

BRIEF COMMUNICATION

OnabotulinumtoxinA as a promising treatment for primary trochlear headache: A retrospective case series

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Abstract

Objectives: To report the efficacy of onabotulinumtoxinA (BoNTA) injections in relieving pain in patients with primary trochlear headache (PRTH).

Methods: Examination of medical records for patients diagnosed with PRTH according to the International Classification of Headache Disorders, 3rd edition criteria and treated with BoNTA. Data were collected for variables related to pain relief, duration of effectiveness, and adverse effects.

Results: Six patients were included in the study. All had previously undergone standard care interventions, including infiltrations or oral treatments, yet experienced treatment failure or symptom recurrence. All patients received 20 units of BoNTA, administered in the corrugator and procerus muscles. Subsequent to the BoNTA injections, all six patients reported substantial pain relief, with five achieving complete remission of symptoms. The analgesic effect persisted for a duration of 3 months. No adverse events were reported in any of the cases.

Conclusions: Our case series presents the first evidence of the potential of BoNTA as a safe and effective treatment option for PRTH. From a clinical standpoint, having a safer alternative is of paramount significance for patients with limited treatment options, such as those with PRTH. Further research is warranted to validate these findings and explore the long-term efficacy of BoNTA in PRTH management.

Plain Language Summary: Primary trochlear headache (PRTH) is a type of headache known for its intense pain and usual treatments (that are not always effective in the long-term) include medications like nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, pregabalin, and gabapentin, and injections of corticosteroids. In our study, we found the first evidence suggesting that onabotulinumtoxinA could be a safe and effective treatment for PRTH. Further research is needed to confirm these findings and understand how well onabotulinumtoxinA works for managing PRTH in the long term.

Abbreviations: BoNTA, onabotulinumtoxinA; PRTH, primary trochlear headache; SO, superior oblique; SON, supraorbital nerve; STN, supratrochlear nerve.

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KEYWORDS

case report, headache, neuro-ophthalmology, onabotulinumtoxinA, trochlear, trochleitis

INTRODUCTION

According to International Classification of Headache Disorders, 3rd edition criteria, primary trochlear headache (PRTH) is characterized by pain in the frontal/periorbital regions, with or without ocular pain, linked to peritrochlear dysfunction and exacerbated by ocular movements.¹ Intense pain primarily locates in the inner-upper orbit, often extending to the ipsilateral forehead. Pathophysiology involves anatomical components such as cartilaginous trochlea, superior oblique (SO) muscle, SO tendon, and fibrovascular sheath, as well as adjacent neural structures, mainly the supraorbital nerve (SON) and supra-trochlear nerve (STN).²

In a Spanish study, PRTH prevalence was estimated at 12 per 100,000, with a notable majority (86.4%) of cases occurring in females. It is worth noting that these data may underestimate the true prevalence, potentially due to limited awareness and diagnostic recognition.³

Pain in PRTH typically follows a continuous pattern with intermittent exacerbations, often reaching severe intensity, commonly rating between 7 to 10 on a numerical rating scale.² It exacerbates during SO muscle contraction, eye movement, or near-work activities such as reading or computer use.⁴ Clinical signs comprise tenderness in the trochlear region, which worsens with vertical eye movements.⁴ PRTH is predominately a clinical diagnosis.¹ Imaging can be used to rule out trochlear inflammation and other potentially critical conditions, such as orbital or cavernous sinus disorders.⁵

Standard of care includes nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, serotonin and noradrenalin reuptake inhibitors, pregabalin, and gabapentin among others.⁵ If these prove ineffective, PRTH often responds well to local corticosteroid plus anesthetic injections (62%–98%^{2,3}); however, remission typically lasts 18 months,⁴ requiring periodic treatment and potentially elevating the risk of side effects, ranging from mild (localized bruising, hematoma) to rare and severe (central retinal artery occlusion).^{6,7}

Considering the above, there is need for a less invasive and safer treatment option. In this case series, we report the initial PRTH patients successfully treated with onabotulinumtoxinA (BoNTA).

METHODS

The medical records of patients with PRTH at the headache unit of a tertiary hospital were systematically reviewed. Inclusion criteria comprised individuals who had undergone treatment with BoNTA and maintained a follow-up of no less than 3 months. Demographic variables, pain characteristics including imaging results, and details of prior and concomitant treatments, were systematically collected. The study received approval from the Research Ethics Committee

of the Fundación Jiménez Díaz University Hospital (EO247-23_FJD), and all patients provided informed consent to have their cases published. The preparation of this manuscript adhered meticulously to the CARE reporting guidelines checklist.

RESULTS

Six patients, aged between 29 and 74 years, diagnosed with PRTH according to the International Classification of Headache Disorders, 3rd edition criteria and treated with BoNTA, were included (refer to Table 1). An ophthalmologist's assessment ruled out alternative pathologies in all cases. Most were female (5), none had bilateral symptoms, and four cases presented with left eye symptoms. All experienced localized trochlear pain, with three cases having additional radiating pain involving the SON and STC innervation regions. A consistent feature was a background dull pain with daily paroxysmal exacerbations rated 7–10 on the visual analog scale. Pressure on the trochlea worsened pain in all cases, but ocular movements were unrestricted.

Three out of the six cases had a different type of primary headache, two had migraine, and one had tension-type headache (Table 1). None of the patients exhibited migraine-like features during pain exacerbations. Also, the patients could clearly distinguish between the two types of pain.

All patients received medical therapy, beginning with oral non-steroidal anti-inflammatory drugs. Additional treatments, including amitriptyline, carbamazepine, gabapentin, and indomethacin, showed varying degrees of partial effectiveness or were entirely ineffective (Table 1). Oral steroids were administered to two patients (Cases 2 and 6) with temporary pain relief. Anesthetic plus corticoid infiltrations were performed in three patients (Cases 4, 5, and 6). While one patient experienced partial efficacy, the other two achieved complete improvement, albeit for a limited duration of 3–4 months. Subsequent infiltrations resulted in similar outcomes, with pain recurrence after 12 weeks. Notably, no adverse effects were reported. The other three patients refused to undergo trochlear infiltrations.

After the recurrence of pain, each patient received 20 units of BoNTA, distributed as 5 units per corrugator muscle and 10 units in the procerus muscle divided into two points, as illustrated in Figure 1. Therapeutic effects were noticeable within 15–20 days post-injection. One month after the initial injection, five patients achieved complete pain relief, while one patient (Case 2) experienced a partial response, reducing pain intensity from 10 to 4 on the visual analog scale, even after the second infiltration. All patients experienced an end-dose effect after 3 months, prompting subsequent injections. Four patients have received three or more infiltrations,

TABLE 1 Demographics and clinical characteristics of the patients.

Case	1	2	3	4	3	6
Age (years)	29	36	74	59	59	45
Age at onset (years)	29	32	70	44	54	45
Other headaches	No	No	No	EM	TTH	EM
PRTH trigger	Unknown	Unknown	Unknown	Unknown	Unknown	Many hours of reading
Clinical characteristics						
Side	L	R	L	R	L	L
Topography	PO, F	PO	PO	PO, F	PO	PO, F
Basal pain intensity (VAS)	10	10	10	9	8	9
Continuous pain	Yes	Yes	Yes	Yes	Yes	Yes
Exacerbations	Yes	Yes	Yes	Yes	Yes	Yes
Blurred vision	No	No	No	No	No	Yes
Diplopia	No	No	No	No	No	No
Tenderness of the trochlea	Yes	Yes	Yes	Yes	Yes	Yes
Exacerbation triggered by eye movements	Yes	Yes	Yes	No	Yes	Yes
Restriction of eye movements	No	No	No	No	No	No
Imaging tests						
Brain and orbits MRI	Normal	Normal	Normal	Normal	Normal	No
Previous treatments						
NSAIDs	TE	TE	TE	TE	TE	TE
Corticosteroids	TE	No	TE	No	No	No
Amitriptyline	No	PE	No	PE	No	No
Carbamazepine	No	I	No	No	No	No
Gabapentin	No	I	No	No	No	No
Previous local injections	Yes	Yes	No	Yes	No	No
First	Lidocaine plus Triamcinolone 20 mg (TE)	Bupivacaine (TE)	-	Dexamethasone 4 mg (TE)	-	-
Second	Lidocaine plus Triamcinolone 20 mg (TE)	Dexamethasone 4 mg (TE)	-	Dexamethasone 4 mg (TE)	-	-
Third	-	Bupivacaine (TE)	-	Dexamethasone 4 mg (TE)	-	-

(Continues)

TABLE 1 (Continued)

Case	1	2	3	4	3	6
Time of PRTH at the time of the first BoNTA injection						
Months	10	24	27	180	60	2
Pain Intensity (VAS) after BoNTA infiltrations						
First month	5	5	5	5	4	6
Third month	0	0	4	0	0	0
Sixth month	0	0	4	0	-	-
Ninth month	0	0	-	-	-	-
Twelfth month	-	0	-	-	-	-
Time to end-dose effect	3 months	3 months	3 months	3 months	3 months	3 months
Number of BoNTA infiltrations	4	5	3	3	2	1
Adverse events	No	No	No	No	No	No

Abbreviations: BoNTA, onabotulinumtoxinA; E, effective; EM, episodic migraine; F, frontal; I, ineffective; L, left; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PE, partially effective; PO, periorbital; PRTH, primary trochlear headache; R, right; TE, temporally effective; TTH, tension type headache; VAS, Visual Analogue Scale.

and the treatment continued to be effective. No adverse effects were reported.

DISCUSSION

PRTH is a disorder with a complex pathogenesis. While corticoid injections are known to be highly effective, some cases prove refractory or necessitate repeated infiltrations, thereby increasing the potential for adverse effects. To the best of our knowledge, this is the first report of successful treatment of PRTH with BoNTA. Notably, the initial use of this treatment was serendipitous. It was administered to the patient of Case 1 for cosmetic purposes, which unexpectedly resulted in complete pain remission. Subsequently, the authors offered this treatment to other patients and observed similar positive responses.

Among the six patients, five received corticosteroid treatment (oral or injected). Although the response was favorable, the remission period was 3–4 months, which differed from previous reports of 18 months.⁴ It is possible that this subgroup of patients represents the most refractory cases. Following the recurrence of pain, a total of 20 units of BoNTA were administered to all patients (Figure 1). In comparison to the PREEMPT protocol, the dosage in the corrugator muscle was increased in an attempt to enhance the effect on the STN (as it is well-documented that BoNTA can diffuse from the injection site) while minimizing cosmetic side effects.

Since the pathophysiology of PRTH remains puzzling and the analgesic mechanism of BoNTA is complex, it is challenging to

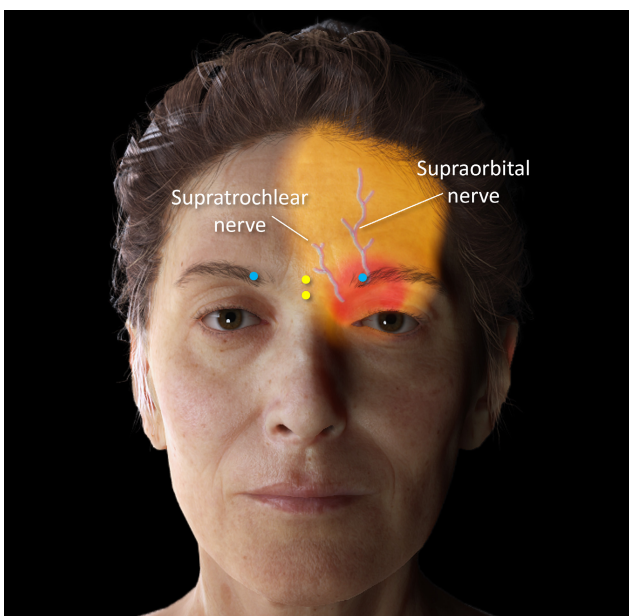


FIGURE 1 Fictitious 3D image created with Character Creator 4® representing the distribution of 20 units of BoNTA: 5 units in each corrugator muscle (blue dots) and 10 units in the procerus muscle, divided into two points (yellow dots).

establish why this treatment proved effective; however, exploring proposed hypotheses might shed light. This hypothesis is supported by a reported case of SO muscle myokymia preceding the onset of trochleodynia.⁸ Additionally, the neuromuscular hypothesis posits that myofascial trigger points in the SO muscle increase nociceptive input from the SON or STN to the spinal trigeminal nucleus caudalis.⁹ In both scenarios, pain relief may result from the blockade of the release of algogenic neuropeptides such as substance P, neurokinin A, and calcitonin gene-related peptide.¹⁰ This mechanism is similar to how BoNTA is theorized to alleviate other conditions like trigeminal,¹¹ auriculo-temporal,¹² and glossopharyngeal neuralgia¹³ even when injections are not administered directly over the sensory distribution of the nerve.¹³

Furthermore, an inflammatory pathogenesis is suggested by perivascular lymphocytic infiltration near trochlear cartilage and SO muscle myofibril invasion in trochleodynia.¹⁴ Although recent research indicates BoNTA may reduce preexisting inflammation, likely by interacting locally and reducing immune cells,¹⁵ it is important to note that none of the patients who underwent magnetic resonance imaging exhibited inflammatory findings in the trochlea.

Although two of the patients had concurrent episodic migraine, it is noteworthy that during the most intense episodes, none exhibited photophobia, nausea, or other migraine-like features. It is important to note that while the pain may not be consistent with migraine, there remains a possibility that trochleodynia could be secondary to a sensitization process. Although this phenomenon is more common in chronic migraine than in episodic migraine, it cannot be completely ruled out.

LIMITATIONS

This case series, while demonstrating successful symptom management in six patients, lacks data on potential long-term treatment outcomes. Despite the possibility of a placebo effect, its impact is likely minimal, given the timing of the analgesic response and the observed end-dose effect consistent with BoNTA's pharmacological activity. Importantly, patients were not concurrently receiving other pharmacological treatments, excluding the possibility of improvement due to other drugs. Spontaneous remission is unlikely, especially considering most patients had symptoms for at least 10 months. The study lacks a control group and may be subject to selection bias, favoring typical or severe cases. Additionally, the retrospective nature of the study may introduce information biases.

AUTHOR CONTRIBUTIONS

Alex Jaimes: Conceptualization; formal analysis; investigation; methodology; software; writing – original draft. **Andrea Gómez:** Data curation; project administration; writing – review and editing. **Olga Pajares:** Data curation. **Jaime Rodríguez-Vico:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Alex Jaimes has received honoraria from Lilly, TEVA, and Allergan-AbbVie. **Olga Pajares** no conflicts to declare. **Andrea Gómez** has no conflicts to declare. **Jaime Rodríguez-Vico** has received honoraria from Lilly, TEVA, Novartis, Allergan-AbbVie, and Exeltis, and research support from Allergan-AbbVie.

DATA AVAILABILITY STATEMENT

Anonymized data not published within this article are available upon request from qualified investigators.

CLINICAL SIGNIFICANCE

BoNTA's increasing application in pain conditions, with its simpler administration technique and enhanced safety compared to corticosteroid injections, underscores its potential; however, its use in PRTH warrants cautious consideration and is still in a preliminary stage.

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