Uporaba botulinusnega toksina za zdravljenje glavobolov in bolečin obraza

Use of Botulinum Toxin for the Treatment of Headache and Facial Pain

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Izvleček

Botulinum toksin (BT) se pogosto uporablja v kozmetiki in klinični praksi. Ta pregled literature obravnava uporabo BT pri zdravljenju glavobolov in obraznih bolečin. Najbolj razširjena in dobro opisana ter odobrena uporaba je preprečevanje kronične migrene v odmerkih med 165 in 196 IE. Po naključnem odkritju je bila potrjena z več raziskavami RCT, predvsem s študijo PREEMPT. Po potrditvi je bila BT odobrena za uporabo pri zdravljenju kronične migrene. V skladu z veljavnimi smernicami se BT uporablja za preprečevanje kroničnih migren pri bolnikih, ki so odporni na druge oblike zdravljenja, npr. triptane ali nesteroidna protivnetna zdravila. Najpogosteje uporabljen protokol vbrizgavanja, ki je bil določen v študiji PREEMPT, priporoča 31–39 mest vbrizgavanja. Pri drugih primarnih

Abstract

Botulinum toxin (BT) is widely used in cosmetics and clinical practice. This literature review explores the applications of BT for the management of headaches and facial pain. The most widespread, well-reported, and ALIMS and EMA approved application for BT is in preventing chronic migraine at doses between 165–196 IU. After an incidental discovery, BT was validated through several RCTs, including most notably, the PREEMPT study. Following validation, BT was approved for use in treating chronic migraines. According to current guidelines, BT is used for the prevention of chronic migraines in patients who are resistant to other forms of therapy, such as triptans or NSAIDs. The most widely used BT injection protocol was established in

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glavobolih, kot so glavoboli tenzijskega tipa, je dokazov o učinkovitosti BT malo in so zmedeni. Pa vendar nekatere manjše študije poročajo, da je BT učinkovitejši od placeba in izboljša bolečino pri trigeminalnih avtonomnih glavobolih. BT se uporablja tudi pri kronični obrazni bolečini, predvsem trigeminalni nevralgiji, pri čemer so rezultati raziskav RCT spodbudni. Čeprav je glavni mehanizem delovanja BT zaviranje sproščanja acetilholina iz terminalnih holinergičnih živcev, je treba pojasniti še bolj specifične mehanizme lajšanja bolečine, zlasti pri migrenskih glavobolih. Po pregledu ustrezne literature je mogoče zaključiti, da je zdravljenje z BT varno, na splošno dobro prenašano in učinkovito.

the PREEMPT study and recommends 31–39 injection sites. In other primary headaches, such as tension-type headaches, there is little and confounded evidence of the efficacy of BT. However, some small-scale studies reported that BT outperformed placebo and improved pain in trigeminal autonomic headaches. BT is also used to treat chronic facial pain, most notably trigeminal neuralgias, with encouraging results in RCTs. While the primary mechanism of action of BT is the inhibition of acetylcholine release from terminal cholinergic nerves, more specific mechanisms of pain relief are yet to be elucidated, especially for migraine headaches. Our review of relevant published literature indicates that BT therapy is safe, generally well-tolerated and efficacious, and is a viable option for the management of certain primary headaches and chronic facial conditions.

INTRODUCTION

Botulinum toxin (BT) is a neurotoxic protein product of the bacillus Clostridium botulinum that induces muscle inactivity by releasing acetylcholine in cholinergic neurons (1). BT was discovered in the 14th century and first obtained in significant concentration in mid-20th century. BT was approved for the treatment of strabismus by the US Food and Drug Administration (FDA) in 1989 (2), which marked the beginning of its therapeutic use. The most common indications for the use of BT are focal and segmental dystonia (e.g., blepharospasm, cervical dystonia), muscle spasms, and in aesthetic medicine. BT is also indicated for hyperhidrosis, urinary incontinence, and migraines that have not responded to previous therapeutic approaches (3).

The use of BT is based on its inhibitory effects on the release of acetylcholine from presynaptic cholinergic neurons, which further affects the muscles or glands (3). BT is naturally found in seven serotypes (A–G), but only types A and B are used in therapy. Ona-, abo- and incobotulinumtoxinA and rimabotulinumtoxinB are four types of BT in wide clinical use and approved by the US FDA (3). Form A (Botulinum Toxin A – BTA) is the most widely used and most clinical applications are based on that variant (1). It is important to note that the forms and doses of different forms of BT are not equivalent.

Headache is one of the most common conditions in the general population (4), and about two-thirds of adults reported headaches in the previous year, most without further treatment or diagnosis (1). Migraine headaches are among the most disabling headaches and have a negative impact on quality of life (3). Headaches are classified according to the International Headache Society (5) system (ICHD-3 System) into primary (idiopathic) and secondary headaches. Primary headaches are divided into migraine, tension headaches, and trigeminal autonomic cephalgia (TAC), which includes the so-called cluster headache. Secondary headaches have different aetiologies, including cerebrovascular, traumatic, or headaches caused by neck pathologies and other maxillofacial structures, ear, larynx, sinus, and nose (5).

After the accidental discovery that BT has a positive effect on reducing headaches, its use in pain treatment was investigated (6). Since 2010, BT has been used

for the prevention of chronic migraines that do not respond to other forms of therapy (3).
BT is also used for chronic facial pain caused by trigeminal neuralgia, temporomandibular joint, and dental pain (3). The use of BT to treat headaches and facial pain has increased since the discoveries made in 2010, with multiple clinical trials, both approved and off-label uses, reported in the literature (6, 7). The mechanisms of action of BT in pain treatment are not fully understood, although recent discoveries provide some explanations (6). This report reviewed the relevant literature and details the therapeutic use of BT in headaches and facial pain.

PHARMACOLOGY AND MECHANISMS OF ACTION OF BOTULINUM TOXIN

BT is the product of the anaerobic Gram-positive bacillus, *Clostridium botulinum*, with seven serotypes that each have a distinct molecular structure. Serotypes A and B are used in the pharmaceutical form. The neurotoxin complex is composed of a toxin (molecular weight of 150 kDa) and a non-toxic protein complex that protects the toxin from deactivation by deactivating factors. The toxin itself (Figure 1)

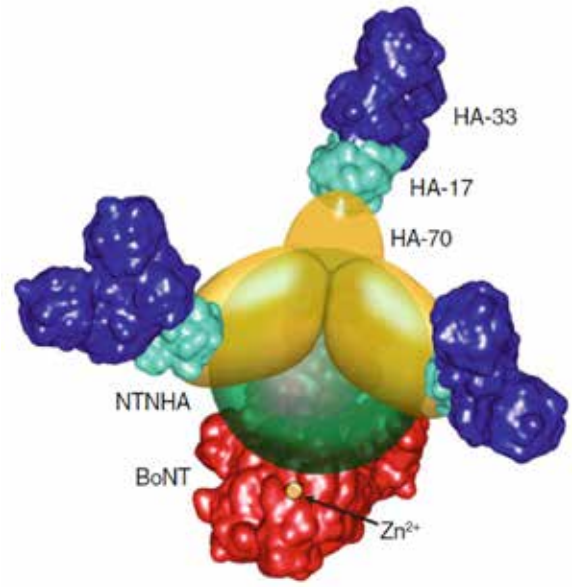

Figure 1. *Molecular structure of BT, based on Jabbari. (3)*

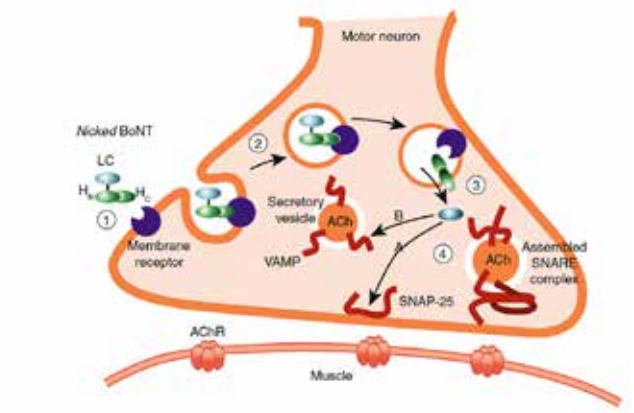

Figure 2. *Synaptic action of BT on the neuromotor plate (schematic), based on Jabbari. (3)*

consists of a heavy chain (HC) of 100 kDa (kilodalton) and a light chain (LC) of 50 kDa bound by a single disulfide bond. The HC contains the protein binding and translocation domains, while the LC is a catalytic domain (3).
Within one minute of intramuscular injection, the toxin dissociates from the protein complex and activation occurs. Serotypes A and B have different membrane receptors, and the toxin is released into the endosome, where the disulphide bond and the HC-LC complex are dissasociated. Then, the HC domain opens a channel in the cell membrane and translocates the LC domain to the cytosol. The LC contains the chemical properties of the zinc-motif proteases and catalyses trans-membrane SNARE complexes present in the presynaptic space. Deactivation of the SNARE complex (Figure 2) causes vesicular fusion and neurotransmitter (mainly acetylcholine) release. After several hours of neurotransmitter release,skeletal muscle weakening becomes observable; however, the clinical paralysis of the muscle becomes evident after seven days. The effect lasts 3 to 6 months. In addition to its action on the neuro-muscular surface, BT binds neurotransmitters on the autonomic ganglia, post-ganglionic sympathetic nerve impulses, and post-ganglionic parasympathetic nerve impulses (8).
The effect of BTA on headaches can be observed on four levels. At the level of axonal transport and transcytosis, model studies suggest the effect of BTA

on anterograde and retrograde axonal transport from nerve terminals to adjacent neurons and glial cells. Injections into M. occipitalis, near N. Occipitalis minor and major, indirectly affect the nociception of the cerebral sheaths. At the neurotransmitter inhibition level, BTA inhibits the release of other neurotransmitters associated with migraine, such as CGRP (Calcitonin gene-related peptide, a migraine mediator), supplement P and glutamate, as well as serotonin, GABA (gamma-aminobutyric acid), norepinephrine, dopamine, and glycine. At the level of neuromodulation, BTA inhibits the expression of several nociceptive receptors (TRPV1, TRPA1, PRX3, TRPM8 and GABA-A), with an agonistic effect on μ-opioid receptors. On the fourth level, BTA modulates cytokines via the anti-inflammatory inhibition of pro-nociceptive interleukins and the stimulation of anti-nociceptive interleukins, which play a role in the inflammatory component of migraine pathophysiology (1).

Initial assumptions that the analgesic effects of BT rest on myorelaxation, leading to the decompression of local blood vessels, are changing in the light of new research. The analgesic action of BT is also considered to be due to its direct action on sodium channels and its ability to reduce the pain-mediating effect of Substance P. Migraine studies have shown that BT acts on the pain mediators Substance P, calcitonin-generated peptide (CGRP), and glutamate, which are essential for the development of migraine (9).

The pharmaceutical form of BT depends on the serotype and the manufacturer. BOTOX® by Allergan will be described here according to the Summary of Medicinal Product Characteristics of the Agency for Medicinal Products and Medical Devices (ALIMS). The medicinal product is available in doses of 50, 100 and 200 units per 0.1 mL. The medicinal product is a white powder that is hardly noticeable at the bottom of the bottle. The reconstituted dilution is clear or slightly yellow. The drug is reconstituted with sterile saline, without preservatives. ALIMS recommends using a bottle with 100 units for easier reconstitution (10). Information on administration in specific cases is provided in the following text.

When used correctly, the adverse effects of BT are rare and minimal. Such adverse effects are related to the injection site itself and to the rare occurrence of systemic adverse effects such as muscle weakness or difficulty swallowing. The text below will provide information on specific adverse effects for different indications. However, BT is considered a drug that is generally well tolerated, and it is significant in treating chronic conditions such as migraines (11).

USE IN HEADACHES

Migraine

Migraines; i.e. migrainous headaches, are among the most painful conditions, with significant representation in the world population (12). Migraines are more prevalent in females at a female-to-male ratio of 2:1 and are most often seen in individuals between 35 and 45 years of age (12). Migraines are presented as frontotemporal headaches with lateralisation (1). The main categorisation of migraines is based on the presence of aura; i.e. sensory changes. Twenty percent of migraines are presented as classic migraines with aura, and the rest are migraines without aura (5). The ICHD-3 system further defines the diagnostic parameters of migraine as episodic or chronic. Chronic migraines are considered migraines where the headache is present for 15 days per month, with migrainous characteristics present for eight of the 15 days (5). Other migraines are considered episodic. The most severe forms of migraine are accompanied by significant changes in vital functions (blood pressure, heart rate, respiratory rate) that must be monitored (13). Although less frequent, chronic migraines are associated with significant health and psycho-social-economic consequences and a significantly lower quality of life (1).

Migraine treatment is carried out in three phases: preventive measures, such as lifestyle changes and the elimination of the triggers; prophylactic treatment; and acute treatment (1). During the acute treatment of migraines, NSAIDs (non-steroid anti-inflammatory drugs) and triptans are used in treating minor cases (3). The use of triptans is limited by cardiovascular comorbidities (3). Topiramate, beta-blockers, histamine and BT can used for prophylaxis.

Newer drugs include CGRP-specific monoclonal antibodies, which act directly on 5-HT receptors in the trigeminovascular nerves, preventing the onset of migraine attacks (14).

Clinical studies on BT for migraines

The potential efficacy of BT for the treatment of migraine was accidentally revealed by patients receiving BTA injections for the aesthetic treatment of facial wrinkles and who experienced the coincidental relief of migraines. Such accidental findings initiated the first open-label clinical trial of BTX-A on 106 patients in 2000. As a key result of that trial, out of 77 patients with the most significant diagnostic criteria for migraine, 36 reported complete elimination of headaches. Although promising, the results of that study were limited by the study design itself, the selection of the study population, and the random categorisation of migraine, as well as by the use of inconsistent methods for measuring improved responses (15). The results of the trial were also used as the basis for the first double-blind, randomised, placebo-controlled clinical trial of BTA.

The use of standardised doses (25 and 75 IU) and standardised pericranial injection sites points to the validity of the aforementioned clinical trial. Patients were assigned to two treatment groups, numbers 2 and 3, which received doses of 25 IU and 75 IU, respectively, and a control group (number 1, placebo). Patients in group 2 reported a reduction in the number of migraines over a month and a reduction in the intensity of migraines, while such improvements were not observed in group 3. No significant adverse events were observed (15).

The two PREEMPT studies on the use of BTA for migraines have been the most important clinical studies confirming the efficacy of BTA (ona-BTA) as a prophylaxis for chronic migraines. However, those studies had limitations. The PREEMPT 1 study was set up as a 24-week randomised, double-blind clinical trial, followed by a 32-week open-label phase, conducted on males and females aged 18–65 years with chronic migraine identified according to the criteria of the then-current ICHD2 standard (16). Ona-BTA was injected in 31 sites on the face and neck according to the protocol, which has since been called the PREEMPT injection protocol. The primary objective of the first PREEMPT study was the mean improvement in the number of headache episodes. That objective was not achieved, while the secondary objectives were achieved. Therefore, the first PREEMPT study was characterised by a high degree of placebo effect. The PREEMPT 2 study aimed to establish a mean improvement in the monthly frequency of headaches and was successful. The pooled analysis showed a statistically significant ($p \leq 0.0027$) advantage of OntobotulinumtoxinA over placebo for the entire 24 weeks of treatment, in terms of the mean improvement in relation to the initial number of headache episodes per month, headache episodes described as moderate, headache episodes, and migraine episodes (16). Additional analyses showed that while the frequency of headaches had not significantly changed in patients with headaches, the severity of headaches did change. Thus, that clinical study showed that patients who received BTA therapy experienced less headache pain measured by the Headache Impact Test 6 (HIT-6) and an improvement in the Migraine-Specific Quality of Life (MSQL) score. Of the adverse events, 4% of patients in the treatment group reported neck pain, 2% reported musculoskeletal pain, and 1% experienced blurred vision (17). Although the PREEMPT studies demonstrated the efficacy of BTA for migraine treatment, the placebo effect was significant and raises questions about the validity of the data (16). The PREEMPT studies, as well as the multinational, open-label COMPEL study, which investigated the clinical benefits of long-term BTA therapy for chronic migraine for two years, confirmed the results of PREEMPT and provided sufficient authoritative evidence for the broader use of BTA as migraine prophylaxis and the foundation for regulatory BTA approvals by the world's major regulatory authorities (16), such as the FDA (2010) and the European Medicines Agency (EMA) in 2010. The FDA established chronic migraine prophylaxis (>15 headache days per month) as an indication for the use of Ont-BTA. Approval in the EU was based on inter-institutional recognition via the Irish regulator.

Indications, however, may differ slightly between member states or may be based on preventing chronic migraines (16). The Serbian ALIMS approved the use of Botox® produced by Allergan Pharmaceuticals in 2021 for multiple indications, of which the most significant was the "alleviation of symptoms in adults with chronic migraine, who meet the criteria for diagnosis (≥15 headache days per month, of which at least eight days with migraine headaches) and patients who do not respond adequately or are intolerant to migraine prophylaxis drugs" (10).

Therapeutic application, protocols, tolerance and therapy efficacy

Several therapeutic guides, including the one by the European Headache Federation, recommend BTA to prevent chronic migraines as one of the two recognised and approved methods, especially in cases where patients do not respond to other therapies or do not tolerate other forms of treatment. The European Headache Federation considers that the evidence for BTA use for chronic migraine is high and that the treatment is effective and well tolerated by patients (18). The same guideline recommends BTA use in patients in whom at least two to three migraine prophylaxis regimens have not been effective, excluding contraindications due to comorbidities. The guideline illustrates the overuse of drugs, especially analgesics in migraine patients, and recommends detoxification before BTA use. The guideline recommends using headache calendars to evaluate the response to continued treatment by comparing the four weeks before and four weeks after each treatment cycle. Discontinuation of the treatment is recommended in patients with less than ten headache days over three months. Re-evaluation is recommended 4–5 months after the discontinuation of therapy (18).

The main injection techniques are categorised as fixed injection sites to track the number and location of injections and "follow-the-pain" techniques that use asymmetric injection sites that are oriented towards the pain sites reported by the patient. Combined techniques use fixed injection sites in the frontal regions, but use supplementary injections for pain monitoring and are characterised by a higher BTA dose. Of the established injection protocols, the most widely used in the literature is the protocol of fixed injection sites defined in the PREEMPT study – the PREEMPT injection protocol (9). This protocol is also recommended by the European Headache Federation (18).

The PREEMPT protocol recommends a dose of 155–195 U of Ont-BTA as intramuscular injections in 0.1 mL (5 IU) into 31 to 39 sites in muscular regions (Figure 3): M. corrugator, 10U at two sites; M. procerus, 5U per 1 site; M. frontalis, 20U per 4 sites; M. temporalis, 40–50U per 8–10 sites; M. occipitalis, 30–40U per 6 to 8 sites; cervical paraspinal muscle group, 20 U per 4 sites, and M. trapezius, 30–50U per 6–10 sites. All muscles should be bilaterally injected, except for M. procerus, which should be injected only in a single central place. The recommended treatment period is every 12 weeks (16).

Cilinical stuidies of migraine consider higher doses more effective and indicated for patients who do not improve with lower doses. Additional doses over 195 IU are indicated in protocols for pain management, where the use of conventional injection sites is also recommended, except for the temporal muscle, where two additional injection sites are recommended. It is recommended to avoid additional injection sites in the M. trapezius (19).

Other injection protocols, such as the one developed at Yale University, with 23 injections and a total dose of 165 IU, emphasize the injections into the temporal muscle but exclude the M. trapezius completely. There are discrepancies between authors regarding whether injections into the temporal lobe result in a greater number of unwanted events, such as muscle weakness (3). The choice of injection protocol and whether to increase the dose above that prescribed by the PREEMPT protocol is individual and depends on patient factors, such as the anatomical characteristics of the patient, the patient's tolerance, and the occurrence of adverse effects such as post-procedure main (9). Studies suggest that the therapeutic results are improved when using an experienced practitioner who has a good understanding of the functional anatomy

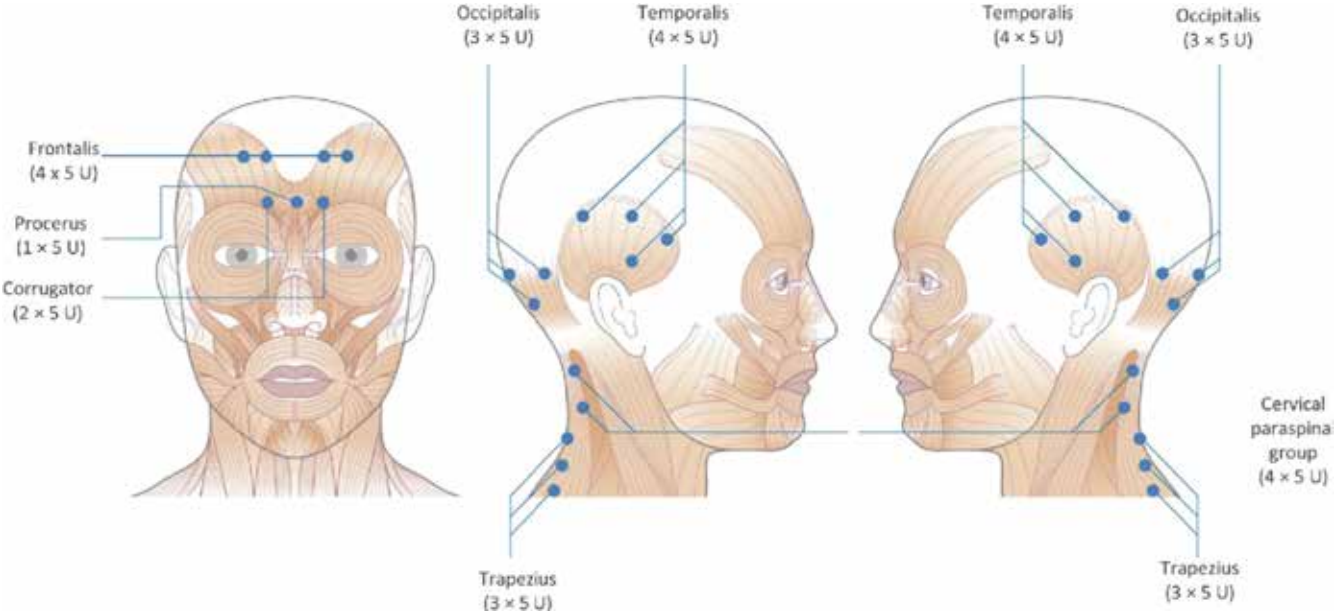

Figure 3. *Injection sites according to the PREEMPT protocol, by Tassorelli C, Sances G, Avenali M, De Icco R, Martinelli D, Bitetto V, et al. BT for chronic migraine: clinical trials and technical aspects. Toxicon. 2018; 147: 111–5.*

of the injected muscle, who has conducted a detailed examination of the patient before the injection, who monitors their side effects (pain, discomfort, muscle weakness) during the interventions, and who employs correct injection techniques (6).

Patients tolerate BTA better than other oral migraine prophylaxis drugs (6). Recent publications classified patients with chronic migraines according to their response to BT therapy, the number of days of headache, and their response to relevant treatment questionnaires (Migraine-Specific Quality of Life Questionnaire), as follows: (1) Excellent response: patients with >75% reduction in headache and who were recommended to increase the dose to 195U using a single injection protocol for three months before reducing the interval to 4 months during the following year and to cease treatment at the end of two years with the same response. (2) Good response: Patients with a 50–70% reduction in headache days, with newer protocols suggesting adjunctive new therapies. (3) Poor response: Patients with a 30–50% headache reduction with either a combination of oral prophylactics (triptans) and BT treatment being recommended for one year, or a change in therapeutic approach in favour of newer therapies (antibodies targeting CGGRP). (4) Patients without a significant response: those with <30% reduction in headache after the second treatment and the addition of oral therapy and discontinuation of BT therapy in favour of other therapeutic options (17).

Several predictive factors determine the success of BT therapy. Patients who respond better to the treatment have more implosive, but not explosive, headaches. The same applies to ocularly-located headaches and early therapy within 12 months after the diagnosis of chronic migraine (9).

BT use is best described in adults, has received regulatory approval for use in adults, and is only indicated for chronic migraines in adults. Off-label use in episodic migraines is described in the literature, but such use is sporadic, and there is insufficient data to justify extending the indication. Off-label use of BT for episodic migraines as an alternative therapy in cases of an inadequate response to other therapeutic options, however, is not unjustified, and such therapeutic

applications should follow the existing therapeutic protocols for chronic migraines. (6). Data and studies on the off-label use of BT for paediatric migraines are scarce, and there is insufficient evidence to justify such use. Nonetheless, randomised clinical trials and paediatric investigative plans for the use of BT in paediatric migraines are in progress. Such studies are being implemented to improve the knowledge and treatment of paediatric chronic migraine (20).

Tension headaches

Tension-type headaches are the most common primary headache. Symptoms of tension-type headaches include dull and irritating pain, sore head muscles and neckaches. Tension headaches are generally less intense than migraines, but they can have a devastating effect on the quality of life. Similar to migraines, tension headaches can be episodic and chronic. Chronic tension headaches have a similar incidence in about 2% of the population (5). Tension headaches are more common in females, as well as in people with a higher level of education, while the triggers include stress and other psychological factors (3). Recent experimental studies indicate that psychological conditions such as anxiety, depression and stress play a significant role in the sensitisation of sensory and neurological pathways, and disturbed nociception, possibly at the level of cholinergic, serotonergic, and inflammatory mechanisms (21). Episodic tension headaches are treated to NSAIDs and ancillary therapeutic methods such as lifestyle modification or psychotherapy. Tricyclic antidepressants and SSRI antidepressants are also used for chronic tension headaches.

In his textbook on the use of Botox for therapy (3), Jabbari details six prospective double-blind studies, of which three are classified as first-class studies according to the American classification. Similar to studies investigating migraines, the studies detailed in the textbook by Jabbari focused on chronic tension-type headaches and doses of BT between 50 and 250 IU. BT did not cause a significant improvement over placebo in any of the studies (3). Generally, studies aiming to establish the effectiveness of BT in treating chronic headaches are inconsistent. Studies on the use of BT in tension headaches are inconsistent, and while some exhibit limited study designs, overall we can observe significant differences in the doses and injection protocols used, making inferences difficult to make. Some studies have had contradictory results, and in studies with small cohorts, BT treatment caused a decrease in the average number of days of headaches in patients and a reduced need for other drug treatments (9, 22, 23). A recent meta-analysis investigating 12 clinical studies for the use of BTA in the prevention of tension headaches found no evidence that BTA injections were superior to placebo in treating severe headaches (21).

Trigeminal autonomic headaches

Trigeminal autonomic headaches are characterised by symptoms such as unilateral headache with prominent ipsilateral cranial autonomic features, lacrimation, conjunctival injections or nasal symptoms. Unilateral headache is a key characteristic of these conditions. They qualify as primary headaches, and the most prominent trigeminal autonomic headache is a cluster headache, while paroxysmal hemicrania, SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing), and SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms) headaches also fall under this category (5, 24). In pathophysiological terms, trigeminal autonomic headaches are characterised by the facilitation of the trigeminal autonomic reflex. The posterior hypothalamic region is currently considered to be crucial for the pathogenesis of trigeminal autonomic headaches since the activation of the region ipsilateral to the affected side is the focus of neuroradiological studies in patients with trigeminal autonomic headaches (24, 25).

A relatively recent systematic review of the literature (24) identified three essential studies from 2007, 2016, and 2018 that investigated the uptake of BT in treating cluster headaches. All three studies were prospective, open-label, and without a control group. Two studies used the PREEMPT injection protocol, while one used injections directly into Meckel's ganglion (Ganglion pterygopalatinum). (26). A specialised applicator was required in a trial

where BTA was administered directly to the G. pterygopalatinum as a block due to inadequate drug diffusion. (27). All three studies showed significant improvements in headache frequencies from as early as the first week after treatment, with a duration of up to 6 months. In a study where the ganglion was targeted directly under anaesthesia, the authors noted significant adverse effects in the patient, including significant bleeding, accommodative weakness of the ipsilateral eye and difficulty chewing. However, studies that used PREEMPT do not show significant adverse events thus far. Although promising, those studies have limitations ranging from a small number of participants to the lack of control groups. Future randomised, placebo-controlled studies may confirm the findings of the studies on BT use in cluster headaches. Considering the pathophysiology of cluster headaches and other trigeminal headaches, it is reasonable to assume that BT could act on the mechanisms responsible for their occurrence, both by inhibiting neurotransmitter release and pain initiation, and by reducing the peripheral sensitisation of nociceptive sensory nerve fibres. Although the studies focused only on chronic cluster headaches, it is assumed that positive therapeutic effects on episodic cluster headaches and other trigeminal headaches are possible (26).

Secondary headaches

Secondary headaches occur at close time intervals to other conditions that cause headaches, where the causal links between primary pathology and secondary headaches are well-known and established. The treatment of secondary headaches aims to treat the primary conditions that trigger the headache. A 2011 retrospective study (28) analysed previously published clinical studies investigating different types of secondary headaches, including primarily neurogenic headaches, and concluded that there is insufficient evidence to support the use of BT in treating secondary headaches. However, two small studies demonstrated that BT can be beneficial for the treatment of cervical dystonia. Following the studies, the FDA approved BT to treat cervical dystonia, a condition that may trigger secondary headaches. In cervical dystonia, injection is administered to the affected muscles, with or without electromyography or ultrasound guidance (29).

A notable, small, randomised clinical study of patients with PTSD indicated that the use of BT following the PREEMPT protocol significantly reduced the frequency of headaches and the level of pain in post-traumatic headaches in trauma veterans (30).

USE IN FACIAL PAIN

Successful facial pain therapy represents a significant challenge in modern pain medicine. Most facial pain is of neuropathic origin, and the use of BT for the treatment of this type of pain is based on the latest research. This section focuses on trigeminal neuralgia, temporomandibular pain, and conditions with sufficient relevant literature on the use of BT. It should be noted that studies on other maxillofacial conditions aside from bruxism are not included in this literature review.

Trigeminal neuralgia

Trigeminal neuralgia is a rare condition and causes one of the most excruciating pain in humans, characterised by unilateral shock-like facial pain. Although the exact prevalence of trigeminal neuralgia is unknown, females are more often affected than males. Dental problems are a frequent initial diagnosis of trigeminal neuralgia, especially when the lower trigeminal branches are involved. Neuralgia can affect any of the trigeminal nerves; however, the ophthalmic and maxillary branches are most commonly affected. The pain is short-lived; however, it has pronounced symptoms, and attacks of pain can occur multiple times per day and can be triggered by a gentle touch. Current empirical evidence suggests that the pathogenesis of trigeminal neuralgia is based on the vascular compression of the trigeminal nerve root (31). The pharmacological approach to treat trigeminal neuralgia is based on antiepileptic drugs such as carbamazepine, oxcarbazepine, or GABA-peptide, which block pain mediators, and drugs that act on GABA receptors such as baclofen, which boost inhibitory mechanisms. The simplest and most

common tool for assessing pain and the effectiveness of therapy is the VAS pain scale (32). Surgical treatment is indicated for patients who cannot manage their condition with medication alone (3).

A 2001 study, which included patients with chronic facial pain, showed that in 8 out of 11 patients, BT treatment resulted in a positive response, including reduced pain episodes (33). In his textbook, Jabbari described eight clinical studies of the efficacy of BT in treating trigeminal neuralgia, focusing on two prospective blinded studies. In the first 2012 study, 42 patients with trigeminal neuralgia participated in a 13-week randomised, parallel-designed, double-blind, placebo-controlled study. BTA, dissolved in 1 cc of saline, was injected with a 16 mm needle between the epidermis and dermis, or submucosally in the affected area, with a total concentration of 25–27 IU BTA. Patients in the treatment group showed a statistically significant ($p < 0.001$) change in the frequency and intensity of pain (VAS score). In another 2012 single-blinded study, patients were administered 40–60 IU BTA to 8–12 affected areas. A statistically significant ($p = 0.0001$) reduction in VAS score was observed 12 weeks after treatment, as was a significant improvement in quality of life and a reduced need for analgesics. (3). A 2020 meta-analysis (34) concluded that most studies on the use of BTA in trigeminal neuralgia have statistically significant and valid results supporting the use of BTA due to its positive effect on the frequency and intensity of pain, and the overall improvement in quality of life. BTA can be used alone or as an adjuvant therapy. Serious side effects include transient facial asymmetry and oedema, while mild side effects include injection site irritation and haematomas (34).

Temporomandibular joint disorders

Temporomandibular disorders (TMJ disorders) are a group of conditions related to the pathological processes of the jaw and the masticatory muscle, and can be arthrogenic (originating in the join) or myogenic (originating in the muscle). Arthrogenic prolapses are caused by inflammatory pathologies of the temporomandibular joint, while myogenic TMJ disorders are caused by pathologies of the masticatory muscles: M. masseter, M. temporalis, and M. pterygoideus lateralis. Pain is a defining characteristic of those conditions and can be either localised at the temporomandibular joint or in the masseter muscles. Conservative treatment methods are non-invasive, such as massage, warm compresses, and physical therapy. Pharmacological treatment is performed with NSAIDs, myorelaxants, tricyclic antidepressants, and antiepileptic analgesics. Surgical intervention is considered the last option for treatment (3).

A2018 study (35) used retrospective methods to establish the efficacy of BTA in treating temporomandibular joint disorders. The injection protocol used for those conditions was as follows: 100 U of BTA was injected into ten sites, three along the masseter and two along the temporalis. If necessary, the dose was increased to 150 IU or decreased to 50 IU in patients experiencing relief. The injection zones are called "trigger" zones because of the electromyogram activity, which is deemed preferable regarding the anatomical identification of the injection zones requiring more experience in administration. The study(35) exhibited encouraging results, showing that BT injections had significantly improved symptoms in 80% of patients. It was concluded that BT can be used as a line of therapy in cases where other conservative, non-invasive methods do not have a significant effect. (35).

A 2019 study focusing exclusively on myogenic conditions resulted in a positive effect in more than half of the patients and concluded that BT has a place in treating that subgroup of temporomandibular conditions, alongside other treatment options (36). However, the limitation of the discussed studies lie in a small cohort, and further studies are necessary to demonstrate and validate the use of BT in temporomandibular disorders. Expertise in BT administration is also a significant predictor of treatment success (37).

CONCLUSIONS

By reviewing the existing literature, this series attempted to detail the use of BT in treating headaches and facial pain. The largest volume of studies and the most convincing evidence has been in migraine prophylaxis. Twelve years after regulatory approval and almost twenty years since its first use, BT is effective in treating migraines that do not respond to other treatments, and there is sufficient evidence to support its clinical use. Although some authors emphasise the financial burden of using BT for migraine and question the effectiveness of the drug, there are significant data highlighting the improvements in the quality of life of patients undergoing such treatment to justify its use. The totality of evidence also suggests patients' good adherence to the treatment and minimal reporting of adverse events, which speaks in favourability of this therapy.

There is a consensus in the literature regarding significant experience in treating BT, which prevents adverse effects in multiple ways. Advances in the development of modern therapies, particularly monoclonal antibodies, as well as an understanding of migraine pathogenesis, have contributed to the improved treatment of migraine; however, there are indications that BT therapy will continue to be an essential adjuvant given its good tolerance and relative non-invasiveness.

Conversely, for other primary headaches, particularly tension headaches, there is no scientific consensus on the use of BT, and the total number of clinical studies performed to date shows no progress in the use of this therapy. BT has its place in the treatment of pathologies causing facial pain, especially temporomandibular disorders, where further clinical studies will confirm or refute the justification for the use of BT.

Although not definitive, this literature review has advanced the picture of BT use in treating headache and facial pain. Further studies are needed to support BT use for pain treatment, focusing on understanding its mechanisms of action for pain reduction.

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