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Botulinum toxin type A as an alternative way to treat trigeminal neuralgia: a systematic review

Hubert Ostrowski[1], Justyna Roszak[1], Oskar Komisarek[2]

[1]Students Scientific Society of Maxillofacial and Orthognathic surgery, University of Medical Sciences, Poznań, Poland
[2]Department of Maxillofacial Orthopaedics and Orthodontics, Poznan University of Medical Sciences, Poznań, Poland

ABSTRACT

Introduction. Trigeminal neuralgia (TN) is one of the most common neurological diseases involving the orofacial region. It affects mainly the older population, usually after the age of 60, and more commonlywomen. It involves the fifth cranial nerve and manifests as paroxysmal, unilateral, severe, shock-like or knife-like pain of from a second to two minutes' duration. Usually pain attacks arise spontaneously, but they can also be precipitated by triggers such as cold weather, brushing teeth or shaving. The ICHD-3 classification divides TN into classical, secondary and idiopathic. Current treatment includes pharmacological and surgical methods. Anticonvulsants, such as carbamazepine and oxcarbazepine, are the first line therapy. Microvascular decompression is the most common and most effective way to treat TN surgically. However, none of these methods is free from complications. Moreover, 25–50% of patients became refractory to drug therapy. Some studies have shown that a new therapy that uses a Botulinum toxin type A can be a safe and effective way to treat trigeminal neuralgia.

Methods. Literature from the PubMed base and the Main Medical Library from the last 18 years was analysed. Forty-three items were obtained; after verification, seven articles were included.

Aim of the study. To look at current guidelines about treating trigeminal neuralgia with Botulinum Toxin type A in patients who are refractory to drug therapy or who do not want to undergo surgical treatment.

Conclusion. BoNT-A therapy is a safe and effective method of treating trigeminal neuralgia.

Key words: trigeminal neuralgia, neuropathic pain, trigeminal nerve, botulinum toxin

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Introduction

Trigeminal neuralgia (TN) is one of the most common neurological pains involving the orofacial region. Epidemiological studies have shown that approximately 4 to 28.9/100,000 persons worldwide experience TN. It affects mainly the older population, usually after the age of 60, and is more common in women than in men [1, 2]. It involves the fifth cranial nerve and manifests as paroxysmal, unilateral, severe, shock-like or knife-like pain lasting between a second and two minutes. Usually pain attacks arise spontaneously, but they can also be precipitated by triggers such as cold weather, brushing teeth or shaving [3].

IHS Classification ICHD-3 divides TN into classical, secondary and idiopathic.

There are two types of classical TN: purely paroxysmal (without persistent background facial pain); and with concomitant continuous pain (with persistent background facial pain). Classical TN is mainly caused by vascular compression.

The classification distinguishes three types of secondary TN: TN attributed to multiple sclerosis, TN attributed to a space-occupying lesion (e.g. brain tumour) and TN attributed to a cause other than those described above.

Idiopathic TN divides in two: purely paroxysmal and TN with concomitant continuous pain [4, 5]

Address for correspondence: Hubert Ostrowski, Studenckie Koło Naukowe Chirurgii Szczękowo-Twarzowej oraz Ortognatycznej Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu, email: hubertostr@gmail.coml

TN can be treated pharmacologically and non-pharmacologically. Anticonvulsants such as carbamazepine and oxcarbazepine are the first-line therapy in patients with trigeminal neuralgia. Unfortunately, about 25–50% of patients become refractory to drug therapy and require higher doses during the therapy. Also, the risk of side effects increases with prolonged use. Patients who are refractory to drugs or who do not tolerate side effects may undergo surgical procedures, i.e. microvascular decompression, gamma-knife radiosurgery, partial sensory rhizotomy, and percutaneous radiofrequency thermocoagulation, which comprise the second-line therapy in TN. But all of these surgical methods are associated with multiple postoperative complications [6, 7]

Some studies have shown that there is a new therapy that uses a Botulinum toxin type A (BTX-A or BoNT-A), a natural neurotoxin derived from the bacterium *Clostridium botulinum* [8, 9]. It inhibits the release of acetylcholine at neuromuscular junctions, causing relaxation of the muscle as well as pain-modulating neurotransmitters, which is why it has been studied for its effectiveness in treating neuropathic pain [10]. BTX-A is commonly used in cosmetic surgery, and in recent years also in medicine to manage conditions such as blepharospasm, hemifacial spasm, chronic migraine, post-stroke spasticity and many other types of headache [11–15].

The present review was undertaken to give an overview of the available evidence that BoNT-A has a therapeutic effect on TN.

Methods

The literature from the PubMed base and the Main Medical Library from the last 18 years was analysed. Key words included: trigeminal neuralgia, botulinum toxin, neuropathic pain, and trigeminal nerve. Forty-three items were obtained; after verification, seven articles were reviewed with attention to the efficacy and safety of Botulinum toxin Type A therapy in trigeminal neuralgia. The works were set out in a tabular form considering the number of patients and the BoNT-A therapy used to reduce the pain in TN patients: this is Table 1. Different types of toxin which were used in the evaluated studies are set out in Table 2.

Results

Wu et al. [16] performed a randomised, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of BoNT-A in the treatment of trigeminal neuralgia. A total of 42 patients were randomly divided into two groups: 22 in the BoNT-A group and 20 in the placebo group. They were followed-up over 12 weeks. Intradermal and/or submucosal injections were performed along the area of pain distribution. A total of 75 U of BoNT-A were given into 15 injection sites. Similarly, patients from the placebo group received an equal volume of 0.9% saline. The object of the study was to estimate the degree of pain relief, which was based on the visual analogue scale (VAS), plus the frequency of pain attacks per day. Patients with a ≥ 50% reduction in mean VAS score at the endpoint of the study were considered to be responders. Out of 42 patients, 21 and 19 patients from the BoNT-A and placebo groups, respectively, completed the study. Fifteen (68.18%) patients from the BoNT-A group and three (15.00%) from the placebo group responded to treatment. Moreover, 17 (77.27%) patients from the BoNT-A and four (20.00%) patients from the placebo group reported a significant or very significant improvement in symptoms. Attack frequency was also reduced in the BoNT-A patients. All of these differences were found to be statistically significant. The authors concluded that Botulinum toxin type-A may be a novel, safe and efficient strategy for trigeminal neuralgia treatment.

Zúñiga et al. [17] treated 36 patients with a subcutaneous injections that contained 1 ml of 0.9% saline or 50 U of BOTOX, depending on the group of patients. Cases with third branch of involved also received either 10 U of BOTOX or placebo into the masseter muscle. This randomised, double-blind, placebo-controlled study was performed to evaluate the tolerability, safety and efficacy of BoNT-A treatment in classical TN. Patients were assigned to two groups, 20 of them to receive BOTOX, and 16 to receive a placebo. Drugs were administered in various sites, 1 cm apart from one another, according to the path of the involved branch. This was always performed by the same physician using the same technique. The aim of the study was to evaluate the reduction in pain severity and attack frequency. Pain was assessed with the visual analogue scale (VAS). All patients completed the study. The initial mean VAS scores was 8.85 and 8.19 for BoNT-A and placebo patients, respectively. One month after intervention, the differences in mean VAS values in both groups were compared, and reported as nonsignificant (VAS 5.05 *vs* 6.06 in BoNT-A and placebo group, respectively). A significant decrease in the number of paroxysms was observed among the patients treated with BOTOX. Two months after the injections, a significant reduction in mean VAS scores in the BoNT-A group was observed and this was maintained until the end of the three-month follow-up period. At the endpoint of the study, the mean VAS score for patients treated with BOTOX was 4.75, and 6.94 for those treated with a placebo. Also, the frequency of attacks was significantly lower than at the beginning in the BoNT-A group (29.1 *vs* 7.1 paroxysms per day). These results were statistically significant. The authors concluded that Botulinum toxin type A is useful in acute treatment of classical TN, and when added to current drug therapy may cause a significant decrease in pain expression. Eighteen patients completed the study.

Shehata et al. [18] carried out a randomised, double-blind, placebo-controlled study. They treated 20 patients with intractable idiopathic TN, which was defined as a failure to achieve 50% reduction in pain intensity (quantified by VAS) and/or paroxysm frequency during the previous three months. The aim

Table 1. Summary of study characteristics

Author, country, year	Title	Placebo group	BoNT-A group	BoNT-A therapy	Results	Conclusion
Wu et al., China, 2012	Botulinum Toxin Type A for the treatment [...]	n = 20	n = 22	I.d. and/or s.m.; 75 U into 15 sites	40 patients completed the study. 17/22 patients from BoNT-A group reported significant or very significant improvement of symptoms *vs* 4/20 patients from placebo group.	BoNT-A may be an efficient, safe and novel strategy for TN treatment.
Zůňiga et al., Argentina, 2013	Acute Treatment [...]	n = 16	n = 20	50 U of BOTOX; $V_{1/2}$ - s.c., according to the path of branches; V_3 - i.m.	Reduction of attack frequency from 1st month and pain intensity from 3rd month.	BoNT-A as an addition to drug therapy and in acute treatment.
Shehata et al., Egypt, 2013	Botulinum Toxin--Type A [...]	n = 10	n = 10	$V_{1/2}$ - s.c., 'follow the pain' method and trigger areas; V_3 - i.m. into posterior part of the masseter; 5 U per site	Significant pain intensity and attack frequency reduction in BoNT-A group *vs* placebo group during 12-week follow-up.	BoNT-A can relieve pain in patients with intractable TN.
Li et al., China, 2014	Therapeutic effect of Botulinum toxin-type [...]		$n_{\leq 5\ U} = 43$ $n_{50\text{-}100\ U} = 32$ $n_{\geq 100\ U} = 13$	Inj. in facial area and trigger points, 2.5–5 U per point; doses from 25 to 170 U	No significant difference in BoNT-A efficacy between groups. Effects of treatment decreased after 3 months.	Maintenance of the therapeutic effect was related to a reduction of the VAS score after the first inj. and not related to different dosages.
Zhang et al., China, 2014	Two doses of botulinum [...]	n = 28	$n_{25\ U} = 27$ $n_{75\ U} = 29$	I.d. and/or s.m. inj. according to patient's expression of pain; 25 U or 75U at 20 sites	80 patients completed the study. No significant differences between BoNT-A groups in terms of VAS score reduction.	Lower dose and high dose are similar in efficacy in short-term.
Zhang et al., China, 2017	Single-dose Botulinum Toxin Type A [...]		$n_{s\text{-}d} = 50$ $n_{r\text{-}d} = 50$	I.d. and/or s.c., 1.25–5U per site; Single-doses from 70 to 100 U; Repeated-doses from 100 to 140 U, 50–70 U per time; 2 weeks break between inj.	Significant decrease in VAS scores in both groups. Duration of efficacy significantly longer in single-dose group.	Repeated dosing has no advantage over single dosing of BoNT-A.
Liu et al., China, 2018	Efficacy and Safety of Botulinum Toxin [...]		$n_{\geq 80y.o.} = 14$ $n_{< 6y.o.} = 29$	I.d. and/or s.m. inj. guided by patient's perception and trigger zones; doses from 45 to 150 U in older and from 30 to 200 U in younger patients.	Significant VAS score reduction in both groups.	Effective and safe treatment for idiopathic TN in older patients at doses similar to those used in younger patients.

Table 2. Types of botulinum toxin

Author, title, country, year	Type of botulinum toxin	Dilution
Wu et al., Botulinum Toxin Type A for the treatment [...]; China, 2012	HengLi® (Onabotulinumtoxin type A); 100 U of Clostridium botulinum type A neurotoxin complex, 5mg gelatin, 25mg dextran, and 25mg saccharose (Lanzhou Biological Products Institute, China)	100 U of BoNT-A in 2 ml 0.9% saline
Zůñiga et al., Acute Treatment [...]; Argentina, 2013	BOTOX® (Onabotulinumtoxin type A)	100 U of BoNT-A in 2 ml 0.9% saline
Shehata et al., Botulinum Toxin-Type A [...]; Egypt, 2013	BOTOX® (Onabotulinumtoxin type A)	100 U of BoNT-A in 2 ml 0.9% saline
Li et al., Therapeutic effect of Botulinum toxin-type [...]; China, 2014	HengLi® (Onabotulinumtoxin type A); 100 U of Clostridium botulinum type A neurotoxin complex, 5mg gelatin, 25mg dextran, and 25mg saccharose (Lanzhou Biological Products Institute, China)	100 U of BoNT-A in 2 ml 0.9% saline
Zhang et al., Two doses of botulinum [...]; China, 2014	HengLi® (Onabotulinumtoxin type A); 100 U of Clostridium botulinum type A neurotoxin complex, 5mg gelatin, 25mg dextran, and 25mg saccharose (Lanzhou Biological Products Institute, China)	Depending on group: 25 U of BoNT-A in 1 ml 0.9% saline or 75 U of BoNT-A in 1 ml 0.9% saline
Zhang et al., Single-dose Botulinum Toxin Type A [...]; China, 2017	HengLi® (Onabotulinumtoxin type A); 100 U of Clostridium botulinum type A neurotoxin complex, 5mg gelatin, 25mg dextran, and 25mg saccharose (Lanzhou Biological Products Institute, China)	100 U of BoNT-A in 2 ml 0.9% saline
Liu et al., Efficacy and Safety of Botulinum Toxin [...]; China, 2018	HengLi® (Onabotulinumtoxin type A); 100 U of Clostridium botulinum type A neurotoxin complex, 5mg gelatin, 25mg dextran, and 25mg saccharose (Lanzhou Biological Products Institute, China)	100 U of BoNT-A in 4 ml 0.9% saline

of the study was to evaluate the efficacy, safety and tolerability of BoNT-A in patients who were refractory to first-line drug therapy. Patients were randomised into either the BoNT-A or the placebo group, 10 subjects in each group. Subcutaneous injections were performed using the 'follow the pain' method. Also, botulinum toxin was injected into the posterior part of the masseter muscle if the mandibular root of the trigeminal nerve was affected. Each injection site received 5 U of BoNT--A. The overall doses ranged from 40 U to 60 U (mean ± SD of 48 ± 5.87 U). All of the patients completed the 12-week study period. Significant reductions in both efficacy measures, i.e. pain VAS scores and attack frequency, were observed in week 2 and were maintained over the follow-up period. At the endpoint, mean VAS scores were decreased by 6.5 and 0.3 for BoNT-A and placebo, respectively. The authors concluded that subcutaneous BoNT-A injections can be an effective treatment option in cases with intractable TN.

Several studies were evaluated for the purpose of assessing the efficacy of different doses and methods in botulinum toxin type A therapy. Li et al. [19] performed a study to investigate the long-term effects and safety of BoNT-A in TN treatment. Eighty-eight subjects with one-branch classical TN were included. Patients were asked to report the expression of pain (measured by VAS) and attack frequency. A patient's overall response to treatment was evaluated over the course of a 14-month follow-up period. The main goal of the study was to estimate the influence of different doses on the therapeutic effect of BoNT-A. Injections were given in the trigger areas at 15–20 points (0.5 cm depth, 15 mm separation, 2.5–5 U per point). Forty-three cases received ≤ 50 U, 32 cases received from 50 U to 100 U, and 13 cases received ≥ 100 U of BoNT-A. Minimal and maximal doses were 25 U and 170 U, respectively. All 88 patients showed an improvement in symptoms within two weeks. At two months, the percentage of patients in whom treatment was effective had reached 100%. After three months, the effectiveness of BoNT-A therapy decreased gradually. The authors concluded that there were no significant differences in effectiveness of treatment or attack frequency between the different dose groups at identical time points between oneand 14 months. Moreover, the maintenance of therapeutic effect was not related to different dosages, but was related to the reduction of VAS score after the first set of injections.

Zhang et al. [20] included 84 patients into a randomised, double-blind, placebo-controlled study to assess the efficacy and safety of two different doses of BoNT-A in TN therapy. All patients suffered from classical TN. Patients were randomly divided into three groups: placebo (n = 28), BoNT-A_{25U} (n = 27), and BoNT-A_{75U} (n = 29), and were followed-up during an 8-week period. Patients received placebo or BoNT-A via intradermal and/or submucosal injections, which were guided by the individual patient's experience of pain. These doses were injected into 20 sites. The purpose of the study was to define

an effective dose of BoNT-A. Pain severity, attack frequency, overall response to treatment, and proportion of responders (≥ 50% reduction in mean pain score from baseline to endpoint) were assessed during the study. 32.1% of patients from the placebo group, 70.4% of patients from the BoNT-A_{25U} group, and 86.2% of patients from the BoNT-A_{75U} group responded to treatment. The VAS scores in the BoNT-A patients reduced significantly one week after the first injections, and were maintained until the end of the study. Pain symptoms vere much or very much improved in 66.7% and 75.9% of patients from the 25 U and the 75 U group, respectively. Only 32.1% of patients who received the placebo reported the same improvement as in the BoNT-A groups. These results showed that both doses were effective in TN treatment, but there were no significant differences between the groups. Thus, the authors concluded that 25 U and 75 U doses are similar in efficacy over a short period of time.

Zhang et al. [21] compared two different methods of BoNT-A administration: single-dose and repeated-dose therapy. They conducted a open-label trial which included 100 patients with classical TN. Fifty patients received an intradermal and/or a submucosal single injection of 70–100 U of BoNT-A at the site of pain. The other 50 patients received two sets of injections using the aforesaid method. The initial injection contained 50–70 U of BoNT-A. Two weeks later, another set of injections was given with an equal volume of BoNT-A. The drug was given in 15–25 sites, with 0.1 cm depth and 15 mm separation between sites. Each point received 1.25–5 U of BoNT-A. Every patient was interviewed for severity of pain (VAS score) and rate of TN occurrence. After a 6-month follow-up, 44 patients from the single-dose group and 37 patients from the repeated-dose group completed the study. Mean VAS scores at the baseline and the endpoint for the single-dose method were 8.26 ± 1.68 and 3.02 ± 3.29, respectively. In the repeated-dose method, mean VAS score at the baseline was 7.98 ± 1.60, which had decreased by the endpoint to 4.32 ± 3.61. In both groups, VAS scores and drug response rates were not significantly different. However, the duration of efficacy in those patients who underwent single-dose therapy was significantly longer than that of the repeated-dose patients. The authors conluded that repeated dosing has no advantage over single dosing of BoNT-A, and that single dosing may be the best choice in TN therapy. Multiple injections should be considered for patients who respond poorly to the first set of injections. Dosing should be adjusted for the individual patient.

A new study, which assessed the efficacy and safety of BoNT-A for treating idiopathic TN in patients ≥ 80 y.o., appeared last year. Liu et al. [22] selected 43 patients who were divided into two groups: ≥80 years old (n = 14) and < 60 years old (n = 29). Prior to treatment, the median pain scores (measured by VAS) in both older and younger patients were 8.5 and 8.0, respectively. BoNT-A was given in similar doses in all groups. Total doses ranged from 30 U to 200 U (mean ± SD of 71.80 ± 33.14 U) and from 45 U to 150 U (91.30 ± 25.64 U) in the < 60 y.o. and the ≥ 80 y.o. patients, respectively. One month after treatment, median VAS scores in older (4.5) and younger (4.0) were significantly lower than the corresponding baseline values. The authors proved that BoNT-A injections are an effective and safe therapy for idiopathic TN in elderly patients at doses similar to those used in younger patients.

The use of BoNT-a in the treatment of TN is confirmed not only by the abovementioned studies, but also by many other publications that were not included in our review.

Discussion

TN is characterised by episodes of spontaneous pain or a triggered intense facial pain that lasts for a short duration [23]. According to the current guidelines of the American Academy of Neurology and the European Federation of Neurological Societies (AAN-EFNS), carbamazepine (CBZ) and oxcarbazepine are recommended as first-line drugs for treating patients with trigeminal neuralgia. Drugs such as baclofen, lamotrigine, phenytoin, topiramate and pimozide may also be considered [24]. However, high dosages and the long-term use of CBZ are not free from complications. These mainly take the form of eliciting drowsiness, dizziness, diplopia, leukopenia, hyponatremia and disturbances of the vitamin D metabolism [25]. The most common adverse effects of oxcarbazepine are usually related to the central nervous system and digestive system, including fatigue, drowsiness, diplopia, dizziness, nausea, vomiting and rashes [26]. If the pharmacological treatment fails, there are surgical options that can alleviate the pain in TN, e.g. microvascular decompression, percutaneous radiofrequency rhizotomy, percutaneous glycerol rhizotomy, balloon compression and gamma knife radiosurgery. Microvascular decompression is the most effective treatment for classical TN: it may provide initial pain control in the range of 80.3% to 96.0%. However, this procedure is not as safe as it might seem to be. The most common postoperative complications are an up to 22% rate of trigeminal nerve deficit, less than 11% of facial weakness, about 7% of hearing loss, and sometimes aseptic meningitis, cerebrospinal fluid leakage and anaesthesia dolorosa [27]. Based on the this knowledge, it is safe to say that there is a need to find a new treatment for TN patients.

The use of BTX-A in trigeminal neuralgia was first reported in 2002 by Michaeli et al. who successfully treated a patient with a hemifacial spasm associated with TN [28]. The main action of BoNT-A is to inhibit the release of acetylcholine at the neuromuscular junction. The mechanism of potential analgesic effect of BoNT-A is still unclear. It can inhibit the peripheral sensitisation of nociceptive fibres, hence reducing central sensitisation by inhibiting the release of glutamate and substance P. Moreover, BTX-A significantly reduces the high expression of TRPA1, TRPV1 and TRPV2 in the spinal trigeminal nucleus, what can directly modulate central sensitisation and exerts an antinociceptive function [29, 30].

A new study performed by Yang et al. revealed that the antinociceptive effects of BoNT-A are connected with the inhibition of upregulated Nav isoform 1.7 in Gasserian ganglion [31]. More research needs to be done to thoroughly understand how BoNT-A relieves the pain in TN.

The studies included in our review promote the use of BoNT-A. This topic enjoys great interest in China, and therefore most of the articles chosen for this review are publications from that particular country. However, it should be noted that attempts to treat trigeminal neuralgia with BoNT-A have also been undertaken in other countries, e.g. Norway, USA, Germany, Iran and Malaysia [32–37].

The percentage of patients who have responded to treatment has ranged from 68% to as much as 100%. Attack frequency and pain severity were predominantly reduced one week and two weeks after injections, respectively. Treatment was effective for about 3-6 months. The most commonly used injection method was multiple intradermal and/or subcutaneous injections in the painful area. However, other methods, such as injections into the masseter muscle or injections above and below the zygomatic arch, should also be considered [38–40]. Doses of BoNT-A have been determined empirically and ranged from 25U to 200 U. In addition, this therapy is not free from complications. All of the reported adverse reactions (e.g. facial asymmetry, oedema, pain, haematoma) were mild and transient.

Despite the above-mentioned information, which highlights the positive effect of BoNT-A treatment, a few points need to be discussed.

The first question is the duration of patient follow-up. Wu et al., Zúñiga et al. and Zhang et al. performed studies with follow-ups of eight or 12 weeks or three months. Such periods are too short to assess the long-term effects of BoNT-A in TN, especially in those studies that set out to compare the effects of different doses. Long-term trials are needed to correctly evaluate whether a high dose of BoNT-A has any advantages over lower doses.

Secondly, was the baseline therapy kept unchanged after BoNT-A treatment? There was no information about the anticonvulsants that patients received after injections. In addition, each patient took different doses or medications before and during BoNT-A therapy, what may have played a role in reducing the primary endpoints, such as pain severity and attack frequency. What is more, Li et al. did not provide any information about the medicines their patients were taking. In Wu et al.'s trial, one patient changed his medications during the BoNT-A therapy. We suggest that doses and medications should be uniform so as to clearly assess the efficacy of a new treatment strategy.

Another problem is that follow-up visits have been carried out by some authors for much longer than one week. Liu et al. and Zuniga et al. estimated patient response to treatment every one or three months after BoNT-A administration, respectively. Such a long period of time made it impossible to detect the early disappearance of pain and any reduction in the number of paroxysms per day.

In the study performed by Shehata et al., the blind phase was not maintained after the first follow-up visit. Despite the correct method of randomisation and blinding, facial asymmetry occurred in some patients and led to failure in the blinded phase. For these reasons, the investigator's impressions could be biased.

Liu et al. included only 14 patients aged 80 or older. For comparison, a group with patients younger than 60 years old compared 29 cases. This number of patients is not sufficient to evaluate whether older patients can receive the same doses as younger ones. A study with more elderly patients is needed.

Finally, Zakrzewska JM [41] reported that Wu et al.'s study is not a high-quality evidence of BoNT-A's effectiveness in trigeminal neuralgia therapy. This is mainly because of too little information being provided about the blinding phase and insufficient measures regarding selection, which can capture all aspects of pain experience.

Conclusions

To conclude, this review suggested that Botulinum toxin Type A injections are a safe and effective treatment option for patients with trigeminal neuralgia, and may be offered before surgery or for those unwilling to undergo surgery or where drug treatment has failed. Despite the possibility of occurrence of transient and mild adverse reactions, it represents a propitious risk-to-benefit ratio. However, future studies are necessary to determine the optimal dosages and injection schemes for BoNT-A treatment, the duration of therapeutic efficacy, and indications as to when repeated injections are needed.

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