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Botulinum toxin injections for the treatment of frontal tension headache

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Abstract We performed a randomized, double-blind, placebo-controlled trial to determine the efficacy of botulinum toxin type A (BOTOX; Allergan) in treating frontal tension-type headache (TTH). A total of 40 patients attending a headache treatment center were randomized to receive 50 U botulinum toxin type A or saline, injected at 10 sites of the forehead. Frequency and severity of headaches before and after injection were compared. The intensity of headaches in the botulinum toxin type A group, but not the placebo group, fell significantly from an average score of 5.19 to 4.65 ($p<0.0001$). Botulinum toxin type A patients and placebo patients experienced an average reduction in the number of headaches per month, but these reductions were not significantly different between groups. Botulinum toxin type A was well tolerated, with no significant adverse events. Botulinum toxin type A injections in the management of frontal TTH has been shown by this study to be both effective and well tolerated. It should be noted that the effect of botulinum toxin on intensity of headache, although statistically significant, was relatively small.

Key words Botulinum toxin type A • Tension headache • Treatment

Introduction

Tension-type headache (TTH), the most common form of chronic headache, is a frequent cause of episodic headache, and has the greatest socioeconomic impact. A study of a Danish population reported 870 workdays lost per 1000 people with TTH, compared to 270 workdays lost per 1000 people for migraine [1].The lifetime prevalence of TTH in the general population is as high as 30% [2]. TTH is characterized by sensations of tightness, pressure, or constriction, and varies widely among patients in fre-

quency and duration [2].The pathophysiology of TTH is poorly understood, although sustained contraction of pericranial muscles may be involved [3].

Episodic tension-type headache (ETTH) is a particularly prevalent condition, with a significant functional impact at work, home, and school [4]. Although chronic tension-type headache (CTTH) is less prevalent than ETTH [4], it usually evolves from the episodic form [5] and causes significant impairments in functioning. In one study, one-third of CTTH sufferers recorded impaired sleep, energy levels, or emotional well-being for 10 days or more per month, and half the patients exhibited clinically significant levels of anxiety or depression [6].

Treatment for CTTH needs to be chosen carefully because of the potential for medication overuse, abuse, and rebound phenomena, particularly when patients attempt to derive prophylactic benefits from acute treatments [7–9].

Botulinum toxin type A is a potent neurotoxin produced by the bacterium *Clostridium botulinum*. Botulinum toxin type A inhibits acetylcholine release at neuromuscular junctions, causing chemodenervation and a subsequent muscle-relaxing effect [10]. The resulting muscle relaxation has been effective in treating conditions linked to overactive striatal or smooth muscle, such as cervical dystonia, blepharospasm, spasticity, and hyperhidrosis [11–14].

Recent evidence suggests that botulinum toxin type A may also be effective in treating headache (including TTH and migraine) [3, 15–17]. Botulinum toxin type A may be cost effective in the treatment of TTH, by reducing the use of analgesic pain medication [18]. The primary objective of this trial was to determine the efficacy of botulinum toxin type A injections into the forehead musculature to relieve TTH with a frontal pain distribution.

Materials and methods

Study design and population

A single-center, randomized, double-blind, placebo-controlled, parallel group trial was conducted to determine the efficacy of botulinum toxin type A injections in the treatment of TTH with frontal pain distribution. A total of 60 patients were recruited and screened from neurology practices of the Department of Neurology, Saint Louis University, Missouri, and from the Greater St. Louis community. Recruitment began in July 1998 and the last patient was evaluated in June 2000.

The inclusion criteria were as follows: all subjects 18 years or older with episodic or chronic frontal headache as defined by the International Headache Society (IHS) with a frequency equal or greater than 1/month and a frontal pain distribution were eligible to be seen for possible inclusion into the study. The exclusion criteria for the study included a history of stroke, migraine alone, previous use of botulinum toxin medication, previous corrugator or frontalis muscle surgery, previous Bell's palsy, active lid ptosis or lagophthalmos, current aminoglycoside therapy, and known adverse reaction to botulinum toxin or human albumin; subjects who were pregnant or nursing were also excluded.

During the recruitment and screening period, a neurologist performed all of the pre-injection history and physical examinations and obtained a psychiatric history on all patients, including any history of depression, seizure, hallucinations, etc., and also asked about the use of neuroleptic medications, antidepressants, etc. All patients who were eligible based on preliminary inclusion and exclusion criteria were then evaluated for confirmation of either inclusion or exclusion based on their history and physical examination by the same neurologist.

The primary outcomes measures for this study were the reduction in both the frequency of headache, measured as the average number of headaches per month, and the intensity of headache. The efficacy of botulinum toxin type A was determined by comparing symptom assessments from headache diaries before and after treatment and between study groups. Headache intensity was evaluated using a Likert-type scale: 1–3 (mild), 4–6 (moderate), 7–9 (severe), and 10 (most painful headache ever). The Likert scale is a well-known and widely used scale measuring attitudes or opinions [19].

After consultation and clinical examination by a neurologist, all patients were instructed to complete a daily headache and medicine log during a 30-day pretreatment period. The log allowed patients to self-rate headache location, symptom severity and frequency, and to record analgesic and headache medicine use before treatment.

Study protocol

After the pretreatment period, patients were randomized to receive injections with saline or botulinum toxin type A. Blinding was achieved by the involvement of 3 physicians. One physician screened the patients for inclusion and classification, performed all the pre-injection history and physical examinations, confirmed each patient for inclusion or exclusion, and gave each included patient a unique identifier. A different physician then randomized patients to saline or botulinum toxin type A treatment and that physician blindly picked a patient when that patient was scheduled for an injection (by randomly choosing a slip of paper with the patient's name and treatment arm from a bag). She then filled the syringe with the selected substance (saline or botulinum toxin type A) and handed it to a third physician who injected the unmarked syringe contents into the patient. The physician who filled the syringes and assigned the subjects to the saline or treatment arm was masked to the patients' identities, histories and clinical data. The physician performing the injections was masked to the contents of the syringe.

Patients received 10 injections of either 5 units (U) botulinum toxin type A (BOTOX; Allergan, Irvine, USA) in 0.1 ml 0.9% preservative-free saline (50 U total), or an equivalent volume of saline. Injections were made at 10 sites on the forehead in the frontalis, corrugator, and procerus muscles (Fig. 1). To standardization the study, there was no individual selection of trigger points and no attempt was made to "follow the pain". After treat-

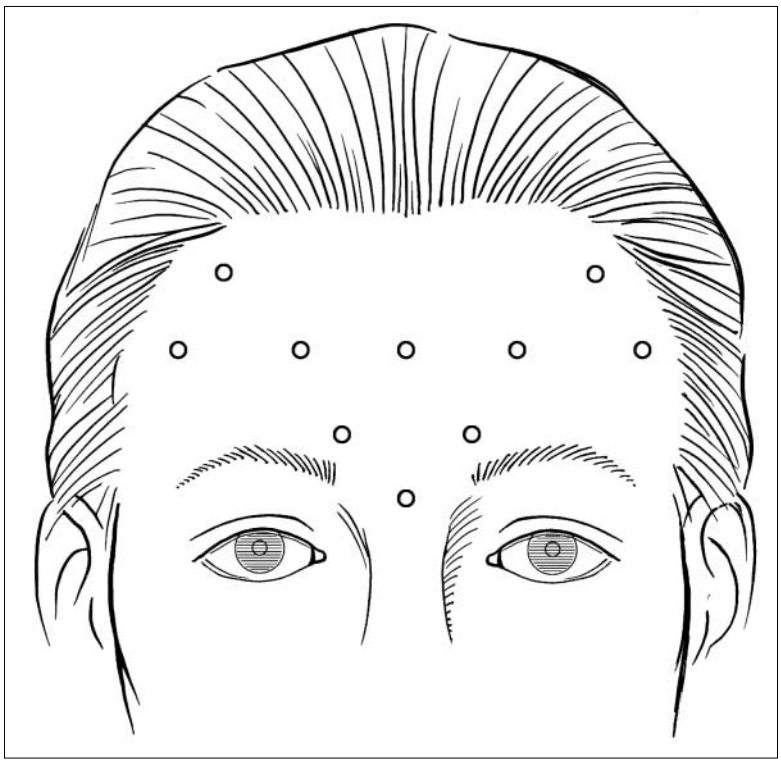

Fig. 1 Sites of injection of botulinum toxin type A. At each site, 5 U toxin was injected for a total of 50 U

ment, patients continued to maintain their daily headache logs for up to 6 months. The diary ratings were made once daily in the evenings before bedtime and referred to the events of that day. Follow-up visits were made once per month, at which time the patients returned their daily logs for analysis.

Signed informed consent forms were obtained from all patients prior to enrollment in the study, and were discussed with the patients on the initial visit before inclusion into the study and before they began their baseline daily logs. The study was approved by the St. Louis University Institutional Review Board.

Statistical analysis

Preinjection characteristics considered to be continuous, such as age, were compared using *t* tests. Categorical variables, such as gender, were compared using chi-squared tests.

To assess whether frequency of headache was different between the botulinum toxin type A and placebo groups, the number of headaches per month before and after injection was computed, and the average difference for each patient was calculated. The average difference in the number of headaches per month was compared between the botulinum toxin type A and placebo groups using analysis of variance (ANOVA).

Headache intensity was analyzed using a repeated measures ANOVA to account for both between and within patient variabilities. The average intensity for four groups was compared: (1) baseline intensity before botulinum toxin type A injection, (2) baseline intensity before placebo injection, (3) intensity after botulinum toxin type A injection, and (4) intensity after placebo injection. If differences were detected between treatment groups, post hoc multiple comparison tests were performed using Tukey's Studentized range test. All statistical analyses were performed using SAS (version 8.1, Cary, USA) statistical software. Statistical significance was declared when p values were less than 0.05.

Results

Of the 60 patients screened for inclusion in the study, 19 did not meet the selection criteria because of previous botulinum toxin type A treatment, a classification of migraine only, lack of frontal pain distribution, and insufficient headache frequency. Since only 1 patient had ETTH, it was decided not to include him as all the remaining patients had CTTH. There were no significant differences in baseline characteristics between the two treatment groups (Table 1). Although there was a greater percentage of patients at baseline with hypertension and depression in the saline treatment group, these differences were not significant. None of the patients had a history of migraine alone or stroke and none had previously undergone botulinum toxin type A injection or forehead surgery. Eleven patients in the botulinum toxin type A group (55%) and 8 patients in the control group (40%) also had headache with migraneous features.

Table 1 Baseline characteristics of 40 patients with chronic tension-type headache with a frontal pain distribution, by treatment group. No difference between the groups is significant. Values are number (percentage) of patients unless otherwise indicated

	BoNT-A (n=20)	Saline (n=20)
Demographics		
Age, years[a]	43.8	49.1
Women, n (%)	16 (80.0)	15 (75.0)
White, n (%)	20 (100)	20 (100)
Attention deficit disorder, n (%)	1 (5.0)	0 (0)
History, n (%)		
Family history of headaches	14 (70.0)	14 (70.0)
Hypertension	2 (10.0)	4 (20.0)
Bipolar disorder	1 (5.0)	1 (5.0)
Depression	8 (40.0)	12 (60.0)
Migraine	11 (55.0)	8 (40.0)
Medication use prior to study, n (%)		
Prescriptions drugs for headache	19 (95.0)	18 (90.0)
Pain relievers	18 (90.0)	19 (95.0)
NSAIDs	8 (40.0)	10 (50.0)
Muscle relaxants	3 (15.0)	4 (20.0)
Antidepressants	15 (75.0)	15 (75.0)
MAO or 5HT inhibitors	12 (60.0)	11 (55.0)
Narcotics	14 (70.0)	14 (70.0)
Other headache medications	16 (80.0)	17 (85.0)

BoNT-A, botulinum toxin type A; *NSAIDs*, non-steroidal anti-inflammatory drugs; *MAO*, monoamine oxidase
[a] Values are mean (SD)

Overall, 95% of patients in the botulinum toxin type A group and 90% in the placebo group were taking preventive headache medications prior to the trial. The majority of both treatment groups had failed at least 2 or more preventive medication regimens.

Thus, a total of 40 patients with chronic tension-type headache (CTTH) with only frontal pain distribution were selected and randomized to receive injection of botulinum toxin type A (n=20) or saline (n=20).

All patients were between 19 and 80 years of age (mean age, 47 years).

The average preinjection follow-up was 37 days while the average postinjection follow-up was 178 days, or slightly under 6 months. All patients completed the trial. A total of 24 patients had a full 6 months of follow-up. All patients turned in their headache diaries. Of 5299 diary entries, 9 (0.017%) were considered missing data points and were dealt with by listwise deletion.

Post-treatment average headache intensity scores were significantly lower for botulinum toxin type A patients compared with pretreatment scores (Fig. 2). The intensity of headache in botulinum toxin type A patients fell from 5.19 to 4.65 ($p<0.0001$). The intensity of headache for placebo-treated patients was not significantly reduced after injection (5.38 vs. 5.27, $p=0.07$). Multiple comparison tests of the average intensity of headache confirmed that the intensity of headache was significantly lower after patients were given botulinum toxin type A injections than after patients were given saline injections (Table 2). The predicted effects of botulinum toxin type A treatment on headache intensity over time are illustrated in Figure 3.

The mean number of headache episodes per month fell from 23.4 to 17.1 in the patients treated with botulinum toxin type A (Fig. 4). This number fell from 23.2 to 18.4 episodes per month for the placebo-treated patients. The changes in headache frequency were not statistically different between the groups.

Botulinum toxin type A injections were well tolerated, with no significant adverse events reported. Three patients reported symptoms of ptosis, although this was not confirmed by clinical examination and their symptoms had resolved by their 30-day follow-up visit. There were no reported cases of diplopia, facial nerve or expression problems, autonomic or systemic side effects, keratopathy, or idiosyncratic or allergic reactions caused by treatment with botulinum toxin type A.

A comparison of average headaches per month by migraine status, depression, antidepressant use, narcotic use, and use of monoamine oxidase inhibitors or selective serotonin reuptake inhibitors (SSRIs) did not show statistical significance.

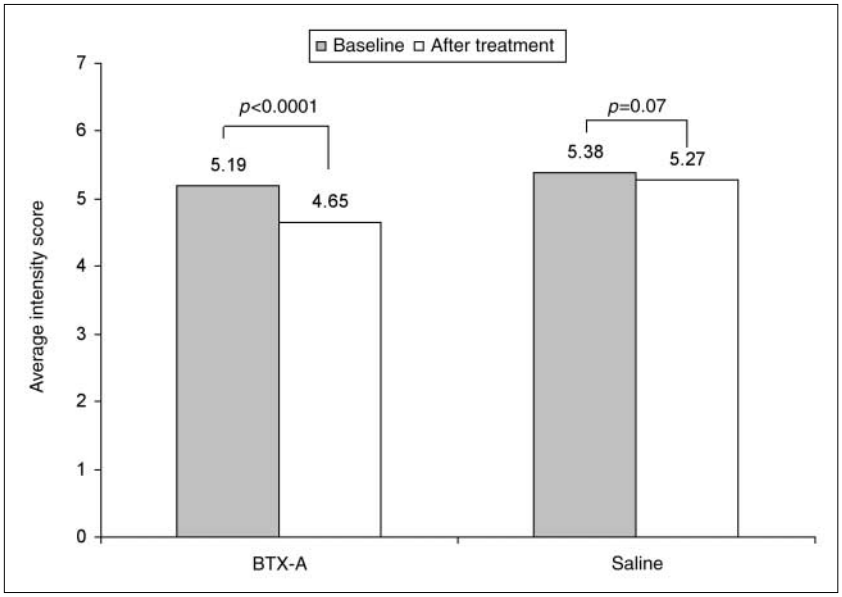

Fig. 2 Headache intensity at baseline and during follow-up after treatment, for 20 patients who received botulinum toxin type A (*BTX-A*) and 20 patients who received saline

Table 2 Multiple comparison tests of average intensity of headache

Comparison	Mean intensity difference	Confidence limits		$p<0.05$
		Lower 95%	Upper 95%	
Saline before → Saline after	0.112	-0.106	0.331	No
BTX-A before → Saline before	-0.190	-0.469	0.090	No
BTX-A before → Saline after	-0.078	-0.307	0.152	No
BTX-A after → Saline before	-0.732	-0.953	-0.511	Yes
BTX-A after → Saline after	-0.620	-0.773	-0.467	Yes
BTX-A after → BTX-A before	-0.542	-0.774	-0.310	Yes

BTX-A, botulinum toxin type A

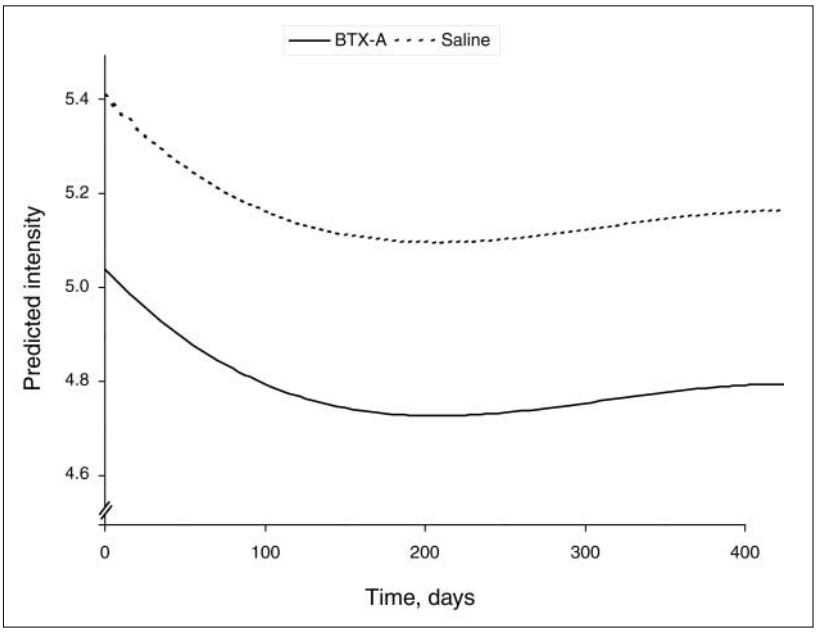

Fig. 3 Predicted effect of treatment on headache intensity over time

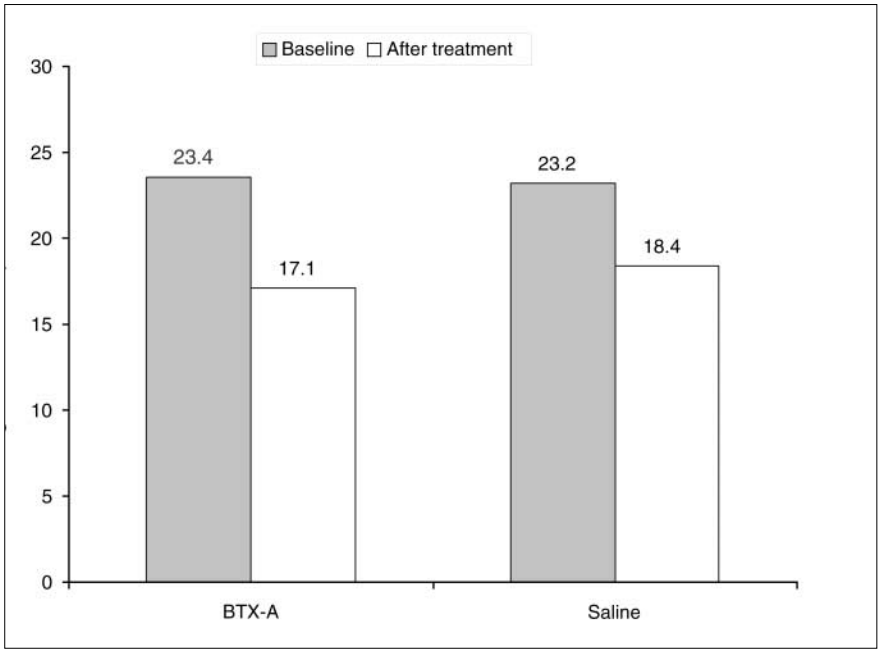

Fig. 4 Effects of treatment on the frequency of headaches. A paired *t* test was used to test the hypothesis that the difference equaled zero. A two-sample *t* test was used to test the hypothesis that the difference in frequency between groups was zero. Neither difference was significant

Discussion

The present study showed that botulinum toxin type A treatment was associated with a significant decrease in average headache intensity during the 6-month follow-up period. Furthermore, botulinum toxin type A was extremely well tolerated, with no confirmation of any adverse events at follow-up.

Two double-blind, placebo-controlled trials did not show a significant reduction in pain severity or pain-free days with the use of botulinum toxin type A to treat patients with CTTH [2, 20]. In contrast, numerous case reports and open-label studies have suggested that botulinum toxin type A is an effective treatment for CTTH [15, 21–25]. In addition, Smuts et al. [3] conducted a 4-month randomized, double-blind, placebo-controlled trial in 37 patients with CTTH. Botulinum toxin type A (100 U in 2 ml saline), divided into two 1-ml doses equivalent to 50 U, was administered to each side of each patient's head (2 sites in the temporal muscles and 4 sites in the cervical muscles). Compared with pretreatment rates, statistically significant improvements in headache intensity and headache-free days were evident by month 3 for patients receiving botulinum toxin type A (p=0.002, p=0.001, respectively) [3]. The conflicting results of these studies suggest that dosing, the sites of injection, and the number of follow-up treatments are important.

A relatively high dose (50–100 U) of botulinum toxin type A injected into multiple sites with follow-up injections may provide a more sustained duration of action and further reduce the frequency of TTH. Furthermore, repeat injections appear to have a step-like therapeutic effect and build on the benefit achieved with prior dosing [15]. However, Silberstein et al. [16], in a randomized, placebo-controlled trial of botulinum toxin type A in the treatment of migraine, found that 25 U was more effective than 75 U. It is clear from the varying results that further work is needed to establish effective botulinum toxin type A dosing regimens, injection sites, and the number of follow-up treatments in the treatment of headache.

The response rate found in the placebo group, although not significant, is unexplained. However, beneficial effects of dry needling or injections of saline and local anesthetics into tender points in a muscle in TTH and a variety of myofascial pain conditions have been reported [26–28]. It should also be noted that the effect of botulinum toxin on the intensity of headache, although statistically significant, was relatively small.

The mechanism by which botulinum toxin type A may be effective in TTH and migraine is unclear, although a muscular component appears possible [16, 28]. The studies performed thus far with botulinum toxin type A suggest that its effectiveness in treating headache may relate to a combination of its muscle relaxant and antinociceptive properties. Further large-scale randomized studies are required to confirm the long-term benefits of botulinum toxin type A injections in this patient population.

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References

1. Rasmussen BK, Jensen R, Olesen J (1992) Impact of headache on sickness absence and utilisation of medical services: a Danish population study. J Epidemiol Community Health 46(4):443–446
2. Rollnik JD, Tanneberger O, Schubert M, Schneider U, Dengler R (2000) Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study. Headache 40:300–305
3. Smuts JA, Baker MK, Smuts M, Stassen JMR, Rossouw E, Barnard PWA (1999) Prophylactic treatment of chronic tension-type headache using botulinum toxin type A. Eur J Neurol 6[Suppl 4]:S99–S102
4. Schwartz BJ, Stewart WF, Simon D, Lipton RB (1998) Epidemiology of tension-type headache. JAMA 279:381–383
5. Jensen K, Norup M (1992) Experimental pain in human muscle induced by hypertonic saline, potassium and acidity. Cephalagia 12:101–106
6. Holroyd KA, Stensland M, Lipchik GL, Hill KR, O'Donnell FS, Cordingley G (2000) Psychosocial correlates and impact of chronic tension-type headaches. Headache 40:3–16
7. Kaube H, May A, Diener HC et al (1994) Sumatriptan misuse in daily chronic headache. BMJ 308:1573–1574
8. Limmroth V, Kazaraw S, Fritsche G et al (1999) Headache after frequent use of new serotonin antagonists zolmitriptan and naratriptan. Lancet 353:378
9. Mathew NT, Reuveni U, Perez F (1987) Transformed or evolutive migraine. Headache 27:102–106
10. Simpson LL (1981) The origin, structure, and pharmacological activity of botulinum toxin. Pharmacol Rev 33:155–188
11. Greene P, Kang U, Fahn S, Brin M, Moskowitz C, Flaster E (1990) Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. Neurology 40:1213–1218
12. Scott AB, Kennedy RA, Stubbs HA (1985) Botulinum A toxin injection as a treatment for blepharospasm. Arch Ophthalmol 103:347–350
13. Brashear A, Gordon MF, Elovic E et al (2002) Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med 347:395–400
14. Naumann M, Lowe NJ (2001) Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. BMJ 323:596–599
15. Gobel H, Heinze A, Heinze-Kuhn K, Jost WH (2001) Evidence-based medicine: botulinum toxin A in migraine and tension-type headache. J Neurol 248[Suppl 1]:34–38
16. Silberstein S, Matthew N, Saper J, Jenkins S (2000) Botulinum toxin type A as a migraine preventative treatment. For the BOTOX Migraine Clinical Research Group. Headache 40:445–450
17. Barrientos N, Chana P (2003) Botulinum toxin A in prophylactic treatment of migraine headaches: a preliminary study. J Headache Pain 4:146–151
18. Coloprisco G, De Filippis S, Santi PG, Fiore G, Rodio A, Martelletti M (2003) Reduction in expenditures on analgesics during one year of treatment of chronic tension headache with BoNT-A. J Headache Pain 4:88–91
19. Likert RA (1932) A technique for the measurement of attitudes. Arch Psychol 22(40):5–55
20. Schmitt WJ, Slowey E, Fravi N, Weber S, Burgunder JM (2001) Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. Headache 41:658–664
21. Relja M (1997) Treatment of tension-type headache by local injection of botulinum toxin. Eur J Neurol 4[Suppl 2]:S71–S73
22. Relja M (2000) Treatment of tension-type headache with botulinum toxin: 1-year follow-up. Cephalagia 20:336
23. Krack P, Hornig C, Dorndorg W (1995) Resolution of chronic tension headache after botulinum toxin treatment of idiopathic blepharospasm. Mov Disord 10:338
24. Schulte-Mattler WJ, Wieser T, Zierz S (1999) Treatment of tension-type headache with botulinum toxin: a pilot study. Eur J Med Res 4:183–186
25. Smuts JA, Barnard PWA (2000) Botulinum toxin type A in the treatment of headache syndromes: a clinical report of 79 patients. Cephalagia 20:32
26. Zwart JA, Bovim G, Sand T, Sjaastad O (1994) Tension headache: botulinum toxin paralysis of temporal muscles. Headache 34:458–462
27. Sola AS, Bonica JJ (1991) Myofascial pain syndromes. In: Bonica JJ (ed) The management of pain. Lea Febiger, Philadelphia, pp 352–367
28. Tfelt-Hansen P, Lous I, Olesen J (1981) Prevalence and significance of muscle tenderness during common migraine attacks. Headache 24:49–54