J Neurol (2001) 248 [Suppl 1]: I/34 – I/38

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Evidence-based medicine: botulinum toxin A in migraine and tension-type headache

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Abstract The therapeutic effect of botulinum toxin in headache was observed coincidentally. The rationale for this new indication initially met with a great deal of scepticism, because the toxin's mechanism of action, cholinergic chemodenervation, does not fit the pathophysiological concept of migraine and other forms of headache. Meanwhile a fair number of studies have been published which indicate efficacy for botulinum toxin and recommend its use for the treatment of tension headache and migraine. According to the evidence-based medicine criteria, grade I evidence has been demonstrated. In addition the use of botulinum toxin for cluster-headache and secondary headache is discussed.

Further large scale studies will be regarded to demonstrate the long-term efficacy.

Key words Botulinum toxin A · Mode of action · Migraine · Tension-type headache · Pain

Introduction

For 20 years botulinum toxin A has been used to treat a variety of disorders characterised by pathologically increased muscle contraction. From the treatment of painful craniocervical dystonia marked analgesic effects of botulinum toxin A have long been known [7]. This prompted research efforts focussing on the use of botulinum toxin A in specific pain therapy, particularly in primary headache syndromes and in myofascial pain syndromes of the neck, shoulder girdle and back. The following summary gives an overview of the clinical studies published so far. The level of evidence of the efficacy of botulinum toxin A for the different headache indications is rated using the Scottish Intercollegiate Guideline Network [18] (SIGN) Guidelines.

Botulinum toxin A in the treatment of migraine

The first evidence for the efficacy of botulinum toxin A in migraine was reported as a surprising side effect in patients primarily treated for hyperfunctional facial lines. Since these early reports several clinically studies have investigated the efficacy of botulinum toxin A in migraine – both in open and in controlled designs. Table 1 lists the studies currently available. Since no guidelines, meta-analyses or systematic reviews have been published on this topic yet, the highest level of evidence is achieved by randomised and controlled studies. Using the 1999 SIGN Criteria for rating clinical studies these studies, reach a level of evidence of I b.

In the year 2000 two randomised and controlled studies were published which showed the efficacy of botulinum toxin A in the treatment of migraine. Brin et al. [2] and Silberstein et al. [19] both conducted double-blind and placebo-controlled studies using a standardised injection design of botulinum toxin A. These studies observed a significant reduction in the intensity of the mi-

Tab. 1 Botulinum toxin A in the treatment of migraine

Study	Design	Outcome	SIGN level
Binder et al., 2000	Open (individual injection choice) N = 77/0 (active drug/placebo)	Positive • 51 % migraine free for an average of 4.1 months • 38 % reduction for migraine frequency of severity by at least 50 %	III
Brin et al., 2000	Double-blind, placebo-controlled (standardised injection) N = 36/12 (active drug/placebo)	Positive • Reduction in pain intensity • Reduction in number of migraine attacks and duration of attacks, but not significant	Ib
Mauskop and Basedo, 2000	Open (individual injection choice) N = 27/0 (active drug/placebo)	Positive (23 out of 27) • Reduction in frequency of migraine attacks Or • Reduction in pain intensity	III
Silberstein et al., 2000	Double-blind, placebo-controlled (standardised injection) N = 82/41 (active drug/placebo)	Positive for a subgroup with lower dose of 25 MU Botox® (n=42, active drug) • Reduction in frequency of migraine attacks • Reduction in average pain intensity • Reduction in number of days with vomiting • Reduction in number of days with acute medication	Ib
Smuts and Barnard, 2000	Open (individual injection choice) N = 19/0 (active drug/placebo)	Positive • 13 out of 19 (68 %) showed positive result (not defined in detail)	III

graine attacks and Silberstein et al. also found a reduction in the frequency of the attacks. The required doses of botulinum toxin A were relatively low, particularly in the case of the study by Silberstein et al. with 25 MU Botox®. The non-significant clinical efficacy of 75 MU in the study by Silberstein et al. is probably explained by a randomisation error due to the standardised choice of injection sites.

Open studies with a consequently lower level of evidence (SIGN III) underline the results of the controlled trials. Mauskop and Basedo [12] using 25 to 100 MU Botox® in an open study with individual injection choice documented a reduction in frequency of migraine attacks or a reduction in pain intensity in 23 out of 27 patients. Using a similar open study design Smuts and Barnard [20] found positive results in 13 out of 19 patients. Binder et al [1] treated 77 migraine patients in an open study with individual injection choice. Of the patients 51 % reported complete response defined as complete symptom elimination for an average of 4.1 months. A further 38 % reported a partial response defined as a reduction of migraine frequency or severity by at least 50 %.

In summary, the efficacy of botulinum toxin A in the prophylactic treatment of migraine has been demonstrated according to the demands of evidence-based medicine.

Botulinum toxin A in the treatment of tension-type headache

The largest number of clinical studies is available for tension-type headache (Table 2). The results however are contradictory. After the first negative report of Zwart et al. [22], who in an open study with individual injection choice did not find an improvement in any of 6 patients treated with 30 to 40 MU Botox®, all later case reports and open studies presented positive results. Krack et al. [11] first described a patient with tension-type headache who became pain free after injection of 160 MU Dysport® (SIGN IV). Relja [14] treated 10 patients with 15 to 35 MU Botox® using individual injection sites. She found a significant reduction in headache duration, pain intensity and pain sensitivity (SIGN III). In a further 24 patients treated using the same design Relja [15] found a lasting effect in long-term use over 15 months (SIGN III). An important point to note is the fact that the repeat injections had a step-like therapeutic effect: the consecutive therapeutic effect of each injection built on the effect previously achieved. In an open study but using a standardised injection design (200 MU Dysport®) Schulte-Mattler et al. [17] significantly reduced the product of pain duration and pain intensity in a group of 8 patients (SIGN III). Smuts and Barnard [20] showed positive results in 30 out of 50 patients treated with 100 MU Botox® in an open and individual fashion (SIGN IIII).

However, when double-blind and placebo-controlled studies were performed it was not possible to detect any significant efficacy of botulinum toxin A. Göbel et al. [8] treated 10 patients each with either 80 MU Botox® or placebo, Rollnik et al. [16] treated 11 patients with 200 MU Dysport® and 10 patients with placebo. In both cases no reduction was found either in pain intensity, pain-free days or in use of analgesics.

These controlled studies chose a standardised design with defined injection sites. For standardisation reasons there was no individual selection of trigger points. Taking account of this point Porta [13] conducted a ran-

Tab. 2 Botulinum toxin A in the treatment of tension-type headache

Study	Design	Outcome	SIGN level
Göbel et al., 1999	Double-blind, placebo-controlled (standardised injection) N = 10/10 (active drug/placebo)	Negative • No reduction in pain intensity • No increase in pain-free days • No reduction in use of analgesics	
Krack et al., 1995	Open (individual injection choice) N = 1/0 (active drug/placebo)	Positive • Free from pain	IV
Porta M., 2000	Double-blind, methylprednisolone-controlled (individual injection choice)	Positive • Significant decrease in the median pain score at day 60 post injection of botulinum toxin A compared to methylprednisolone • Gradual decrease in median pain severity scores at 30 days and 60 days post treatment with botulinum toxin A • Beneficial effects of botulinum toxin A continued to improve 60 days after injection, whereas the effects of steroid therapy at this time point began to decline	Ib
Relja, 1997	Open (individual injection choice) N = 10/0 (active drug/placebo)	Positive • Reduction in headache duration • Reduction in pain intensity • Reduction in pain sensitivity	III
Relja, 2000	Open (individual injection choice) N = 24/0 (active drug/placebo)	Positive • Increase in number of pain-free days • Reduction in pain intensity	III
Rollnik et al., 2000	Double-blind, placebo-controlled (standardised injection) N = 11/10 (active drug/placebo)	Negative • No reduction in pain intensity • No reduction in headache frequency • No reduction in headache duration • No reduction in use of analgesics • No reduction in pain sensitivity	
Schulte-Mattler et al., 1999	Open (standardised injection) N = 8/0 (active drug/placebo)	Positive • Reduction in product of pain duration and pain intensity • Reduction in number of headache days, but not significant	III
Smuts and Barnard, 2000	Open (individual injection choice) N = 55/0 (active drug/placebo)	Positive • 30 out of 50 (55 %) showed positive result (not defined in detail)	III
Zwart et al., 1994	Open (individual injection choice) N = 6/0 (active drug/placebo)	Negative • No reduction in pain intensity • No reduction in pain sensitivity	

domised comparative trial of botulinum toxin A and methylprednisolone in the treatment of tension-type headache injected into individual tenderpoints in cranial muscles. A significant decrease in the median pain score at day 60 post injection of botulinum toxin A was found compared to methylprednisolone. All patients treated with botulinum toxin A experienced a gradual decrease in median pain severity scores at 30 days and 60 days post treatment. The beneficial effects of botulinum toxin A continued to improve 60 days after injection, whereas the effects of steroid therapy at this time point began to decline (SIGN Ib).

Thus an important finding of experience to date with botulinum toxin A in therapy of tension-type headache is that the injection should be performed at the site of the pain or the trigger points, and not on a standardised basis. Just as the injection is made specifically into the affected muscle in the treatment of dystonia cases, this must also be done in the treatment of pain. It is essential that this crucial point be observed in future controlled studies and in open use. If one considers the range of doses of botulinum toxin A used, which in the positive studies ranged from 15 to 100 MU Botox® or 160 to 200 MU Dysport®, the total dose injected would appear to be of secondary importance.

It would also appear to be important that a particularly good efficacy seems to result in cases where both migraine and tension-type headache exist [10, 21] (Table 3). Most studies dealt with either one syndrome or the other. Klapper et al. treated patients with chronic daily headache in a double-blind, placebo-controlled trial using 25.5 to 72.5 MU Botox®. In a subgroup with 2 injection regions (n=19, active drug) they found a reduction in headache duration and in frequency of moderate and severe headaches. Wheeler achieved the same results in a group of 4 patients treated open with 20 to 120 MU Botox®.

Botulinum toxin A in the treatment of cluster headache

For cluster headache there are only individual case reports (Table 4), thus it is not yet possible to make any pronouncement about the efficacy of botulinum toxin A. An improvement was nevertheless also found here in some cases that were hitherto therapy resistant. In all documented case reports so far botulinum toxin A was used in an open design with individual injection choice. Ginies et al. [6] were the first to present positive results. In 3 out of 5 patients they managed to end the current cluster period. In the case report of Freund and Schwartz [5] the cluster period ended in 2 out of 2 patients, whereas Smuts and Barnard [20] found positive results in 2 out of 4 patients. Larger and controlled studies are necessary to permit a better assessment of the therapeutic effect.

Botulinum toxin A in the treatment of headache attributed to disorders of the neck

In the case of headache attributed to disorders of the neck all open studies or case reports published so far demonstrated the efficacy of botulinum toxin A (Table 5). The first case report was presented by Hobson et al. [9]. 50 MU Botox® lead to a 50 % reduction in headache frequency in one patient (SIGN IV). Freund and Schwartz [4] found a reduction in pain intensity and an increase in neck mobility in a group of 8 patients treated (SIGN III). Smuts and Barnard [20] treated one patient successfully (SIGN IV).

In a double-blind, placebo-controlled study Freund and Schwartz [3] managed to underpin the positive results of these open studies. After injection of 100 MU Botox® in 14 patients there was both a reduction in pain intensity and an increase in neck mobility compared to the placebo group with 12 patients (SIGN Ib).

Tab. 3 Botulinum toxin A in the treatment of migraine plus tension-type headache

Study	Design	Outcome	SIGN level
Klapper et al., 2000	Double-blind, placebo-controlled (standardised injection) N = 38/18 (active drug/placebo)	Positive for a subgroup with 2 injection regions (n=19, active drug) • Reduction in headache duration • Reduction in frequency of moderate and severe headaches	Ib
Wheeler, 1998	Open (individual injection choice) N = 4/0 (active drug/placebo)	Positive • Increase in number of pain-free days • Reduction in pain intensity	IV

Tab. 4 Botulinum toxin A in the treatment of cluster headache

Study	Design	Outcome	SIGN level
Freund and Schwartz, 2000	Open (individual injection choice) N = 2/0 (active drug/placebo)	Positive • In 2 out of 2 patients end of current cluster period	IV
Ginies et al., 1996	Open (individual injection choice) N = 5/0 (active drug/placebo)	Positive • In 3 out of 5 patients end of current cluster period	IV
Smuts and Barnard, 2000	Open (individual injection choice) N = 4/0 (active drug/placebo)	Positive • 2 out of 4 patients showed positive result (not defined in detail)	IV

Tab. 5 Botulinum toxin A in the treatment of headache attributed to disorders of the neck

Study	Design	Outcome	SIGN level
Freund and Schwartz, 1999	Open N = 8/0 (active drug/placebo)	Positive • Reduction in pain intensity • Increase in neck mobility	III
Freund and Schwartz, 2000	Double-blind, placebo-controlled (individual injection choice) N = 14/12 (active drug/placebo)	Positive • Reduction in pain intensity • Increase in neck mobility	Ib
Hobson et al., 1997	Open (individual injection choice) N = 1/0 (active drug/placebo)	Positive • 50 % reduction in headache frequency	IV
Smuts and Barnard, 2000	Open (individual injection choice) N = 1/0 (active drug/placebo)	Positive • Positive result (not defined in detail)	IV

Special features

Botulinum toxin A represents a completely new option for patients with chronic pain syndromes, especially migraine and tension-type headache. Although studies have been conducted only for a relatively short time, the level of evidence for the efficacy of botulinum toxin A in the treatment of headache disorders is already high. Use of this active substance does not result in any side effects on the CNS. Owing to undesirable side effects of the medication used, headache patients in particular frequently suffer considerably from fatigue, giddiness, reduced concentration, increased appetite and weight, hair loss and changes in libido. These side effects are unknown with botulinum toxin A. No cases of damage to organs have been reported to date. Neither have allergic complications been observed to date. Thus the tolerability and safety of this therapeutic measure are very high. Its long-term action lasting several months obviates the need to remember to take medication several times a day. Numerous clinical studies are currently investigating in detail the new applications of botulinum toxin A in the field of specific pain therapy. The data and findings already available open up new approaches to the treatment and analysis of the pathomechanisms of these widespread chronic pain syndromes.

References

1. Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pogoda JM (2000) Botulinum toxin type A (Botox) for treatment of migraine headaches: an open-label study. Otolaryngol Head Neck Surg 123:669–676
2. Brin MF, Swope DM, O'Brian C, Abbasi S, Pogoda JM (2000) Botox for migraine: double-bind, placebo-controlled region-specific evaluation. Cephalalgia 20:421–422
3. Freund B, Schwartz M (2000) The use of botulinum toxin A in the treatment of refractory cluster headache: case reports. Cephalalgia 20:329–330
4. Freund BJ, Schwartz M (1999) Treatment of whiplash associated neck pain with botulinum toxin-A: report of 8 cases. J Rheumatol 26:756–758
5. Freund BJ, Schwartz M (2000) Treatment of chronic cervical-associated headache with botulinum toxin A: a pilot study. Headache 40:231–236
6. Ginies PR, Fraimout JL, Kong A Siou D, Chevallier J, Mann C, Colson P (1996) Treatment of cluster headache by subcutaneous injection of botulinum toxin. 8th World Congress on Pain 1996. Poster presentation: 50
7. Göbel H, Deuschl G (1999) Dauerkontraktionen kranialer oder zervikaler Muskeln – Wenn Dystonien Kopfschmerz bereiten. Münch Med Wschr 139:30–31
8. Göbel H, Lindner V, Krack P, Heinze A, Gaartz N, Deuschl G (1999) Treatment of chronic tension-type headache with botulinum toxin. Cephalalgia 19:455
9. Hobson DE, Gladish DF (1997) Botulinum toxin injection for cervicogenic headache. Headache 37:253–255
10. Klapper JA, Mathew NT, Klapper A, Kailasam J (2000) Botulinum toxin type A (BTX-A) für the prophylaxis of chronic daily headache. Cephalalgia 20:291–292
11. Krack P, Hornig C, Dorndorf W (1995) Resolution of chronic tension headache after botulinum toxin treatment of idiopathic blepharospasm. Mov disord 10:388
12. Mauskop A, Basdeo R (2000) Botulinum toxin A is an effect prophylactic therapy of migraines. Cephalalgia 20:422
13. Porta M (2000) A comparative trial of botulinum toxin A and methylprednisolone for the treatment of tension-type headache. Curr Rev Pain 4:31–35
14. Relja MA (1997) Treatment of tension-type headache by local injection of botulinum toxin. Eur J Neurol 4 (suppl. 2):71–72
15. Relja MA (2000) Treatment of tension-type headache with botulinum toxin: 1-year follow-up. Cephalalgia 20:336
16. 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
17. 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
18. Scottish Intercollegiate Guidelines Network (1999) SIGN Guidelines – an introduction to SIGN methology for the development of evidence-based clinical guidelines. Edinburgh, SIGN Publication Number 39. SIGN Secretariat. Royal College of Physicians
19. Silberstein S, Mathew N, Saper J, Jenkins S (2000) Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. Headache 40:445–450
20. Smuts JA, Barnard PWA (2000) Botulinum toxin type A in the treatment of headache syndromes: a clinical report of 79 patients. Cephalalgia 20:332
21. Wheeler AH (1998) Botulinum toxin A, adjunctive therapy for refractory headaches associated with pericranial muscle tension. Headache 38:468–471
22. Zwart JA, Bovim G, Sand T, Sjaastad O (1994) Tension headache: botulinum toxin paralysis of temporal muscles. Headache 34:458–462