The effectiveness of botulinum toxin A for persistent upper limb pain after breast cancer treatment: a double-blinded randomized controlled trial

Botox for pain after breast cancer treatment.

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Acknowledgements

We thank Roxane Van Hemelrijck for measuring the patients and Nele Vervloesem and Sophie De Geyter for treating the patients. We thank Kristel Van de Loock for assisting with the infiltrations. We are grateful to the nurses of the department of surgical oncology and medical staff of the multidisciplinary breast clinic to motivate the patients to participate in our study. Finally, we thank all patients who took part in this study.

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. No support from any organisation for the submitted work; no financial relationships with any organisations that might have 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 have 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.

Trial Registration: Nederlands Trial Register NTR4944

Ethical Committee of the University Hospital Leuven: s57283

49 Funding: MSD OncoAward 2014, Grant from BVOT (Belgische Vereniging voor Orthopedie

50 en Traumatologie)

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Abstract

Objective: To investigate the effect of a single Botulinum Toxin A infiltration in the pectoralis major muscle in addition to a standard physical therapy program for treatment of persistent upper limb pain in breast cancer survivors.

Design: Double-blinded (patient and assessor) randomized controlled trial

Setting: University Hospital Leuven, Belgium

Participants: Fifty breast cancer patients with pain.

Intervention: The intervention group received a single Botulinum Toxin A (BTX-A) infiltration. The control group received a placebo (saline) infiltration. Within one week after the infiltration, all patients attended an individual physical therapy program (12 sessions) during the first 3 months and a home exercise program up to 6 months after infiltration.

Main outcome Measures: The primary outcome was change in pain intensity at the upper limb (Visual Analogue Scale (VAS) (0-100)) after 3 months. Secondary outcomes were prevalence rate of pain, pressure hypersensitivity, pain quality, shoulder function and quality of life. Measures were taken before the intervention and at 1, 3 and 6 months follow-up.

Results: No significant difference in change in pain intensity after 3 months was found (mean difference in change of 3/100; 95% CI -13 to 19). From baseline up to 6 months, a significantly different change in upper limb pain intensity was found between groups in favor of the intervention group (mean difference in change of 16/100; 95% CI 1 to 31).

Conclusion: A single Botulinum Toxin A infiltration in combination with an individual physical therapy program has been found to significantly decrease pain intensity at the upper limb in breast cancer survivors up to 6 months. However, the effect size was not clinically relevant and no other beneficial effects were found.

78 **Keywords:** breast neoplasms, pain, botulinum toxin, physical therapy modalities, shoulder
79 function
80

Introduction

Upper limb pain after breast cancer treatment is a common and difficult to treat problem. Prevalence rates range between 12-82% up to one year after surgery and between 9-72% later on.[1-4] In the domain of physical therapy, several modalities have been proven to be effective for treatment of persistent pain after breast cancer. These modalities include specific exercises, myofascial therapy and the combination of mobilizations and stretching.[5, 6] However, up to 50% of patients still experience upper limb pain both at short and long term.[1, 4, 7] Therefore, additional treatment modalities are warranted.

Several studies have indicated the possible contribution of the pectoral muscles to pain and upper limb dysfunctions after breast cancer treatment. [3, 8-10] In the acute treatment phase of the cancer, breast and axillary surgery and radiotherapy cause scar tissue formation, wound healing, fibrosis and shortening of soft tissues, such as the pectoral muscles.[3, 8-10] Initially, this may lead to an increase in muscle tone of the pectoral muscles and local postoperative or post-radiotherapy pain.[3, 10] In a further postoperative stage, forward shoulder position, induced by the shortened, hypertonic pectoral muscles and narrowing of the subacromial space may lead to rotator cuff pathologies, which can be painful and contribute to upper limb dysfunctions as well.[3, 8, 11] A causal treatment for the shortened, hypertonic pectoral muscles may break the vicious circle of further increasing muscle tone and pain after breast cancer treatment.

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. [2, 12, 13] BTX-A is a commonly used therapy in other populations than the breast cancer population for the treatment of hypertonic muscles and pain. In children with cerebral palsy, the use of BTX-A is a well-established and evidence based intervention to improve pain and function associated with muscle spasticity.[14-17] In patients with hemiplegic shoulder pain after stroke, a single BTX-

A infiltration in the pectoralis major muscle [18] or in selected muscles of the shoulder girdle [19] was found to be beneficial for pain relief. For myofascial pain, several reviews of randomized controlled trials show promising but mixed results for the effectiveness of BTX-A for treatment of pain at several body regions.[20-23]

In breast cancer patients, a recent review showed good results for BTX-A in the pectoral muscle on postoperative pain associated with breast reconstruction with a tissue expander.[24] Only one well-designed randomized controlled trial confirmed these beneficial effects of a BTX-A injection in the pectoral muscles on postoperative pain associated with tissue expander reconstruction.[25] Another trial comparing BTX-A injection on one side and saline injection on the other side in bilateral procedures could not find beneficial effects.[26]

To our knowledge, no studies investigated the effect of BTX-A for treatment of pain at the pectoral region in breast cancer survivors. Therefore, the aim of the present study was to investigate the effectiveness of a single BTX-A injection in the pectoralis major muscle, followed by a standard physical therapy program and home exercise program for treatment of persistent pain at the upper limb region in breast cancer survivors.

Patients and 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 Netherlands Trial Registry (NTR4944).

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. maximum 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

Patients were randomized into an intervention group (receiving a standard physical therapy program and one BTX-A infiltration) or a control group (receiving a standard physical therapy program and one saline infiltration). The random allocation sequence was computer-generated and with a 1:1 ratio. Randomization was performed by using permuted blocks (size=4). The allocation to the groups was concealed to the physical therapists, patients and assessors. A different person from the one doing the recruitment and physical therapy treatments carried out

148 the randomization. The sequence of randomization was determined by the patient's
149 identification number, which she received after inclusion in the study.
150
151 *Interventions*
152 Patients in the intervention group received an intramuscular injection of BTX-A (100 units,
153 Allergan Botox) in the pectoralis major muscle. Patients in the control group received a placebo
154 infiltration consisting of 50 ml saline (Mini-Plasco 20 ml B. Braun NaCl 0.9%). Injections were
155 evenly spread over the muscle belly, including the clavicular and sternal part. Injections were
156 given after baseline assessment and before the first physical therapy session by one orthopedic
157 surgeon (PD).
158
159 Within the first week after the BTX-A or saline infiltration, all participants started an individual
160 standard physical therapy program of 12 weeks (one session per week) at the University
161 Hospital Leuven. The sessions were individual and lasted 30 minutes. An overview of the
162 different physical therapy modalities, their purpose and method is given in Table 1.[5, 6]
163
164 Three manual therapists (ADG, NV, SDG) performed the standard physical therapy sessions of
165 the patients of both groups. All therapists were Masters in Rehabilitation Sciences, two with 6
166 years and one with 2 years of clinical experience. At several times during the study, training
167 sessions were organized for all therapists to ensure standardization and similarity of the
168 treatment sessions.
169
170 *Outcomes*
171 All patients were evaluated before the infiltration and start of the treatment program (= baseline
172 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.[6, 27, 28] The outcome of interest was pain. Four dimensions were evaluated: pain intensity (primary outcome parameter), pain prevalence rate, local pressure hypersensitivity and pain quality. Additionally, shoulder function (DASH score) and quality of life (SF-36) were assessed. An overview of the measurement method and references to their psychometrics is given in Table 2.

Sample size and statistical analyses

Calculation of the sample size was based on a previous project on the effectiveness of physical therapy for treatment of upper limb pain in breast cancer patients.[6] A difference in means of 20 points on the Visual Analogue Scale (VAS) score between the intervention and control group is considered as clinically relevant, and a SD of 25 is assumed for all groups. If we apply a power of 80%, an alpha level of 5%, and take into account the dropouts (10%), we have to include 50 patients.

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 analysis was change in pain intensity at the upper limb region 3 months after baseline. As secondary analysis, 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

198 effect size. Statistical significance was taken as $p < 0.05$. All data were analyzed with SPSS
199 22.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Mac, Version 24.0. Armonk, NY:
200 IBM Corp).

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Results

Figure 1 shows the flow of patients. All referred patients (n=103) were screened and 50 (47%) agreed to participate. The 53 non-participants had more pN1 and less pN2-3 tumors (p=0.028) and had less radiotherapy (p=0.016) compared to participants. Fifty patients were included in the study and were randomized in an intervention group (n=25) and a control group (n=25). Baseline characteristics of the two groups are given in Table 3.

For **pain intensity** (Table 4, Figure 2) at the entire upper limb region, no differences in change from baseline up to 1 month and 3 months were found between groups (primary analysis). From baseline up to 6 months, a significantly different change in pain intensity at the upper limb was found between groups in favor of the intervention group (p=0.040) (Table 4 and Figure 2). The mean difference in change was 16 points on the VAS (0-100) (95% CI: 1 to 31). For pain intensity at the pectoral region, a larger decrease in the intervention group up to 6 months after baseline was found as well. However, this difference was not statistically significant compared to the control (mean difference in change 13/100; 95% CI: -4 to 31). Moreover, both significant results are not clinically relevant, i.e. a decrease of at least 20/100 on the VAS.

Pain prevalence rates at the entire upper limb were comparable between both groups. After the intervention (i.e. 3 months), 68% of patients in the intervention group and 76% in the control group still had pain (p=0.754). Six months after baseline, prevalence rates increased again up to 84% and 88% in the intervention and control group, respectively. Results for the pectoral region itself are remarkably better. After the intervention, 40% in the intervention group and 52% in the control group still had pain. Six months after baseline, 40% of patients in the intervention group still got pain. In the control group, this number increased again up to 60%.

Despite this clinically relevant difference of 20% between groups at 6 months, this difference was not significant (p=0.258). (Table 4)

For **pressure hypersensitivity** at the upper limb region, no differences in change over time were found between groups in general. Only for the serratus anterior muscle a significantly different change was found (0.61 kg/cm^2; 95% CI: 0.07 to 1.15) after 1 month, meaning that the control group had a larger improvement compared to the intervention group (Table 4). However, pressure pain thresholds were already higher at baseline in the intervention group (3.09 versus 2.44 kg/cm^2). For **pain quality**, no differences between groups were found at any point in time (Table 4).

For **upper limb function**, no differences were found between groups either. Only 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). For **quality of life**, a borderline significant result for mental functioning was found in favor of the control group. Additionally, the remark should be made that at baseline the intervention group had higher scores (Table 5).

No adverse events after the infiltrations occurred.

Discussion

A single Botulinum Toxin A infiltration in combination with an individual physical therapy program and home exercise program has been found to significantly decrease pain intensity at the upper limb region in breast cancer survivors up to 6 months after the infiltration compared to physical therapy alone. However, the effect size was not clinically relevant. Moreover, at short term and for the other outcomes no added value of the BTX-A infiltration was found.

This is the first study that investigated the effectiveness of a single BTX-A infiltration for treatment of pain at the upper limb region in breast cancer survivors. Remarkably, only long term beneficial effects were found with a difference in change between groups in pain intensity at the overall upper limb region of 16/100 and at the pectoral region of 13/100 on the VAS. For the overall upper limb region, this result is statistically significant but not clinically relevant.[29]

BTX-A acts locally in the peripheral nervous system by blocking the release of Acetylcholine in the presynaptic neuromuscular junction with a peak working within 1-2 weeks.[30, 31] This action is irreversible but after 2-3 months, function can recover by formation of new synaptic contacts.[30, 31] Consequently, any additional beneficial effects would have been expected at short term (i.e. 1 and 3 months after baseline). Therefore, the beneficial results at 6 months in this trial are probably not due to the BTX-A that is still working but due to the late effects of the standard physical therapy program and the home exercises. The standard physical therapy program applied in the present study has already been proven to be beneficial for treatment of upper limb pain at short term.[6] A possible explanation may be that, due to the addition of BTX-A, the pectoral muscle was less hypertonic during the first 3 months of physical therapy, increasing the effectiveness of the physical therapy modalities and thus more profound, long lasting effects. Additionally, the home exercise program from 3 to 6 months may be more

effective when the pectoral muscles are less hypertonic as well. However, this hypothesis should be confirmed in a larger trial.

The hypothesis on the additional beneficial effects of BTX-A for the decrease in pain intensity is twofold. First, increased tone of the pectoral muscle has been postulated as underlying cause of altered postures and movement patterns after breast cancer treatment.[3, 5, 13, 32] By decreasing the tone of the pectoral muscle, these consequent problems causing upper limb pain may resolve. This is reflected in the present trial by the beneficial effects of BTX-A on pain intensity at the overall upper limb region. Second, BTX-A may also have a direct influence on nociceptive nerve terminals, possibly inhibiting local nociceptive pain at the pectoral region itself.[33, 34] This is reflected by a decrease in the prevalence rate of local pain at the pectoral region from 100% to only 40% in the intervention group, compared to a decrease to only 60% in the control group. Despite the clinical relevance of these findings, this was not statistically significant.

A borderline significant and clinical relevant difference between groups for the prevalence rate of patients with upper limb dysfunctions was found after 1 month. Possibly, BTX-A may have 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. However, previous studies have indicated that shoulder function in breast cancer survivors can be influenced by many factors so further research is necessary to explore the effectiveness of BTX-A on shoulder function.[35] Similar as for shoulder function, quality of life is a complex construct influenced by other factors such as e.g. general physical health and fatigue.[36] Given the generic content of the SF-36 it is possible that this questionnaire is not sensitive enough to detect a significantly different change when only pain intensity improved in the intervention group.[37]

Despite the promising results of this study, no strong recommendations for the combination of a single BTX-A infiltration and a standard physical therapy program can be made to decrease pain at the upper limb region after finishing breast cancer treatment. The significant beneficial effects are limited and of poor clinical relevance. A larger trial should confirm the results of the present study. For now, a physical therapy program consisting of passive mobilizations of the shoulder girdle, stretching and transverse strain of pectoral muscles, myofascial therapy consisting of manual myofascial release techniques on active myofascial trigger points at the upper limb region and on myofascial adhesions in the pectoral, axillary and cervical region and scars can be recommended. Exercises to stretch the pectoral muscles and mobilize and stabilize the shoulder girdle should be added.[5, 28, 38]

The present study has several **strengths**. First, a sample size calculation was performed before the start of the study, randomization was concealed and both, assessors and patients were blinded. Second, despite the missing data of 2 participants at one assessment point, there were no drop-outs.

Study limitations

Some **limitations** should be addressed as well. First, the primary endpoint of the study used for sample size calculation was pain intensity at 3 months after baseline. Consequently, the significant results at long term should be interpreted with caution. Second, due to the high number of questionnaires and burdening for the patient, the McGill Pain questionnaire was not administered at 1 month follow-up. Additionally, not all participants filled out the questionnaires completely to the extent that they could not be used for analysis. Third, patients were given the advice to practice twice a day at home. However, the extent to which each patient performed their exercises at home was not recorded. Fourth, despite the sample size calculation, the total number of participants is relatively small. Given this and the multiple testing, a high

risk of false positive findings has to be taken into account. Fifth, a third group receiving no physical therapy was available. Consequently, no conclusions on the effectiveness of BTX-A alone can be made. At last, no data on other pain interventions before entering the trial and during the trial was available.

Despite these beneficial effects of the physical therapy program and small added value of BTX-A, not all patients got pain free. This result illustrates the complex nature of cancer pain, its different treatment modalities and its different dimensions contributing to a patient's pain experience.[39, 40] Among other things, the simultaneous presence of other pain mechanisms such as local neuropathic pain at the upper limb region or more widespread pain in patients with dominant central sensitization mechanisms may interfere with the effectiveness of BTX-A.[39-41] As indicated in several other studies on the effectiveness of physical therapy interventions, identifying patients who would benefit the most of a certain intervention is highly important.[38, 42] The significant results found in the present study were only secondary analyses so further research and a larger clinical trial is needed to confirm any beneficial effects of BTX-A.

Conclusion

A single Botulinum Toxin A infiltration in combination with an individual physical therapy program has been found to significantly decrease pain intensity at the upper limb region in breast cancer survivors up to 6 months. However, the effect size was not clinically relevant and no other beneficial effects were found.

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Figure 1: Flow chart of the study

Figure 2: Pain Intensity at the overall upper limb (UL) region (2a) and the pectoral region (2b). Mean scores (95% Confidence Intervals) on the Visual Analogue Scale (VAS) are given (0-100). Intervention group = full line; Control group = dotted line; Mo=Month