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RESEARCH ARTICLE

Efficacy of incobotulinumtoxinA for Spasticity-Associated Pain in a Series of Patients with Spasticity of Diverse Etiologies

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ABSTRACT

Background: Spasticity is a motor disorder that appears as a cause of upper and lower limb motor disability, frequently causing pain. IncobotulinumtoxinA (IncoA) has proved effective for treating diverse musculoskeletal pathologies, including spasticity and spasticity-related pain.

Aims: The aim was to determine the efficacy of IncoA for the treatment of pain associated to limb spasticity of diverse etiologies.

Methods: Prospective, single-center study including 30 patients treated with IncoA between May and August 2021 at the University Hospital Center of Central Lisbon (Lisbon, Portugal). Primary endpoint was improvement in spasticity-related pain, assessed by employing pain numerical rating scale for pain at baseline and 12 weeks post-injection, scoring between 0 (no pain) and 10 (severe pain).

Results: Patients showed spasticity due to different etiologies, mainly ischemic stroke (46.7%), hemorrhagic stroke (23.3%) and cerebral palsy (20.0%). Mean pain score significantly decreased from baseline (mean: 6.8, range: 2-10) to 12 weeks post-injection (mean: 1.6; range: 0-5). Mean reduction of pain was of -5.2 points (95%CI: -5.9, -4.5). All patients achieved minimum clinically significant difference in pain reduction, showing sustained effect over 12 weeks regardless of spasticity etiology.

Conclusion: IncoA may be considered as an alternative for the treatment of spasticity-associated pain of diverse etiologies in upper and lower limbs.

Keywords: spasticity; pain; incobotulinumtoxinA; efficacy

Introduction

Spasticity is a motor disorder defined as a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, as a consequence of hyperexcitability of the stretch reflex.[1] It is a common cause of upper and lower limb disability in subjects who have experienced stroke, acquired brain injury, spinal cord injury, multiple sclerosis (MS), or cerebral palsy (CP).[2] Evidence has shown that spasticity involves not just hypertonia but also secondary peripheral structural changes in muscle fiber and extracellular matrix composition[3,4], sarcomere number and length, and muscle rheological properties.[4] It may present with different degrees of severity, from mild (producing muscle tightness) to severe cases (causing painful spasms and abnormal joint positioning in upper and lower limbs).[5] Spasticity-related pain (SRP) is a common symptom among patients who have had a stroke.[6]

Spasticity-related pain does not only affect the quality of life of patients, but also of caregivers, since the disability especially impacts on hygiene and dressing domains.[7,8]

The prevalence of SRP varies from 46% to 76% depending on the patient population studied[9-13], being of approximately 65% in upper motor neuron lesions (stroke, CP, and MS), and more than 40% in amyotrophic lateral sclerosis.

Despite the high prevalence, pathophysiological mechanisms underlying the pain associated with spasticity are still not fully characterized.[14,15] Pain can be the result of damage in soft tissue and joint pathology[15], impaired reflex function[16], changes in rheologic muscle stiffness, fibrosis, and atrophy[17], lesions in the peripheral nerves and increased tendon traction[16]. Abnormal muscle contraction and tonic muscle activation could produce stamping out of muscle vessels, leading to hypoxia, release of inflammatory substances, activation of nociceptive receptors, and ultimately pain.[14,15]

The management of spasticity-associated pain includes non-pharmacological (e.g., kinesiotherapy)[6] and pharmacological therapies, including antispastic (e.g. baclofen, tizanidine) and analgesic agents[18], peripheral nerve blocks with neurolytic agents (e.g., phenol and alcohol)[19], and intramuscular injections with botulinum neurotoxin (BoNT).[20-23]

The reduction of pain is usually one of the most important outcomes in the treatment of spasticity associated with upper motor neuron syndromes.[6,9] Some guidelines include BoNT injections as first-line treatment in a multidisciplinary rehabilitation plan for spasticity-related pain of different neurological diseases, such as stroke.[21,24,25]

According to ULIS-II[26] and ULIS-III[27] clinical trials, BoNT-A has shown 83.6% and 65.9% rates of goal achievement for the reduction of spasticity-associated pain in 61 (13.4% of participants) and 235 (64.3% of participants) of patients, respectively.

The efficacy of BoNT-A in reducing pain in patients with upper and lower limb spasticity has been investigated in additional clinical studies, either as a primary outcome[10-12,28-32] or a secondary outcome[33-40]. However, pain-relief results have been conflicting.

This neurotoxin is the most potent natural toxin produced by *Clostridium botulinum* and other strains from the same family that has been used therapeutically in a wide range of medical conditions.[41] The mechanism of action involves the inhibition of the release of acetylcholine and the blockade of the cholinergic transmission at the neuromuscular junction.[42] Sensory pathways are also targeted by BoNT, especially the nociceptive system which is thought to lead to the reduction of pain.[42] Moreover, BoNT inhibits substance P, glutamate and CRGP synaptic release, which are excitatory neurotransmitters that have an influence on pain generation and transmission.[43] In addition, BoNT also interacts with TRPV1 receptors, inhibiting its translocation to the cell membrane.[44] In clinical practice, incobotulinumtoxinA (IncoA) has demonstrated its efficacy and safety for treating focal spasticity, with a significantly higher number of patients treated with the toxin improving their DAS pain scores compared with placebo.[13]

The objective of the present study was to determine the efficacy of IncoA for the treatment of pain associated to limb spasticity of diverse etiologies in a series of patients.

Materials and Methods

Study design

Prospective, open-label, single-arm, real-world study carried out in patients with spasticity-associated pain who received treatment with IncoA, between 1-1-2021 and 31-12-2021, at the Centro Hospitalar Universitário de Lisboa Central (Lisbon, Portugal). This is a descriptive study with data from patients with spasticity treated at the hospital during 2021, therefore no formal sample size calculation was performed.

The inclusion criteria included:

(1) Presence of limb spasticity, as defined by Lance, due to any cause;

(2) Initial score of ≥2 in a 0-10 pain numerical rating scale (NRS) in the spastic limb(s);

(3) Spasticity graded as at least ≥2 in the modified Ashworth scale in the painful body segment(s);
(4) Relief of SRP with IncoA was part of the patient-centred treatment goal(s);
(5) If pretreated with BoNT-A, last treatment occurred >16 weeks, and documentation was available.
The exclusion criteria included:
(1) Pain that was or could probably be due to other causes (e.g., bursitis, tendinitis), as assessed by a medical specialist in Physical Medicine and Rehabilitation;
(2) Existence of other systemic diseases that could cause diffuse pain syndromes (e.g., fibromyalgia).
(3) Patients with hypersensitivity to the active substance Botulinum neurotoxin type A or to any of the excipients, generalized disorders of muscle activity (myasthenia gravis, Lambert-Eaton syndrome) or infection at the proposed injection site.
(4) Any change that occurred in the usual kinesiotherapy, physical agents, oral pharmacotherapy or any other therapeutic act deemed to possibly interfere with pain during the previous 2 weeks before BoNT-A injection, and during the follow-up period of 12 weeks.
Procedures were approved by a local Ethics Committee.

Intervention
IncoA doses and injected muscles were selected as deemed necessary by the attending doctor to achieve the patient-centred goals defined with the patient and/or caregiver. A descriptive analysis of the etiology of the spasticity, doses used, and muscles injected as well as the number of injections received, and the duration of effect was included in the study.

Study endpoints
The primary endpoint was the improvement in spasticity-associated pain, assessed by employing the NRS for pain, scoring between 0 (no pain) to 10 (severe pain).[25] This scale is commonly used for assessing pain, since it provides a valid, reliable and appropriate tool with good sensitivity.[45]

Timing
The NRS score was measured at baseline and at twelve weeks post-injection (T1). The minimum clinically significant difference was established as a change of -1.39, according to Kendrick *et al.*[46]

Statistical analysis
Discrete variables are expressed as the mean and the range (minimum-maximum values), whereas continuous ones as absolute and relative frequencies. The comparison of NRS for pain between baseline and T1 was carried out with the paired t-test. Statistical significance threshold was $p<0.05$. All statistical procedures were performed with SAS 9.4 software.

Results

A total of 30 patients were included in the study out of 96 spastic patients screened (frequency of spasticity-associated pain 31.25%). The number of painful spastic patterns treated was 34. The mean age of the patients was 54.7 years (range: 23-77). Patients presented spasticity due to different etiologies: stroke (70.0%; including ischemic stroke, in 46.7%, and hemorrhagic stroke, in 23.3%), cerebral palsy in 20.0%, multiple sclerosis in 6.7%, and meningioma sequalae in 3.3%. The mean number of years since diagnosis was 14.5 years (range: 3-48; Table 1).

They were treated with a mean number of injection cycles of 12.0 (range: 2-31) before the injection cycle pertaining this study. The mean total dose of IncoA used in the affected body segments was 126.0 U (range: 35-450). The anatomical regions treated were, in order of frequency: shoulder (26.5%), foot (17.6%), elbow (17.6%), wrist (11.8%), hip (8.8%), hand (5.9%), ankle (5.9%), and other regions (5.9%; Table 2).

Table 1. Baseline characteristics of patients

	Patients(N=30)
Age, mean years (range)	54.7 (23-77)
Sex, n (%)	
Male	13 (43.3)
Female	17 (56.7)
Diagnosis, n (%)	
Ischemic stroke	14 (46.7)
Hemorrhagic stroke	7 (23.3)
Cerebral palsy	6 (20.0)
Multiple sclerosis	2 (6.7)
Meningioma	1 (3.3)
Years since diagnosis, mean (range)	14.5 (3-48)

Table 2: Characteristics of injections and spasticity pattern

	Total injections (N=34) in 30 patients
Total dose, mean UI (range)	126 (35-450)
Region/spasticity patter, n (%)	
Shoulder	9 (26.5%)
Shoulder adduction	1
Shoulder adduction/internal rotation	8
Elbow	6 (17.6%)
Elbow flexion	4
Forearm pronation	1
Forearm pronation/Elbow flexion	1
Feet	6 (17.6%)
Feet flexion	5
Hallux flexion	1
Wrist / Wrist flexion	4 (11.8%)
Hip	3 (8.8%)
Hip adduction	2
Hip adduction/flexion	1
Hand	2 (5.9%)
Clenched fist	1
Intrinsic hand	1
Ankle	2 (5.9%)
Ankle flexion	1
Pes equinus	1
Knee / Knee flexion	1 (2.9%)
Central pain post-stroke / Right body	1 (2.9%)

Injections were performed in 80 different muscles. The most frequently injected muscle was the *Latissimus dorsi* (10.0% of injected muscles), followed by *Flexor digitorum longus*, *Brachialis*, and *Flexor hallucis longus* (7.5%). While *Adductor pollicis* and *Flexor hallucis brevis* were injected with lower IncoA doses (both with 25 U), *Pronator teres* (50-100 U), *Adductor magnus* (50-100 U) and *Flexor carpi ulnaris* (50-80 U) were among the muscles with the highest range of administered doses (Table 3).

Table 3: Administered doses per treatment region

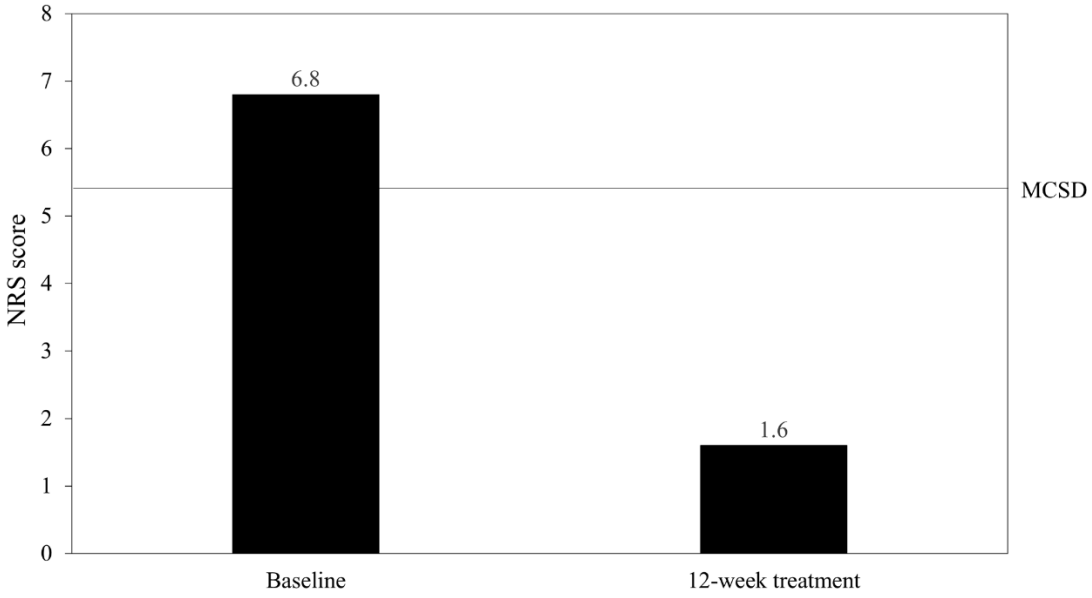
Muscle	**n**	**Dose (U)**								
		25	**30**	**35**	**40**	**50**	**70**	**75**	**80**	**100**
Latissimus dorsi	8 (10.0%)					4	3	1		
Flexor digitorum longus	6 (7.5%)	1		1		1	2	1		
Brachialis	6 (7.5%)	1	1			1	2			1
Flexor hallucis longus	6 (7.5%)	1				2	2	1		
Biceps brachii	5 (6.3%)		2		1	1				1
Flexor carpi radialis	5 (6.3%)	1				3			1	
Subscapularis	4 (5.0%)					1	3			
Brachioradialis	4 (5.0%)	1	1	1	1					
Flexor carpi ulnaris	4 (5.0%)					3			1	
Pronator teres	3 (3.8%)					1	1			1
Adductor longus	3 (3.8%)	2	1							
Pectoralis major	3 (3.8%)					3				
Adductor magnus	3 (3.8%)					1				2

Gastrocnemius lateral	2 (2.5%)	1						1		
Soleus	2 (2.5%)	1						1		
Flexor digitorum profundus	2 (2.5%)					2				
Teres major	2 (2.5%)					1		1		
Flexor digitorum superficialis	2 (2.5%)					2				
Gastrocnemius medial	2 (2.5%)	1						1		
Tibialis posterior	1 (1.3%)					1				
Adductor brevis	1 (1.3%)		1							
Iliopsoas	1 (1.3%)						1			
Flexor hallucis brevis	1 (1.3%)	1								
Lumbricals	1 (1.3%)				1					
Quadratus plantae	1 (1.3%)	1								
Flexor digitorum brevis	1 (1.3%)					1				
Semimembranosus	1 (1.3%)					1				

Primary endpoint: Pain assessment

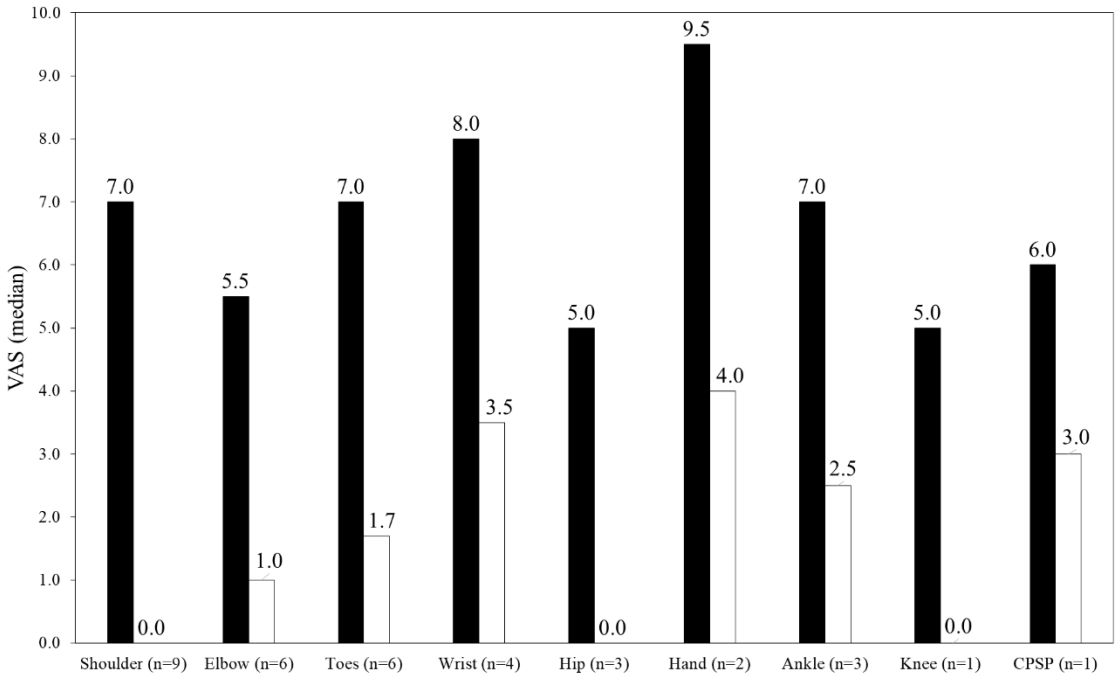
The mean NRS for pain score significantly decreased from baseline (mean: 6.8/10, range: 2-10) to twelve weeks post-injection (mean: 1.6/10; range: 0-5; p=0.001; Figure 1). The mean reduction of pain was -5.2 points (95% confidence interval: -5.9, -4.5). All patients achieved the minimum clinically significant difference of -1,39 (range: -2 to -10). 44,1% of painful segments treated achieved complete pain relief.

Figure 1. Change of spasticity-related pain with IncoA. MCSD: minimum clinically significant difference.



Pain reduction was reported for all anatomical regions. The highest NRS score decrease was observed in the shoulder (from 7.0 to 0.0 at baseline and 12 weeks, respectively), hand (from 9.5 at baseline to 4.0 after 12 weeks) and toes (from 7.0 at baseline to 1.7 after the 12-week period; Figure 2).

Figure 2. Pain decrease vs. anatomical region



This reduction in pain was also observed for all spasticity etiologies. The highest change in NRS scores was reported for meningioma sequelae (from 8.0 to 0.0 at baseline and 12 weeks), followed by multiple sclerosis (from 7.0 at baseline to 0.0 after 12 weeks; Figure 3).

Finally, no relation was observed between the time since onset of spasticity and pain reduction after the treatment (r=0.10; p=0.563; Figure 4).

Figure 3. Pain decrease vs. spasticity etiology

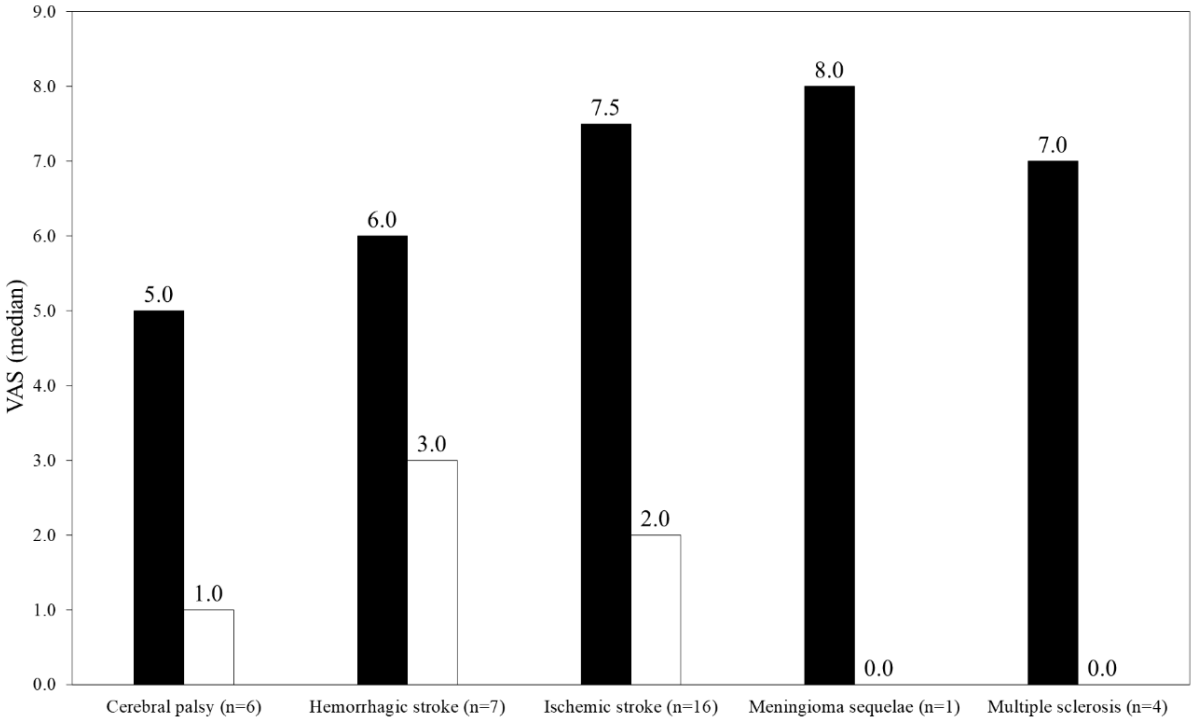
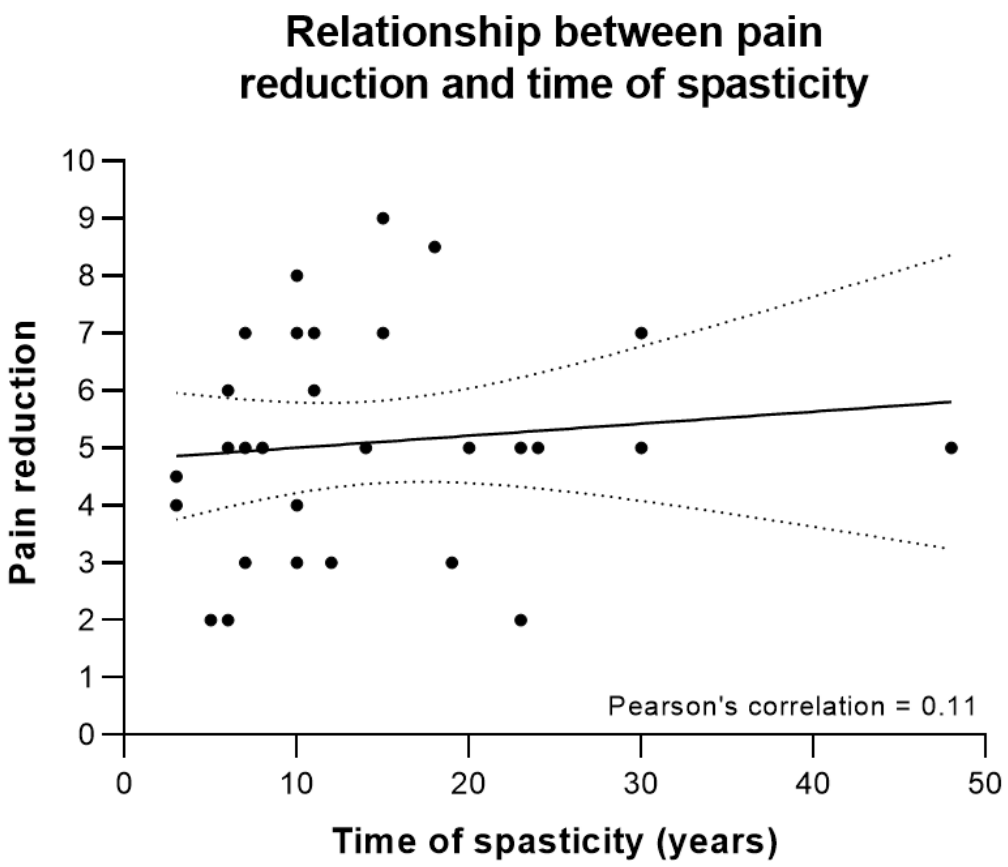


Figure 4. Relationship between pain reduction and time of spasticity



Discussion

Spasticity-related pain is a common consequence of upper motor neuron syndromes with high prevalence in patients with stroke, CP, and MS.[9] However, pharmacological treatment is frequently associated with systemic side effects which limit their clinical use[16]. The intramuscular injection of BoNT type A is recommended in European[20,47] and North American[48] guidelines for the treatment of focal and multifocal spasticity of the upper and lower limbs. The efficacy and safety of IncoA in the treatment of spasticity is well established.[30,39,49-52] However, the number of studies specifically designed to ascertain the efficacy of BoNT in spasticity-related pain are limited.[13,53] Furthermore, among those available, they mostly included patients with stroke or CP.[13,24,30,49,51,54] To our knowledge, the efficacy of IncoA for the treatment of pain related to spasticity in patients with meningioma or MS has not yet been included in previous trials concerning spasticity-associated pain. Thus, the goal of our study was to describe and assess the effectiveness of the real-world use of IncoA in spasticity-associated pain in a series of patients with spasticity due to diverse etiologies.

In our study, IncoA injections led to a significant reduction of spasticity-associated pain (due to stroke, MS, CP, and meningioma) after twelve weeks post-injection. The mean reduction in the pain NRS reported in this study (-5.2) was higher than previously reported in clinical trials, with values varying from -2.0 and -3.4 after 30 and 90 days, respectively[55], to -4.1 and -4.0 after four and 16 weeks[57]. Also, in the BEST trial, a randomized placebo-controlled-study in which onabotulinumtoxinA was used, a mean pain reduction of -0.8 was reported after a 12-week post-treatment assessment, an improvement that stands lower than the one we have observed in our open-label study.[12] These differences can be explained for distinct populations included in all the studies analyzed.

Other studies have shown the efficacy of BoNT in spasticity. A systematic review and meta-analysis, involving 37 randomized controlled trials, corroborated the efficacy of BoNT for spasticity, namely in upper and lower limbs. By contrast, no significant effects were found for pain relief[42], but

the quality of the evidence was deemed to be low/very low for that outcome. On the other hand, various studies have shown a significant improvement in spasticity-related pain with BoNT injections.[54,57,58] Wissel *et al.*[16] carried out an open-label, prospective, multicenter trial in 60 patients with upper and/or lower limb spasticity. Pain was the primary spasticity-related complaint. Local intramuscular IncoA injection resulted in 90% of patients with significant pain relief, compared with baseline. No serious AEs were reported. Similarly, Pedreira *et al.*[54], in an open, prospective, clinical trial, evaluated the efficacy of IncoA (mean dose 280 U) in 16 patients who complained of pain associated with spastic hemiparesis secondary to stroke. Patients were followed-up for four months. A significant pain reduction (by VAS) was reported at week 1 and remained until the fourth month of follow-up. Dunne *et al.*[54] assessed the efficacy of BoNT in a cohort of patients with moderate-to-severe spasticity in the upper or lower limbs, and refractory to conventional physical and medical treatments. Results showed pain reduction in 28 of 31 patients (8 related to painful flexor spasms and 23 to passive stretching). At the end of the study, moderate pain relief occurred in 90%. Of them, 26% experienced complete resolution of pain, which is somewhat below our findings (44.1% of complete pain relief in the treated body segments). Finally, Wissel *et al.*[13] recently performed a pooled data analysis on pain relief from six different studies in which IncoA was administered to 544 adults with limb muscle spasticity. The results showed that a higher number of IncoA-treated participants reported an improvement in their DAS pain scores after four weeks compared to those in which placebo was administered (52.1% vs. 28.7%, respectively). In addition, IncoA patients were less likely to report no changes in their DAS pain scores (43.2% vs 65.1%). Finally, after the four-week treatment, 27.1% and 12.4% of patients treated with either IncoA or placebo achieved complete pain relief.

Although the peak effect of BoNT on reducing muscle tone is usually observed 6-8 weeks after the injection, several trials have determined a significant decrease in pain values at week four.[10,59] Also, by week 12, the primary endpoint of our study, most patients have experienced reemergence of their spasticity. The sustained analgesic effect of IncoA by week 12, reported in the present study, points to the fact that pain relief with BoNT involves mechanisms other than muscle relaxation.

In our patients, the shoulder was the most painful joint at baseline, which is in agreement with the incidences published in the literature. In the post-doc analysis from the TOWER study (NCT01603459) performed by Wissel *et al.* [40], showed that from the baseline to 4 weeks post-injection, subjects who were treated in the shoulder also experienced a greater mean improvement in DAS pain score than those not treated in the shoulder: cycle 1: –0.5 (SD=0.8) vs –0.3 (SD=0.7); cycle 2: –0.5 (SD=1.1) vs –0.2 (SD=0.7); and cycle 3: –0.4 (SD=0.7) vs –0.2 (SD=0.9), respectively.

Finally, in our study, we observed that IncoA efficacy seemed to be independent of the severity and duration of spasticity-related pain, as it provided a significant clinical benefit even to patients with long-standing spasticity (14.5 years).

Other studies have shown the efficacy and safety of IncoA in the treatment of spasticity-related pain in other populations. Results from TIM, TIMO and XARA clinical trials showed that IncoA is also effective at reducing CP-related spasticity over multiple injection cycles spanning 24–98 weeks in children/adolescents with CP.[60-62] In a post-hoc study, Bonfert *et al.* [63], analyzing data from these 3 phase III studies observed evidence of substantial, clinically meaningful reductions in the frequency and intensity of spasticity-related pain after IncoA treatment in 332 children and 155 adolescents with CP-related spasticity.

The main limitations of the study were its open-label design and the relatively low number of patients. Besides these limitations, our results are in agreement with previous studies in which a different botulinum toxin was used.[13,15,54,57]

Conclusion

All patients treated with IncoA in this study achieved at least the minimum clinically significant difference in pain reduction, which was sustained over the subsequent 12 weeks. In addition, a significant benefit was observed regardless of the spasticity etiology. Therefore, IncoA may be considered an alternative for the treatment of spasticity-associated pain in upper and lower limbs of diverse etiologies. Further long-term studies, involving larger cohorts of patients, and with different etiologies, are required to corroborate these results.

Conflicts of Interest Statement: Dr. Alexandre Camoes-Barbosa has received honoraria from Merz, Abbvie/Allergan and Ipsen.

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Author contributions: All authors contributed equally to the conception and design, acquisition of data, and drafting of the article. All authors

approved the final version of the manuscript and agree to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work.

Institutional Review Board Statement: This study was approved by a local Ethics Committee.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available upon reasonable request.

Ethics statement: All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

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