radiotherapy, IMC and medial supraclavicular	25 (100%)	24 (96%)
Radiotherapy, axilla	2 (8%)	2 (8%)
Chemotherapy	16 (64%)	17 (71%)
Neo-adjuvant chemotherapy	4 (16%)	6 (24%)
Immunotherapy	1 (49%)	3 (12%)
Endocrine treatment		
Tamoxifen	12 (48%)	8 (32%)
Aromatase Inhibitors	10 (40%)	15 (60%)

BMI=Body Mass Index

Table 3: Outcome parameters according to treatment allocation. Numbers (%) or mean (Standard Deviation) are given.

	Intervention group		Control group		P value	Effect size[1] 95% CI
Active forward flexion ROM (°)		n		n		
Baseline	141 (21)	25	136 (20)	25	0.375	
At 1 months	145 (20)	24	144 (21)	24	0.367	3 (-4 to 11)
At 3 months	153 (17)	25	142 (22)	25	0.197	-5 (-14 to 3)
At 6 months	152 (18)	25	142 (25)	25	0.312	-5 (-16 to 5)
Active abduction ROM (°)						
Baseline	124 (30)	25	119 (33)	25	0.538	
At 1 months	131 (30)	24	125 (35)	24	0.984	0 (-8 to 7)
At 3 months	141 (23)	25	129 (30)	25	0.219	-7 (-18 to 4)
At 6 months	138 (29)	25	131 (30)	25	0.897	-1 (-16 to 14)
Prevalence of impaired forward flexion ROM (%)						
Baseline	10 (40%)	25	14 (56%)	25	0.396	
At 1 months	7 (28%)	24	6 (24%)	24	0.949	-16% (-196 to 54)
At 3 months	5 (20%)	25	9 (36%)	25	0.345	44% (-43 to 78)
At 6 months	5 (20%)	25	9 (36%)	25	0.345	44% (-43 to 78)
Prevalence of impaired abduction ROM (%)						
Baseline	14 (48%)	25	15 (52%)	25	0.774	
At 1 months	13 (52%)	24	11 (44%)	24	0.846	-18% (-109 to 33)
At 3 months	8 (32%)	25	8 (32%)	25	1.000	0% (-124 to 55)
At 6 months	10 (40%)	25	10 (40%)	25	1.000	0% (-97 to 49)
Handgrip strength (kg)						
Baseline	22.6 (6.5)	25	19.1 (6.1)	24	0.058	
At 1 months	23.9 (5.5)	23	20.5 (5.3)	22	0.849	0.2 (-1.8 to 2.1)
At 3 months	23.7 (5.2)	25	19.9 (7.1)	25	0.880	-0.1 (-2.1 to 1.8)

At 6 months	23.2 (6.1)	24	21.2 (7.3)	23	0.246	1.3 (-0.9 to 3.4)
Prevalence of impaired handgrip strength (%)						
Baseline	3 (12%)	25	3 (13%)	24	1.000	
At 1 months	0 (0%)	23	1 (5%)	22	0.489	1% (NaN to 1)
At 3 months	0 (0%)	25	2 (8%)	25	0.490	1% (NaN to 1)
At 6 months	2 (8%)	24	3 (13%)	23	0.666	36% (-248 to 88)
Acromion-Table Index (% of body length)						
Baseline	3.9 (0.8)	25	4.3 (1.1)	25	0.171	
At 1 months	3.5 (0.9)	24	4.0 (0.9)	24	0.746	0.1 (-0.4 to 0.7)
At 3 months	3.8 (0.6)	25	4.2 (0.7)	25	0.786	0.0 (-0.3 to 0.4)
At 6 months	4.1 (1.1)	24	4.3 (0.6)	25	0.536	-0.1 (-0.5 to 0.3)
Pectoralis Minor Index (% of body length)						
Baseline	8.8 (1.1)	25	8.9 (1.1)	25	0.569	
At 1 months	8.6 (1.6)	24	8.6 (0.9)	24	0.595	-0.1 (-1.0 to 0.8)
At 3 months	8.9 (0.8)	25	8.8 (0.9)	25	0.644	-0.2 (-0.8 to 0.4)
At 6 months	8.4 (0.8)	24	8.4 (0.8)	25	0.551	-0.1 (-0.8 to 0.5)
Scapular upward rotation in rest (°)						
Baseline	-1 (5)	23	-1 (4)	23	0.654	
At 1 months	-1 (5)	22	0 (5)	19	0.518	1 (-2 to 5)
At 3 months	0 (3)	25	0 (4)	25	0.388	-1.1 (-4 to 1)
At 6 months	-1 (5)	22	-1 (4)	25	0.889	0 (-3 to 3)
Scapular upward rotation at 45° scaption (°)						
Baseline	4 (4)	23	4 (5)	23	0.972	
At 1 months	4 (7)	22	5 (7)	19	0.486	1 (-2 to 5)
At 3 months	4 (5)	25	5 (5)	25	0.596	1 (-2 to 4)
At 6 months	4 (5)	22	5 (4)	25	0.689	1 (-3 to 5)

Scapular upward rotation at 90° (°)						
Baseline	18 (7)	23	19 (9)	23	0.410	
At 1 months	19 (7)	22	21 (10)	19	0.322	2 (-2 to 5)
At 3 months	20 (10)	25	20 (7)	25	0.993	0 (-5 to 5)
At 6 months	21 (8)	22	21 (7)	25	0.673	-1 (-6 to 4)
Scapular upward rotation at 135° (°)						
Baseline	36 (11)	19	39 (10)	19	0.329	
At 1 months	38 (10)	20	40 (13)	16	0.933	0 (-8 to 7)
At 3 months	41 (10)	23	42 (10)	22	0.437	-3 (-9 to 4)
At 6 months	42 (10)	21	44 (10)	22	0.919	0 (-8 to 7)
Scapular upward rotation at maximal scaption (°)						
Baseline	49 (8)	7	44 (8)	5	0.361	
At 1 months	45 (10)	5	44 (5)	4	0.397	6 (-8 to 19)
At 3 months	47 (12)	8	49 (5)	5	**0.042**	9 (0 to 19)
At 6 months	48 (8)	7	48 (5)	6	0.434	6 (-9 to 21)
Shoulder function (DASH 0-100)						
Baseline	33 (15)	25	40 (17)	25	0.115	
At 1 months	28 (15)	23	33 (12)	23	0.667	-3 (-14 to 9)
At 3 months	25 (14)	24	31 (15)	25	0.838	1 (-9 to 11)
At 6 months	25 (15)	25	34 (17)	25	0.714	2 (-7 to 10)
Impaired shoulder function (%)						
Baseline	24 (96%)	25	23 (92%)	25	1.000	
At 1 months	17 (74%)	23	22 (96%)	23	**0.096**	23% (0 to 40)
At 3 months	18 (75%)	24	21 (84%)	25	0.496	11% (-19 to 33)
At 6 months	20 (80%)	25	22 (88%)	25	0.702	9% (-16 to 29)

Figure 1: Flow chart