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Botulinum toxin type A and myofascial pain syndrome: A retrospective study of 301 patients

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Abstract.
BACKGROUND: Botulinum toxin type A (BTX-A) intramuscular injections have been used for the treatment of myofascial pain syndrome (MPS), although its efficacy remains still unknown and its safety is controversial.
OBJECTIVE: To analyze the effectiveness and safety of the injection protocol for BTX-A in the shoulder-scapular and lumbar-pelvic girdles combined with physiotherapy in patients with primary and secondary MPS.
METHODS: Retrospective descriptive study including 301 medical files of patients with persistent MPS. Positive responses to treatment were considered to be a satisfactory level of effectiveness with 50% pain relief or a fully satisfactory level of effectiveness at 80%.
RESULTS: Overall, 58.1% of patients obtained a positive result at 6 months. Differences in effectiveness were found between primary MPS (82.9% of patients) and secondary MPS (54.9%; $p = 0.002$). In patients with secondary MPS, differences in effectiveness arose based on pathologies associated with MPS ($p = 0.03$). In 23.9% of cases, mild and temporary adverse effects were observed post-infiltration.
CONCLUSIONS: BTX-A injections and physiotherapy is an alternative to conventional treatment which should be considered when treating refractory MPS. Nonetheless, the differences in effectiveness based on diagnosis suggest the need to clarify the criteria used to select patients with MPS in future clinical trials and applications.

Keywords: Botulinum toxin type A, myofascial pain syndromes, adverse effects

1. Introduction

Myofascial pain syndrome (MPS) is a neuromuscular pathology characterized by the presence of myofascial trigger points [1]. The specific pathophysiology of myofascial trigger points is unknown; however, there are several lines of research that have evidenced changes in myofascial trigger points at different levels: biochemical changes include the presence of inflammatory mediators [2,3]; neurophysiological changes include disorders of neuromuscular transmission [4]; structural and vascular changes include an increase in stiffness and blood flow changes in myofascial trigger points [5,6]; and maladaptive neuroplastic changes include central sensitization [7]. MPS can be classified as a primary syndrome that is not related to other medical conditions, and a secondary syndrome that occurs in conjunction with other pain conditions including whiplash, radicular pain, osteoarthritis, fibromyalgia, fractures, and many others [6,8].

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Botulinum toxin type A (BTX-A) intramuscular injections have been used as a muscle relaxant as well as to provide pain relief. In most studies, BTX-A is infiltrated in MPS of the scapular girdle and cervical region (SGC) [9–15], which is related to myogenic headache [16,17] or MPS secondary to whiplash syndrome [18,19]. Fewer studies have addressed the effect of BTX-A paravertebral infiltration in MPS of low back pain [20–24], secondary MPS with fibromyalgia [25] and muscles in the pelvic girdle (PG) [26–29]. However, the efficacy of BTX-A still remains unknown due to the limited number of studies and sample size used and the variability of the doses per point employed [30].

Given the high prevalence of MPS in the chronic pain unit and the positive effects of BTX-A in certain studies, the University Hospital of Getafe Pain Unit established a BTX-A (Botox®) injection and a physiotherapy protocol for patients with MPS who satisfied the diagnostic criteria established by Simons et al. [31]. The main objective of this study was to analyze the effectiveness and safety of the BTX-A infiltration protocol to relieve pain at 6 months in patients with MPS at the University Hospital of Getafe Pain Unit.

2. Material and methods

A retrospective descriptive study was designed. Data were collected from the medical histories of patients between May and June 2008. The study's subjects were those patients with MPS for whom BTX-A was approved for palliative care in the treatment of MPS between 1 March 2004 and 19 May 2008 at the University Hospital of Getafe (Madrid). A list provided by the Hospital Pharmacy ($n = 453$) was used to determine treated patients. The inclusion criteria were availability of the medical history file in the Pain Unit; confirmation in the patient's medical history of the administration of BTX-A following Pharmacy approval; muscle infiltration within the previous 6 months; and finally, appropriate registration of the Visual Analogue Scale (VAS) scores of pain from the first medical visit. The following exclusion criteria were selected: no pain response recorded (or not correctly recorded), in accordance with the criteria for classifying the degree of effectiveness; coexistence of the pain response by the use of other invasive techniques related to the pathology within 6 months of receiving BTX-A infiltration; and coexistence of the pain response by surgical, traumatic or other pathological incidents within 6 months of infiltration and failure to assist follow-up appointments.

2.1. Data registration and outcomes

The following data were recorded for all subjects: Medical diagnosis, which differentiated secondary MPS from primary MPS if other concomitant pathology that could act as a perpetuating factor according to Gerwin et al. [8]; initial pain measured with VAS (0–10) and the Lattinen Index, which is a validated multidimensional scale to evaluate chronic pain; this scale rates several items such as intensity, frequency, impairment, analgesic consumption and sleeping quality from 0 to 4 [32,33]; and methodological variables associated with the injection procedure, such as location of the infiltration (SGC and/or PG), the number of points infiltrated in the SGC and the number of muscles infiltrated in the PG and re-infiltration in the same or a different location.

In order to evaluate the effectiveness of the treatment, 4 levels were established based on the percentage improvement in pain reported by the patient and explicitly expressed in the patient's medical history six months after infiltration: "*Worse*" indicated an increase in pain explicitly reported in the medical history; *"Unsatisfactory"* denoted no change in pain or improvement of less than 50%; *"Satisfactory"* showed improvement in pain between 50% and 80%; and *"Fully satisfactory"* stated improvement in pain between 80% and 100%. The adjuvant pharmacological treatment used after injection according to the World Health Organization (WHO) Pain Ladder [34] (NSAIDs, opioids, muscle relaxants, anti-epileptic drugs and/or antidepressants) was evaluated to determine whether it had to be increased, maintained, reduced or even totally withdrawn after the BTX-A injection. Data regarding adverse effects associated with the injection procedure were obtained from the clinical history file.

2.2. BTX-A infiltration protocol

The BTX-A injection methodology followed a standardized protocol proposed by De Andrés et al. [33]. SGC trigger points were located by physical examination according to the following criteria: (1) pain related to the use of one specific muscle; (2) a trigger point that becomes painful and tender after pressure; (3) mechanical stimulation of the trigger point not only induces intense local pain but referred pain as well, which is different from that expected on the basis of nerve root compression alone and often accompanied by withdrawal of the stimulated muscle (positive jump sign); (4) a taut band of muscle fibers often identified

Table 1
Number of patients excluded from the study and criteria by which they were excluded

Exclusion criteria	n
Not medical history on file in the Pain Unit	42
The response variable was not taken	30
Have undergone infiltration 6 months earlier	26
Not confirmation in the patient's medical history of the administration of BTX-A	25
To the wait of appointment for infiltration	10
Not to have a record of the VAS from the first visit	10
Confused response variable	9
Total	152

BTX-A: Botulinum Toxin Type A; VAS: Visual Analogue Scale; n: Number of subjects.

with trigger point palpation; and (5) immediate pain relief afforded by local anesthetic injection (0.2% Ropivacaine, see below) [33,35]. Furthermore, additional electromyography guidance was used to localize the motor end-plate to confirm the presence of SGC myofascial trigger points [36], and multiplanar continuous fluoroscopic imaging control was used to reveal the intramyofascial spread of contrast solution (Iohexol®, 240 mg/mL) and confirm the presence of PG trigger points (Iliopsoas, Quadratus Lumborum and/or Piriformis) [33].

Once the trigger point(s) were identified, a diagnostic injection of 0.2% Ropivacaine and a vial of Betamethasone (10 ml) was administered to evaluate BTX-A candidates. If a positive effect was registered over the first week, a second diagnostic injection was administered 15 days after the first one. BTX-A infiltration was performed between 1 and 2 months later, only when the short-term effects of both diagnostic injections had disappeared [26]. Botulinum Toxin A was infiltrated at different doses depending on the region. Ten International Units (IU) were infiltrated per injection site in the SGC and 100 IU were infiltrated per muscle in the PG. The proportion of saline solution for every 100 IU was 10 ml. Patients followed a standardized physiotherapy program consisting of 30 min of stretching and active mobilizations following post-infiltration, with one and six month check-ups to observe and record the evolution of pain and any possible adverse effects

2.3. Statistical analysis

The level of statistical significance was established with two tails (error α) $p < 0.05$. Parametric tests were used to analyze quantitative variables when variances were homogeneous (Levene's test). The chi-square test was used for nominal variables and non-parametric tests were used for ordinal variables.

3. Results

Of the 453 patients included in the list initially provided by the Hospital Pharmacy, 152 patients were excluded for reasons shown in Table 1. Of the 301 patients finally included in the study, 228 (75.7%) were women. The mean age was 52.2 years (CI 95%, 50.6–53.8). No significant differences were observed either according to age or gender. The assessment of pain prior to intervention revealed an average value of 7.1 cm (CI 95%, 6.9–7.3) measured with the 0–10 cm VAS and the Lattinen Index revealed an average value of 12.4 points (CI 95%, 12.2–12.7). Significant correlation was found between the two pain evaluation scales (Rho = 0.54; $p < 0.01$).

Regarding the initial diagnosis, 11.6% of subjects were diagnosed as primary MPS while the remaining 88.4% were diagnosed as secondary MPS due to the presence of other pain pathologies related to MPS that might have been further perpetuating factors (See Table 2), as described by Gerwin et al. [8]. No diagnostic differences based on gender were observed ($p = 0.13$).

3.1. Variables associated with the BTX-A injection procedure

Infiltration was performed in 51.5% ($n = 155$) of patients in the PG and 42.5% ($n = 128$) in the SGC, without significant differences in the proportions ($p = 0.10$). Both the PG and SGC locations were infiltrated in 6% ($n = 18$) of patients. The mean number of trigger points infiltrated in the SGC was 8.3 (CI 95%, 7.8–8.7), while between 1 and 4 muscles were infiltrated in the PG (average 1.1 muscles, CI 95% 1.0–1.3). The number of points infiltrated in the SGC and the number of muscles infiltrated in the PG did not correlate with the initial VAS.

The mean dose in the PG muscles was 209.2 IU (CI 95%, 198.0–220.5) and in the SGC trigger points it was 82.7 IU (CI 95%, 78.2–87.3; $p < 0.01$), indicating

Table 2
Percentage of patients presenting primary MPS and secondary MPS in conjunction with other concomitant pathologies

Diagnostic	Percentage (%)
Primary Myofascial Pain Syndrome (MPS)	11.6
Nonspecific back pain	17.9
Failed back surgery syndrome	16.6
Fibromyalgia	13.6
Cervical spondylosis and/or osteophytosis	11.0
Discopathies	9.6
Spinal canal stenosis	6.3
Neurological pathology of Central Nervous System (CNS)	3.0
Vertebral fractures, spondylolisthesis	2.7
Complex regional pain syndrome	2.0
Whiplash syndrome	2.0
Others (Scoliosis, Psychiatric major diseases,)	3.7
Total	100.0

Those diagnoses with a frequency of less than 5 are grouped under the heading 'others'. MPS: Myofascial Pain syndrome.

that larger muscle areas require larger dosages. With regards to BTX-A re-infiltration, 67 patients (22.2%) were re-infiltrated in the same location and 18 patients (6%) in another location.

3.2. Effectiveness of the treatment

More than half of the patients (58.1%) revealed a "satisfactory" or "fully satisfactory" improvement at 6 months after BTX-A infiltration and 42.2% reduced or withdrew adjuvant pharmacological treatment (Fig. 1A). There was a correlation ($\rho = 0.84$, $p < 0.01$) between the improvement expressed by the patient and the change in adjuvant pharmacological treatment. No differences were observed in the effectiveness of the treatment based on gender ($p = 0.73$), nor was there any correlation between effectiveness and age (Rho $= -0.04$, $p = 0.43$).

When comparing the effectiveness between primary MPS and secondary MPS, it was found that, in the case of primary MPS, 82.9% of patients expressed a positive effect, while there was a 54.9% positive effect in the case of secondary MPS ($p = 0.002$; Fig. 1B). Significant differences in effectiveness were also found based on initial diagnosis ($p = 0.001$). Effectiveness of BTX-A infiltration based on "satisfactory" and "fully satisfactory" levels was highest in primary MPS (82.9%) and secondary MPS associated with vertebral fractures (75%) and discopathies (72.4%), compared to lower effectiveness in patients with secondary MPS associated with canal stenosis (21%; $p < 0.05$) and fibromyalgia (39%; $p < 0.05$; Fig. 1C).

Treatment effectiveness did not correlate with the number of points or number of muscles infiltrated or the total dose administered. Although the dose per injection site in the SGC was lower than the dose per muscle in the PG, and the total dose administered was higher in the PG than in the SGC (see above), no differences in the effectiveness of BTX-A was observed between SGC and PG ($p = 0.46$). Attending to re-infiltrated patients, the effectiveness was higher in patients re-infiltrated in the same location (77.9%) compared to those that were not re-infiltrated (62.5%; $p = 0.002$).

3.3. Adverse effects

Temporary adverse effects appeared following infiltration in 23.9% of cases; the most common was "flu-like syndrome" (11.3%), followed by "worse/acute pain" (9.3%) and "transitory muscular paralysis" (3.3%). Adverse effects based on demographics indicated that the proportion of women (27.6%) presenting adverse effects was higher than men (13.3%; $p = 0.008$). However, no differences were observed regarding the adverse effects based on age ($p = 0.15$), diagnosis ($p = 0.1$), initial VAS scores ($p = 0.64$), location of the infiltration (PG or SGC; $p = 0.22$) nor total dose administered in PG muscles ($p = 0.09$) or the SGC points ($p = 0.15$).

4. Discussion

The results of this study show that more than half of patients (58.1%) can benefit from BTX-A infiltration with a reduction in pain of more than 50% and a decrease in adjuvant pharmacological treatment. However, these results varied based on the presence of other pathologies associated with MPS. This variation may partly explain the great variability in results obtained for other studies. In this way, patients who present sec-

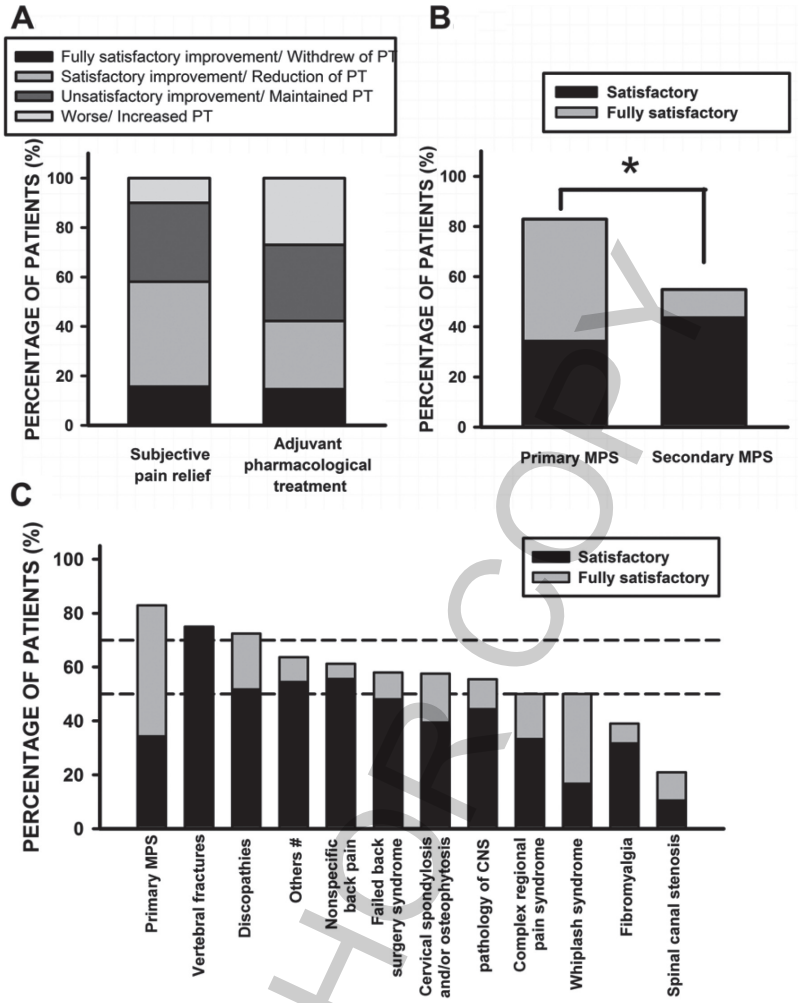

Fig. 1. Effectiveness of the Botulinum Toxin Type A (BTX-A) injection in patients with Myofascial Pain Syndrome (MPS). **A)** Effectiveness of the pain relief treatment/adjuvant medication. Left column indicates the effectiveness of the treatment with BTX-A in MPS based on 4 levels of subjective pain relief (Fully satisfactory $> 80\%$, Satisfactory $> 50\%$, Unsatisfactory $< 50\%$, Worse/increased pain). Right column indicates the variations in the adjuvant pharmacological treatment (PT). **B)** Comparison of effectiveness between primary MPS and secondary MPS. Overall, 82.9% of patients with primary MPS expressed a positive effect (48.6% fully satisfactory and 34.3% satisfactory), while 54.9% of patients with secondary MPS expressed a positive effect (11.3% fully satisfactory and 43.6% satisfactory). *: $p = 0.002$. **C)** Effectiveness of the BTX-A injection based on initial diagnosis. Bars are ranked from higher (left) to lower proportion (right) of positive effect (satisfactory level + fully satisfactory). The effectiveness of diagnoses of "primary MPS" (82.9%), "vertebral fractures" (75.0%) and "discopathies" (72.4%) was greater than 70%, and the effectiveness of diagnoses of "fibromyalgia" (39.0%) and "spinal canal stenosis" (21.0%) was lower than 50%. Others #: scoliosis, psychiatric major diseases.

ondary MPS together with other painful pathologies may be more difficult to treat than those presenting primary MPS [30], making it necessary for researchers to clearly define the inclusion and exclusion criteria related to the presence of the associated pathologies. In the present study, it was found that BTX-A infiltration is more effective in primary MPS (82.9% of patients treated), which is in accordance with other studies that obtained more positive results than the placebo or corticoids and lidocaine, excluding other concomitant pathologies [12,26,28]. However, other studies which only addressed primary MPS treatment failed to obtain better effects than with lidocaine one month after BTX-A injection [10], meaning that it was not recommended due to the high cost and the small differences seen with control treatments [24].

Results are more contradictory when other pathologies are present or when the inclusion criteria are imprecise. With chronic neck pain, Wheeler et al. did not explicitly exclude degenerative pathologies or other

common disorders, and they found no positive effects with BTX-A infiltration when compared to saline solution [9]. In another study of MPS associated with temporomandibular disorders, no clinically relevant effect was reported [37]. In a pilot study, Braker et al. did not obtain any statistically significant differences when referring to secondary MPS associated with whiplash syndrome [19], which is in contrast to positive results obtained in another study [18].

The results of our study were positive with regard to secondary MPS associated with spinal fracture/spondylolisthesis and lumbar discopathy, with the treatment considered "satisfactory" in 70% of patients, although the effectiveness was lower than among patients with primary MPS. One reason may be that the principal cause of pain in these pathologies was associated with muscle contracture. Foster et al. obtained similar results in low back pain (paravertebral infiltration) with pain relief reported at 3 weeks in 73% of patients [20]. On the other hand, in the results reported here, it can be seen that the treatment was "not satisfactory" in more than half of the patients treated with MPS associated with canal stenosis and fibromyalgia. This is in contrast with the positive effects found by [25] in fibromyalgia patients, although they carried out toxin re-infiltrations every two months. In our study, patients who underwent re-infiltration recorded greater effectiveness.

With respect to adverse effects, several patients reported non-specific effects up to several days after injection, including weakness, fever and tiredness that disappeared within a few days without the need for intervention and which patients described as mild [12, 19,21]. This variability could be associated with the dose and the location of the infiltration. No adverse effects were found when using a very low dose (5 IU per point) in the SGC compared to the injection of a saline solution. However, this dose was found to be ineffective [13]. Other authors registered adverse effects in approximately 40% of subjects using doses of 400 IU (40 IU per point) [12] and 200 IU (50 IU per point) [19] in the surface muscles of the SGC [19]. However, other studies reported adverse effects in around 4% of cases [21,22] when using similar dosages in paravertebral lumbosacral musculature.

When the deep muscles of the PG (Iliopsoas, piriformis, quadratus lumborum) are infiltrated, dose ranges from 100 IU to 200 IU per muscle have been used, depending on the author [26–29]. In all of these studies, no adverse effects were recorded, or only very mild effects were present. In our study, adverse effects with Botox® were registered in 24% of patients using an average total dose of 80 IU in the SGC and 200 IU in the PG. Despite the difference in dose between the two locations (10 IU for SGC and 100 IU for PG per injection site), no difference was found in effectiveness or adverse effects, suggesting that not only is the dose important to identify adverse effects, but that the location is also critical to determine the dosage that is both effective and safe. Importantly, the current study observed more adverse effects in women, which had not been previously identified, suggesting that gender-specific problems with BTX-A injections should be addressed in the future.

Although the major limitation of this study is the retrospective design, there are other limitations that should be addressed. During recent years, a biomechanical approach for treatment with BTX-A injections has been developed [38,39]; however, the objective of BTX-A injections in our study was to specifically treat myofascial trigger points. Finally, although a decrease in adjuvant pharmacological treatment according to the WHO Pain ladder was registered, no specific drugs were recorded.

In conclusion, we believe that the high prevalence of MPS in Chronic Pain Units and the positive results obtained with the BTX-A infiltration protocol combined with physiotherapy, which produced only limited and temporary adverse effects, support the application of this technique as a viable therapeutic tool for the treatment of primary MPS and some types of secondary MPS. It will be necessary to establish randomized and controlled prospective studies in Chronic Pain Units with clearly defined inclusion criteria that account for the concomitant pathologies associated with secondary MPS.

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