Case Reports in Neurology

Case Rep Neurol 2023;15:192–198
DOI: 10.1159/000532096
Received: April 26, 2023
Accepted: July 17, 2023
Published online: August 22, 2023

Case Report

Botulinum Toxin-A for the Treatment of Neuropathic Pain after Decompressive Craniotomy in Stroke: Two Cases

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Keywords
Neuralgia · Botulinum toxin-A · Stroke · Case report · Craniotomy

Abstract
Botulinum toxin-A (BoNT-A) is recommended as third-line off-label treatment for the management of neuropathic pain. BoNT-A has been reported as treatment for different neuropathic pain conditions; however, not for neuropathic pain after decompressive craniotomy for stroke. The aim of this retrospective case series is to provide information on safety, the effect, and the application method of BoNT-A in clinical practice for the treatment of neuropathic pain after trepanation. This case series describes 2 patients treated in 2021 at a BoNT outpatient clinic for chronic neuropathic pain at the incisional site after decompressive craniotomy for stroke who were resistant to pain medication. Cases were a 48-year-old woman and a 63-year-old man suffering from chronic neuropathic pain since 3 and 6 years, respectively. They were treated regularly with BoNT-A with a total dose of 100 mouse units of incobotulinumtoxin-A injected into peri-incisional sites of the scalp. Both patients reported subjective decrease in pain frequency (40% and 60%), in pain intensity (60% and 90%), and an increase of quality of life (80%). BoNT-A should be further investigated as treatment for neuropathic pain – especially in underreported conditions such as neuropathic pain after craniotomy in stroke.

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Introduction

Neuropathic pain substantially affects quality of life and mental health [1]. Botulinum toxin-A (BoNT-A) is widely used in the treatment of neurological conditions. It has been approved for the treatment of involuntary muscle hyperactivity such as limb spasticity, blepharospasm, hemifacial spasm, cervical dystonia, or neurogenic detrusor overactivity and for autonomic disorders such as primary hyperhidrosis [2]. In general, its use is safe when applicated by trained and authorized medical personnel [2]. In movement disorders, the relaxation of hyperactive muscles is probably responsible for pain relief. BoNT-A might induce an analgesic effect independent of muscle relaxation, and experts recommend BoNT-A as third-line pharmacological treatment for neuropathic pain [3–5]. However, the only approved pain indication so far, is chronic migraine [4, 6].

Clinical trials have reported the safety and efficacy of BoNT-A injections for pain reduction in various neuropathic pain syndromes. The best evidence is available for trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy [6–8]. However, strong evidence is still missing including data for optimal dose, injection site, and the duration of the effect. Here, we report 2 cases of patients with peri-incisional neuropathic pain after trepanation for malignant ischemic or hemorrhagic stroke treated with BoNT-A. To our knowledge, the use of BoNT-A to treat neuropathic pain at the craniotomy site has never been described.

Case Report

All adult patients treated with BoNT-A between January 1, 2021, and December 31, 2021, at a BoNT outpatient clinic (Landesklinikum Horn-Allentsteig) in Austria, were retrospectively reviewed for neuropathic pain in the region of the head. In the context of this study, we defined neuropathic pain as pain described by the patients with typical words such as burning or sudden sharp, short-lasting pain attacks in addition to the presence of allodynia or hyperalgesia triggered by a thermal or mechanical stimuli. Furthermore, the presence of allodynia/hyperalgesia had to be demonstrated during the clinical visit by a slight touch with the fingertip.

Subjective changes in pain intensity, pain frequency, and quality of life were assessed using a visual analog scale (range: 0–100%). These simple and unspecific scales were selected because the assessments had to be applicable for the large range of conditions routinely treated at the BoNT outpatient clinic including patients with communication deficits such as poststroke aphasia.

This study was approved by the Ethics Committee of the University for Continuing Education Krems (EK GZ 06/2021-2024). Written informed consent for publication was obtained from the patients.

Overall, we identified 5 cases, three with trigeminal neuralgia and two cases with neuropathic pain after decompressive craniotomy for malignant ischemic or hemorrhagic stroke (Table 1). Because there is some evidence from small randomized controlled trials on the efficacy of BoNT-A on trigeminal neuralgia [8], we focus here on the 2 cases with craniotomy. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532096).

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Table 1. Characteristics of 2 patients treated with incobotulinumtoxin-A for neuropathic pain after craniotomy

	Case 1	Case 2
Sex	Female	Male
Age, years	48	63
Diagnosis	ICH, basal ganglia	Malignant MCA infarction
Stroke date	03/2018	05/2015
Pain onset	3 months poststroke	6 weeks poststroke
First BoNT-A injection	06/2021	05/2019
Pain medication (ongoing)	None	AEDs, ADepr
Total dose BoNT-A (MU)	100*	100
Inter-injections interval, weeks	12	8
Change pain frequency, %	−60	−40
Change pain intensity, %	−90	−60
Change QoL, %	80	80

ADepr, antidepressants; AEDs, antiepileptic drugs; BoNT-A, botulinum toxin-A; ICH, intracerebral hemorrhage; MCA, middle cerebral artery; MU, mouse units; QoL, quality of life.

*The patient is treated with another 600 MU for the treatment of spasticity in the left upper and lower extremities.

Case 1

A 48-year-old woman presented with a history of intracerebral hemorrhage in the basal ganglia on the right side which was treated surgically by osteoclastic decompressive craniotomy. Clinically, the patient presented a severe arm-accentuated hemiparesis left and a neglect syndrome. The patient is able to walk without aids, there is a slightly unsteady spastic-ataxic gait pattern with circumduction on the left and balance deficits, and for longer distances she uses a cane or a wheelchair. Approximately 3 months after the craniotomy, she experienced a tingling, burning pain in the area of the craniotomy site, which was present permanently and aggravated by light touch.

During an inpatient stay at the rehabilitation center 3 and a half years after stroke, the indication for botulinum toxin therapy was given for spasticity of the left upper and lower extremities. Initially, 500 mouse units (MU) of incobotulinumtoxin-A were injected, later dosage was 600 MU.

Neuropathic pain could not be significantly reduced by administration of antiepileptic drugs, antidepressants, opioid analgesics, cannabinoids, local capsaicin cream, or transcutaneous electrical nerve stimulation. Therefore, BoNT-A was chosen as therapy for refractory neuropathic pain.

The neuropathic pain area on the right frontotemporal side of the skull was well demarcated and BoNT-A was injected according to the following scheme: 5 MU of incobotulinumtoxin-A at intervals of 1 cm intracutaneously. A total of 100 MU were injected and distributed over the pain area. The effect of BoNT-A started 8 days after injection and lasted 3 months. The patient reported a subjective decrease in intensity (90%) and frequency (60%) of neuropathic pain; quality of life increased by 80%. In the meantime, a total of three treatment cycles took place with individual inter-injection intervals of 11–14 weeks. The good clinical effect could be reproduced with no change of the injection regimen.

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Case 2

A 63-year-old man presented with a history of osteoclastic decompressive craniotomy after malignant middle cerebral artery infraction. Clinically, he presented with a residual mild right hemiparesis and motor aphasia. The patient was able to walk without any aids. Neuropathic pain in the left frontal craniotomy area occurred approximately 6 weeks after craniotomy. The pain was described as burning, suddenly piercing, and stabbing; it was constantly present and aggravated by light touch and temperature change. Neither antiepileptic nor antidepressant drugs reduced pain. Four years after craniotomy, the first injection of BoNT-A was administered according to the following scheme: 5 MU of incobotulinumtoxin-A at intervals of 1 cm intracutaneously. A total of 100 MU were injected, distributed over the pain area at the left front of the skull (Fig. 1). The effect of BoNT-A started about 5 days after injection and lasted nearly 8 weeks. The patient reported a subjective decrease in intensity (60%) and frequency (40%) of neuropathic pain; quality of life was increased by 80%. Since the effect of treatment lasted only 8 weeks, the injection interval was adjusted accordingly. In total, the patient has had 12 treatments with BoNT-A so far. The effect is still given to the same extent, the dosage of BoNT-A did not have to be increased over time. In both patients, no adverse events or side effects were reported after repeated administration.

Discussion

To our knowledge, these 2 stroke cases are the first demonstrating the pain-relieving effect of BoNT-A in patients suffering from chronic neuropathic pain after decompressive craniotomy refractory to previous pharmacological treatment. Decompressive craniotomy is used as treatment for malignant intracranial pressure in neurological emergencies such as malignant middle cerebral artery infarction or traumatic brain injury. It has been shown to reduce mortality significantly, however leaves the surviving patients often with severe disability and dependency [9]. So far, the occurrence of neuropathic pain after decompressive craniotomy has not been reported systematically and its prevalence is unclear. This is however not surprising in view of more prominent sequels such as persistent severe functional deficits, seizures, or the sunken flap syndrome, i.e., the development of new neurological symptoms associated with sunken skin at the craniectomy site. Clinicians may not specifically look for neuropathic pain or document these symptoms under more general terms such as headache or pain. Despite the high morbidity after decompressive craniotomy, surveys suggest that a number of patients and caregivers might have adapted to the situation and are satisfied with their postoperative quality of life [9]. Neuropathic pain has a large impact on quality of life and its treatment may thus contribute to long-term well-being of these patients.

The underlying mechanism for neuropathic pain after craniotomy is not clear but may be similar to other conditions where BoNT-A has successfully been applied. Successful BoNT-A treatment has been reported for the treatment of chronic post-craniotomy headache and pain in 2 case series with a total of 7 patients [10]. One of these cases might be comparable to the 2 stroke cases. It reports BoNT-A injections in the peri-incisional region of a patient with chronic post-craniotomy headache after traumatic brain injury [11]. However, post-craniotomy headache is not confined to neuropathic pain, includes different etiologies, and the choice of the optimal analgesic treatment may vary accordingly.

The 2 cases reported here share characteristics and probably pathophysiological mechanisms with cases of secondary nummular headache where the symptoms were attributed to an underlying structural lesion. There is some evidence from cases series on successful treatment of nummular headache with BoNT-A [12].

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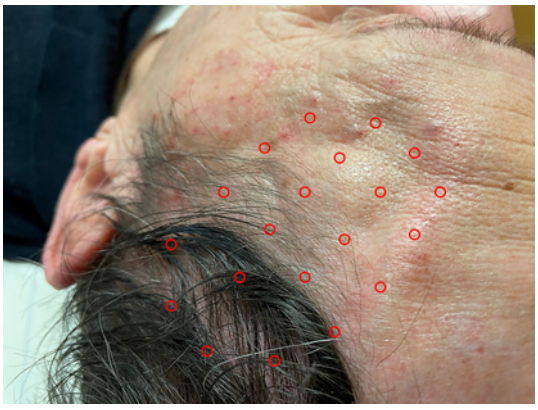

Fig. 1. Injection sites used for BoNT-A. Picture of a 63-year-old man who presented with neuropathic pain at the incision site of osteoclastic decompressive craniotomy after malignant middle cerebral artery, 6 years ago. Circles mark the injection of 5 MU incobotulinumtoxin-A. The patient gave his consent to use his picture.

Furthermore, neuropathic pain is often reported after surgery [13]. This may result from nerve damage during the procedures but may also result from other processes including nerve entrapment within the scars. BoNT-A is used in the prevention and treatment of scars and has been shown to be effective in relieving itching and pain associated with pathological scars [14]. The 2 patients described here reported no itching at the incision site.

The major advantage of BoNT-A compared to classic analgesic drugs is its long-lasting but reversible effect after a single injection, especially in cases where neuropathic pain is refractory to medical management [2, 5]. Despite the reoccurrence of pain after 8–12 weeks, both patients reported important pain relief and returned for further injections.

The exact mechanism of analgesia caused by BoNT-A is still unclear but evidence supports that the action of BoNT-A is not limited to peripheral nerve terminals and can directly affect central circuits [5]. Multiple sites of action along the pathway of pain transmission from the peripheral to the central nervous system might be involved. Apart from effects on peripheral sensory nerve endings other mechanisms have been suggested including the inhibition of the release of neurotransmitters and neuropeptides, anti-inflammatory effects, and interactions with ion channels – specifically with the transient receptor potential vanilloid 1 (TRPV1) [5]. The main site of action involved in the antinociceptive effect seems to be at the level of the segmental spinal dorsal horn and the brainstem sensory region associated with the injection area. Further particularities of BoNT-A related to pain seem to be its selectivity to certain sensory neurons such as capsaicin-sensitive neurons and its interaction with the endogenous opioid and GABA neurotransmitter system.

Because of the complex mechanism of the antinociceptive effect of BoNT-A and because of the heterogenous pathophysiology of neuropathic pain syndromes, the specific patient group that might profit from this therapy is still unclear [4, 5]. Further research is needed to identify specific subgroups of patients (e.g., according to specific combinations of symptoms) profiting from different treatment options and thereby allowing a personalized treatment of neuropathic pain [15].

While an increasing number of studies report successful treatment with BoNT-A in a variety of pain conditions, most of these studies are small and of low quality. This underlines the potential of BoNT-A to be more than a third-line off-label treatment option for specific pain conditions refractory to other pain treatment. However, further high-quality studies are needed to increase evidence for the effect of BoNT-A in pain in general and to neuropathic pain specifically.

Patients with chronic neuropathic pain at the incision site after decompressive craniotomy for stroke might be another yet unidentified population that can benefit from BoNT-A treatment. While this group of patients might not be large, it might particularly profit from an increase in quality of life.

Acknowledgments

We thank Helga Theisl and Doris Gressl for their assistance during patients visits.

Statement of Ethics

This study was approved by the Ethics Committee of the University for Continuing Education Krems (EK GZ 06/2021-2024). Patients have been informed and signed consent form for the BoNT-A treatment during the clinical routine. Due to the retrospective aspect of the study, no additional data have been collected and no treatments have been performed for the study only. Written informed consent was obtained from the patients for the publication of this report (including details of their medical case) and the accompanying image.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was obtained for this study.

Author Contributions

M.P. conceived the idea of the study and acquired and interpretated the data; Y.T. analyzed the data and drafted the manuscript; C.B., A.D., and K.M. interpretated the data and critically revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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