

# OnabotulinumtoxinA injections for atypical odontalgia: an open-label study on nine patients

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**Background:** Atypical odontalgia (AO) manifests as continuous pain in the region of one or several teeth, in the absence of signs of dental pathology. Currently, there is insufficient evidence to establish treatment guidelines for AO. The aim of this study was to describe the effectiveness and safety of treatment with OnabotulinumtoxinA (OnabotA) on a series of patients with AO.

**Methods:** Nine patients with AO (four males and five females, aged between 31 and 77 years) received injections of OnabotA in the region of pain. The dosage used in each procedure ranged between 10 and 30 U, spread between 4 and 12 injection sites along the gums (n=9), the lips (n=3), and the hard palate (n=1). The median follow-up time was 27 months (interquartile range, IQR 20–40) and the median number of injection sessions per patient was seven (IQR 4.5–9). The assessment variables included the change in the maximal intensity of pain on a 0–10 numerical rating scale (NRS), the response latency, and the duration of the effect.

**Results:** All patients experienced a significant improvement, with ≥50% of reduction in the intensity of the maximal pain. The median of reduction of maximal pain after treatment was six points on the NRS (IQR 5–8.5). The response latency was 2–15 days and the duration of the effect was 2–6 months. No significant adverse reactions were registered.

**Conclusion:** OnabotA may be a safe and effective option for the treatment of AO.

**Keywords:** neuropathic pain, orofacial pain, painful trigeminal neuropathy, persistent dentoalveolar pain, persistent idiopathic facial pain, phantom tooth pain

## Introduction

Atypical odontalgia (AO) constitutes one of the multiple causes of orofacial pain, affecting up to 6% in patients following endodontic procedures.<sup>1,2</sup> According to the literature, this condition is known under several names, such as persistent dentoalveolar pain<sup>3</sup> or phantom tooth pain.<sup>4</sup> According to the third edition of the International Classification of Headache Disorders (ICHD-3), currently this condition is considered to be a subtype of persistent idiopathic facial pain. However, seeing as on occasions there is a traumatic trigger, according to the ICHD-3, this condition may also be considered to be a subform of post-traumatic painful trigeminal neuropathy.<sup>5</sup> Despite the heterogeneity in the classification and the diagnostic criteria proposed in the literature, the clinical characteristics are well defined. AO leads to a situation of continuous pain, located on one or several teeth or in the alveolus after a tooth extraction, in the absence of signs of dental illness upon examination or in the imaging tests. Within the temporal pattern of chronic pain, some patients experience acute worsening. The quality of pain is variable, and it can irradiate to the maxillary and jaw region and/or other orofacial regions.

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On occasions, hypo- or hyperesthesia and/or allodynia may exist in the symptomatic area.<sup>1</sup>

The pathophysiology of AO is not fully known, and several hypotheses have been proposed. The most supported hypothesis suggests a neuropathic origin, considering that trauma to teeth and/or periodontal structures may alter the tissue continuity and, therefore, generate changes in the periodontal nerve plexus leading to the appearance of peripheral sensitization.<sup>6</sup> This hypothesis is based on some studies of animal models of dental extraction that demonstrate that the loss of dental pulp in an inflammatory environment induces pathological changes in the periodontal plexus.<sup>7</sup> Furthermore, the abnormalities found during neurophysiological tests, for example, a decreased response of the blink reflex,<sup>8</sup> and in quantitative sensory testing<sup>9</sup> in patients with AO suggest the existence of abnormalities in the processing of trigeminal nociceptive information.

The treatment of this condition is based on the results of case series and recommendations by experts, most of which recommend the use of tricyclic antidepressants and anti-epileptics.<sup>1,6,10</sup> Nonetheless, their effect is usually insufficient and often there are tolerance problems that limit their use. Other therapeutic modalities, such as the local injection of anesthetics,<sup>11</sup> have also demonstrated inconsistent results. A therapeutic alternative could be the local injection of botulinum toxin, considering this was found to be effective in a case series of four patients published in 2016 by our own research group,<sup>12</sup> as well as one case report.<sup>13</sup>

Onabotulinumtoxin A (OnabotA) is a polypeptide that has an analgesic effect, on the peripheral level, as well as centrally.<sup>14</sup> Although its mechanism of action is not completely known, it has demonstrated to be effective in the treatment of many types of neuropathic pain, such as trigeminal neuralgia (TN),<sup>15–18</sup> post-herpetic neuralgia,<sup>19</sup> and painful diabetic neuropathy.<sup>20</sup> The aim of this study was to describe our experience with the local injection of OnabotA on a series

of nine patients, extending the follow-up of the previously reported four patients with the addition of five new patients.

## Methods

From January 2014 to April 2018, we performed a quasi-experimental, prospective, open-label, non-controlled study on a consecutive cohort of patients with a diagnosis of AO treated via local injection of OnabotA at the Headache Unit of the Hospital Clínico San Carlos (HCSC). Inclusion criteria were 1) age over 18; 2) AO according to the criteria of the ICHD-3;<sup>5</sup> and 3) stable pharmacological treatment over the previous three months with a partial or null effect. Exclusion criteria were 1) pregnancy or nursing; 2) history of drug or alcohol abuse; 3) history of a major psychiatric disorder; 4) history of an unstable medical condition (eg, neoplastic); 5) history of other chronic pain syndromes; 6) any dental or orthodontic procedures within the past three months; 7) known hypersensitivity to botulinum toxin; and 8) inability to understand and complete an informed consent or to conduct a proper record of the pain. The study received approval from the Clinical Research Ethics Committee of the HCSC, and all the patients signed the informed consent.

In this series, four patients were included from a prior study performed by our group (case no. 1–4),<sup>12</sup> extending their follow-up time. OnabotA was distributed upon several sites of the gingival mucosa in the symptomatic area, adding additional injection sites in other symptomatic regions of the oral cavity and/or adjacent facial regions (Figure 1), up to a maximum of 12 sites and a maximal dosage of 30 U. The total dose of OnabotA and the number of injection points were adapted to the extent of the painful area and to the needs of each patient. A dilution of 5 U per 0.1 mL of physiological saline solution 0.9% was performed, injecting 2.5 U per site using a sterile 30-gauge needle. Repeated procedures were performed when requested by the patients after at least 3 months.



**Figure 1** (A and B) Injection of OnabotulinumtoxinA (OnabotA) into the facial papillae of the interdental gingiva. (C) Injection of OnabotA into the labial mucosa (patient 5).

The assessment variables were the following: the minimum and maximum values of pain intensity both at baseline and after treatment (measured with the 0–10 numeric rating scale of pain, NRS), the change in the maximal intensity of pain on the NRS, the time between treatment and the beginning of the analgesic effect, and the duration of this effect from the time of the intervention. The response rate was defined as the proportion of patients showing a reduction of 50% or greater in the maximal pain. Furthermore, the adverse reactions attributable to either the procedure itself or the drug were also registered.

## Results

Nine patients were included in the study (five females and four males), aged between 31 and 77 years (median age 51 years). The median age at the beginning of the symptoms was 38 years (interquartile range, IQR, 31.5–42.5), with five of the nine patients presenting a dental extraction as a precipitating event. All subjects presented chronic dentoalveolar pain, without data of dental pathology, having been evaluated by at least one dentist, and with normal blood tests (including erythrocyte sedimentation rate and C-reactive protein) and imaging (orthopantomography and computerized tomography of the maxillofacial region). The median of maximal pain was eight points on the NRS (IQR 7.5–10). All patients had received treatment with antidepressants, antiepileptics, nonsteroidal anti-inflammatory drugs, opioids, and/or simple analgesics for over six months, without a satisfactory response. The details regarding the demographic and clinical characteristics of participants are presented in Table 1.

The nine patients received injections in the facial papillae of the interdental gingiva on the painful region. All patients with a history of dental extraction presented phantom pain in the dental alveoli of the extracted teeth; in these cases, injection sites were added in these alveoli. Furthermore, three patients received OnabotA infiltration in the subcutaneous tissue of the hemi-lip on the symptomatic side and one patient on the hard palate, as these patients presented irradiated pain to these areas. The total dosage of OnabotA per cycle varied from 10 to 30 U (median 20 U), spread out between 4 and 12 injection sites (median eight sites). The median follow-up time was 27 months (IQR 20–40) and the median number of injection sessions per patient was seven (IQR 4.5–9).

After treatment with OnabotA, all patients experienced  $\geq 50\%$  reduction in the intensity of their maximal pain so that the pain was rated between 0 and 3 on the NRS. One patient obtained a complete remission (patient no. 3) and four patients were left with intermittent mild pain (patients

no. 2, 4, 6, and 8), whereas the remainder reported mild continuous pain. The median of reduction of maximal pain after treatment was six points on the NRS (IQR 5–8.5). Furthermore, all patients experienced a reduction of the painful area and the use of drugs, to the extent that patients 1, 3, 6, and 9 were able to interrupt the use of oral medication. The response latency was 2–15 days (median, 7 days; IQR 7–14) and the duration of the effect was 2–6 months. The magnitude of reported effect remained stable, but some patients had longer duration of effect after several treatment sessions (patients 1, 2, 3, 5, and 6). No significant adverse reactions were registered.

## Discussion

AO is a therapeutic challenge as there is insufficient evidence to establish treatment guidelines or recommendations.<sup>1,2,9,10</sup> The different topical and systemic treatments that have been used show heterogeneous and often suboptimal results, as well as adverse effects that limit their use. Seeing as the most accepted pathophysiological hypothesis suggests a neuropathic origin,<sup>6</sup> it is logical to assess therapeutic alternatives with demonstrated efficiency in cases of neuropathic pain, such as the local injection of OnabotA. In this sense, our research group published a series of four cases of AO in 2016, which is included in the present series, and in which a complete or almost complete response was obtained with the infiltration of OnabotA.<sup>12</sup> Herrero-Babiloni et al reported a similar response in another patient in the same year.<sup>13</sup> In the current series all nine patients experienced significant pain relief, with a latency of 2–15 days and a duration of the effect of 2–6 months. Otherwise, none of our nine patients had significant adverse events while the case described by Herrero-Babiloni only reported mild side effects (dryness in the area of injection and facial asymmetry).

Although the mechanism via which OnabotA exercises an analgesic effect is not completely understood, it is known that the toxin degrades the SNAP-25 protein (synaptosomal-associated protein of 25 kDa), which is a type of SNARE protein (soluble N-ethylmaleimide sensitive factor attachment protein receptor) necessary for the exocytosis of certain neurotransmitters in the terminal axon. In this manner, the liberation of local nociceptive neuropeptides and neurotransmitters such as calcitonin gene-related peptide, substance P, bradykinin, and glutamate is inhibited, which leads to a reduction of the peripheral pain sensitization. Other complementary mechanisms have also been proposed, such as the decreased translocation of the transient receptor potential vanilloid

**Table 1** Demographic and clinical features of the patients included in this series

Patient no.	1	2	3	4
Sex	Male	Female	Male	Female
Age, years	31	72	53	52
Age at onset, years	24	32	38	44
Previous dental extraction	First left upper molar	No	No	No
Previous treatment	Amitriptyline, CBZ, GBP, PGB, LCS, VPA, ZNS, duloxetine	Amitriptyline, CBZ	CBZ, DPH	Ibuprofen, tramadol
Current treatment	Tramadol	Venlafaxine, clonazepam, tramadol	PGB, tramadol, metamizole	Amitriptyline, PGB
Location	Left upper dental arch and missing molar	Superior and inferior paramedian dental arches	Right upper dental arch	Left lower dental arch
Spread of the pain	Left lower dental arch (exacerbations) and hard palate	Upper lip (continuous)	Ipsilateral pre-auricular region (exacerbations)	Ipsilateral jaw (continuous)
Quality	Dull, throbbing	Burning	Pressing, throbbing	Throbbing
Temporal pattern	Continuous with exacerbations	Continuous	Continuous with exacerbations	Continuous with exacerbations
Intensity (NRS)	8–10	7	1–10	2–8
Injection sites <sup>a</sup> (no. of injection points)	Left upper gum (4), left lower gum (4) and hard palate (2)	Upper gum (4), lower gum (4) and upper lip (4); paramedian distribution	Right upper gum (6)	Left lower gum (8)
Total no. of injection points	10	12	6	8
Total dosage OnabotA (U)	25	30	15	20
Latency for analgesic effect (days)	7	10	14	7
Intensity of pain after injections (NRS)	1	0–2	0	0–2
Duration of analgesic effect (months)	3–5	3–4	2–4	6
Follow-up (months)	48	48	32	28
No. of injection sessions	10	10	8	8
Interval between sessions (months)	3–6	3–7	3–7	3–7
Adverse effects	No	No	No	No

**Notes:** <sup>a</sup>Gums were injected at the facial papillae over the symptomatic area, with additional injection points in the dental alveoli in patients with previous dental extraction and pain in the missing tooth/teeth. NRS: 0, no pain; 10, the worst imaginable pain.

**Abbreviations:** CBZ, carbamazepine; DPH, phenytoin; ESL, eslicarbazepine; GBP, gabapentin; LCS, lacosamide; NRS, numeric rating scale of pain; OnabotA, OnabotulinumtoxinA; PGB, pregabalin; VPA, valproic; ZNS, zonisamide.

1 (TRPV1). The decrease in the peripheral sensitization leads to a decrease in the central sensitization, with the corresponding reduction in pain.<sup>14</sup>

Our results and those of Herrero-Babiloni et al<sup>13</sup> are in consonance with those described in other cases of neuropathic pain treated using OnabotA. In 2016, a meta-analysis was published that included four randomized controlled clinical trials (RCTs), in which a greater effectiveness was reported for the control of pain using OnabotA when compared to the use of a placebo in the treatment of the TN.<sup>17</sup> The latency of the therapeutic effect was 1–2 weeks, the duration of the effect was less than three months, and no severe adverse effects were registered. The dosage of injected OnabotA varied between 25 and 100 U, although one of the RCTs included found that low dosages (25 U) had a similar effect to high dosages (75 U).<sup>18</sup> Furthermore, in an open clinical trial not included in the meta-analysis, a clinical response was observed with even lower dosages of OnabotA.<sup>15</sup> All these characteristics were similar in our study, as well as in

RCTs of OnabotA in post-herpetic neuralgia<sup>19</sup> and diabetic neuropathy.<sup>20</sup>

## Conclusion

Our study suggests that local injections of OnabotA may be an effective and safe therapeutic option for the treatment of AO. Nonetheless, further RCTs are needed to corroborate these findings with a greater level of scientific evidence. Moreover, future studies could help to determine the influence of the patients' clinical and demographic characteristics or the presence of pain-related biomarkers on the therapeutic response. Furthermore, it would be interesting to explore the effect of OnabotA in other orofacial pains of the spectrum of persistent idiopathic facial pain.

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5	6	7	8	9
Male	Male	Female	Female	Female
51	46	48	42	77
31	46	33	41	40
Third left lower molar ESL	No Ibuprofen, metamizole	Left upper molars CBZ, ESL	Second left lower molar Ibuprofen, metamizole	First left lower molar ESL
GBP, fluoxetine	Oxicam, tramadol	Amitriptyline	Ibuprofen, metamizole	GBP
Missing molar and left side of lower lip	Right lower dental arch	Left upper dental arch and missing molars	Missing molar	Missing molar
Left lower dental arch (continuous)	Ipsilateral mandibular angle	Left side of upper lip (exacerbations)	No	Left lower dental arch
Pressing Continuous	Electric Continuous with exacerbations	Pressing Continuous with exacerbations	Throbbing Continuous with exacerbations	Dull Continuous
5–8	8–10	2–10	5–8	4
Left lower gum (6) and left side of the lower lip (2)	Right lower gum (6)	Left upper gum (6) and left side of the upper lip (2)	Left lower gum (4)	Left lower gum (6)
8	6	8	4	6
20	15	20	10	15
14	15	7	2	7
1–3	0–3	1–2	0–3	2
4–5	3–6	3	3	3
27	22	22	18	12
7	5	5	4	4
3–5	3–6	3–9	3–6	3
No	No	No	No	No

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## Disclosure

The authors report no conflicts of interest in this work.

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