

Botulinum toxin and the management of chronic headaches

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Purpose of review

There is an increasing number of reports on botulinum toxin in pain therapy, in particular in headache treatment. Therefore, the studies available from reference systems and published congress contributions on the prophylactic treatment of idiopathic and cervicogenic headache with botulinum toxin were analyzed with respect to study design, headache diagnosis, and the significance of results.

Recent findings

For the prophylactic treatment of tension-type headache, migraine, and cervicogenic headache, no sufficient positive evidence for treatment with botulinum toxin is obtained from randomized, double-blind, placebo-controlled trials to date. For the treatment of miscellaneous headache, there is some but no consistent positive evidence.

Summary

Most open studies and case reports suggest an efficacy of botulinum toxin in headache prophylaxis but double-blind, placebo-controlled studies do not confirm this assumption. Larger controlled studies are needed for a definite evaluation of subgroups that might possibly benefit from such a treatment. Migraine, tension-type headache, and cervicogenic headache cannot be regarded as a general indication for a treatment with botulinum toxin.

Keywords

botulinum toxin, tension-type headache, migraine, cervicogenic headache, chronic daily headache

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Introduction

Besides its use in the treatment of dystonic movement disorders and increased muscle tonus, botulinum toxin has been heavily discussed for the treatment of pain, in particular of headache. After the first case reports and controlled studies were documented, several reviews were published [1–10] showing conflicting results and conflicting interpretations regarding the use of botulinum toxin in idiopathic headache disorders. In this review, the published evidence for the treatment of different headache disorders with botulinum toxin is analyzed. The review is based on a literature research in medical databases (MEDLINE, Embase, Current Contents, Science Citation Index) and on published congress reports of the relevant headache and pain congresses during the past 6 years. Key words were botulinum, headache, and migraine. The studies were separated in randomized, double-blind, and placebo-controlled trials and in open studies or case series. Because there are very few case reports on the acute treatment of headache with botulinum toxin [11,12], only studies on the prophylactic treatment of headache were considered. As recommended by the International Headache Society, headache frequency was regarded as the most important primary end point of the studies both for the prophylaxis of migraine and tension-type headache [13,14]. Studies on patients with different headache diagnoses or with coexisting headaches were grouped as miscellaneous.

Because there are now studies available both with botulinum toxin A and with botulinum toxin B for headache treatment, only the term botulinum toxin will be used.

Tension-type headache

In Table 1 [15–28] the studies on botulinum toxin in the prophylactic treatment of tension-type headache are listed. Six randomized, double-blind, and placebo-controlled studies on patients with tension-type headache were analyzed [15–20]. Apart from one study, all these studies did not show any evidence for an efficacy of botulinum toxin in reduction of headache frequency. The only study with a significant reduction of headache days in the treatment group but not in the placebo group, however, did not perform a formal statistical comparison between the two groups [16]. In some secondary end points, such as headache intensity or headache duration, a positive trend or significant subgroup analysis could be

Table 1. Studies of botulinum toxin in the prophylactic treatment of tension-type headache

Reference	Indication to treatment	N	Methods	Results
Göbel <i>et al.</i> (1999) [15]	Chronic tension-type headache	10	r, db, pc	No significant reduction of pain intensity, headache hours, or use of analgesics
Smuts <i>et al.</i> (1999) [16]	Chronic tension-type headache	41	r, db pc	Significant reduction of headache intensity and pain-free days in month 3 compared with baseline data in group with botulinum toxin but not in placebo group
Rollnik <i>et al.</i> (2000) [17]	Chronic tension-type headache	21	r, db, pc	No significant differences between botulinum toxin and placebo in all headache parameters
Burch <i>et al.</i> (2001) [18]	Chronic and episodic tension-type headache	41	r, db, pc	No significant difference in headache frequency
Schmitt <i>et al.</i> (2001) [19]	Chronic tension-type headache	59	r, db, pc	No significant differences between botulinum toxin and placebo in all headache parameters
Schulte–Mattler and Krack (2003) [20]	Chronic tension-type headache	113	r, db, pc	No significant reduction in all efficacy end points
Zwart <i>et al.</i> (1994) [21]	Chronic tension-type headache	6	Open, not randomized, not controlled	No significant reduction of pain intensity and “pressure pain threshold”
Relja (1997) [22]	Chronic tension-type headache	10	Open, not randomized, not controlled	After 8 weeks, 2 patients were pain-free and 6 patients had reduced pain intensity from severe to mild; after 12 weeks, no effects any more
Schulte–Mattler <i>et al.</i> (1999) [23]	Chronic and episodic tension-type headache	9	Open, not randomized, not controlled	No significant reduction of headache days, but significant reduction of “area under curve” (product of duration and intensity of headache)
Porta (2000) [24]	Chronic (n = 7) and episodic (n = 13) tension-type headache	20	r, single-blind comparison of botulinum toxin A and lidocaine with methylprednisolone and lidocaine	Significant headache reduction after 60 days in botulinum toxin group
Relja (2000) [25]	Tension-type headache (unspecified)	25	Open, not randomized, not controlled	Significant increase of pain-free days over 15 months, significant reduction of pain intensity in months 9, 12, and 15 compared with months 3 and 6
Relja and Klepac (2001) [26]	Foresaid study continued	27	Patients of foresaid study; r, db, pc	Significant reduction of headache days and intensity compared with the control group; no difference of “total tenderness score” between botulinum toxin and placebo
Rollnik <i>et al.</i> (2001) [27]	Chronic tension-type headache	8	r, db, not blinded	No significant differences between botulinum toxin and placebo in headache (area under curve)
Freund and Schwartz (2002) [28]	Chronic tension-type headache	46	Open, not randomized, not controlled	All patients reported more than 50% pain reduction (all with temporomandibular disorder)

r, randomized; db, double blind; pc, placebo controlled.

observed. The studies used different doses and different injection sites; thus, no direct comparison is possible. The design of these studies mainly followed the guidelines of the International Headache Society for studies on tension-type headache [13], including the diagnosis according to the International Headache Society criteria [29]. In particular, the primary end point was the reduction of headache frequency.

Eight further studies without a complete randomized, double-blind, and placebo-controlled design could be evaluated. These studies showed conflicting results. In three studies [21,23,27], no significant efficacy of botulinum toxin on headache frequency or headache days could be observed. In some secondary end points, however, such as area under the curve [23], statistical significance was reached. The comparison between an injection of botulinum toxin plus lidocaine and methylprednisone plus lidocaine showed a significant difference after 60

days, with less headache in the group with botulinum toxin compared with the patients treated with methylprednisone plus lidocaine [24]. In another study [30], the treatment with botulinum toxin in both frontal and suboccipital sites caused a significant reduction of headache compared with three other treatment subgroups with less injection sites. Two studies by the same author [22,25] showed an improvement of headache in a majority of patients, as did another study [28]. These latter studies, however, were open and observational. In a long-term, blinded, placebo-controlled study, the efficacy of botulinum toxin was maintained over 1 year in some patients [26].

In summary, all but one randomized, double-blind, placebo-controlled study on botulinum toxin in the prophylactic treatment of tension-type headache showed negative results whereas most open studies were in favor of botulinum toxin.

Migraine

For the prophylactic treatment of migraine (Table 2 [31–39]), three randomized, double-blind, placebo-controlled studies are available. Two of these studies did not show a significant reduction of migraine frequency by botulinum toxin [32,33]. However, one study showed a significant reduction of pain intensity by botulinum toxin [32]. In one study, the low-dose group of botulinum toxin (25 U) was significantly superior to placebo in reducing migraine attacks after 3 months. The higher dose (75 U), however, did not result in a significant improvement of migraine [31].

All open studies on migraine prophylaxis with botulinum toxin showed positive results, with a majority of patients experiencing improvement by the injections [11,34–39]. These studies, however, were in part with mixed patient groups and only retrospective chart analyses. Furthermore, improvement in some studies was based only on the impression of the patient but not on diary measures.

Cervicogenic headache

Regarding pure cervicogenic headache, only three studies were available (Table 3 [40–42]). One study treated 24 patients with cervicogenic headache and six patients with possible cervicogenic headache (a clear distinction between cervicogenic headache and tension-type headache was not possible) [40]. The control examination after 4 weeks showed significant pain reduction but no significant improvement of headache frequency in the botulinum toxin group. A further randomized, double-blind, placebo-controlled trial showed only a trend to a lower analgesic use and a trend to a reduction of pain

duration during weeks 5 to 9 after the injection of botulinum toxin, but no improvement of headache frequency either [41]. Beside these studies, only positive case reports are available [42,43].

Cluster headache

The application of botulinum toxin for the treatment of cluster headache was published only in case reports (Table 4 [44–46]). One author treated four patients with chronic and two patients with episodic cluster headache [44]. Two patients experienced abrupt pain relief, two patients had a moderate effect with a reduction of attack frequency, and two patients had no effect. Another study reported four patients, of whom two had a benefit after injection [43]. Of two patients, one was pain free after 6 days and the other was pain free after 9 days [45]. One successful case report on the treatment of chronic paroxysmal hemicrania was published [46].

Miscellaneous studies

A number of studies has been published on mixed headache patients or on patients with chronic daily headache, which is not an entity defined by the International Headache Society (Table 5 [47,48•,49–56]). Mostly, patients with headache medication overuse and subsequent chronic daily headache are enrolled in these studies. Furthermore, patients with a combination of different headache types such as coexisting migraine and tension-type headache have been examined. There are three randomized, double-blind, placebo-controlled studies of these miscellaneous headache populations. Two of these studies [30,48•] showed some benefit from botulinum toxin (*e.g.*, in pain intensity), but the primary end point of

Table 2. Studies of botulinum toxin in the prophylactic treatment of migraine

Reference	Indication to treatment	N	Methods	Results
Silberstein <i>et al.</i> (2000) [31]	Migraine	123	r, db, pc	Significant reduction of migraine frequency in group with 25 U compared with the control group; no significant results in 75-U group
Brin <i>et al.</i> (2000) [32]	Migraine	56	r, db, pc	No significant reduction of migraine frequency and duration; significant reduction of pain intensity in week 12
Schwaag <i>et al.</i> (2003) [33]	Migraine	60	r, db, pc	No significant results
Binder <i>et al.</i> (2000) [11]	Migraine	106	Open, not randomized, not controlled	51%, no attacks for 4.1 months; 38%, improvement \geq 50% for 2.7 months
Mauskop and Basdeo (2000) [34]	Migraine	27	Retrospective study	23 patients with complete remission or reduction of pain intensity by > 50%, 4 patients without improvement
Opida (2002) [35]	Transformed migraine	47	Open, not randomized, not controlled	64% patients with improvement
Barrientos <i>et al.</i> (2003) [36]	Migraine	30	r, pc, open	Significant reduction of migraine frequency in botulinum toxin group but not in placebo group
Tamura and Chang (2003) [37]	Migraine	10	Open, not randomized, not controlled	Significant improvement when injecting botulinum toxin in acupuncture points
Behmand <i>et al.</i> (2003) [38]	Migraine	29	Open, not controlled, not randomized	83% of the patients with more than 50% reduction of migraine frequency of intensity
Eross and Dodick (2003) [39]	Episodic and chronic migraine	61	Open, not randomized, not controlled	62% of patients with at least 50% reduction of migraine frequency

r, randomized; db, double blind; pc, placebo controlled.

Table 3. Studies of botulinum toxin in the prophylactic treatment of cervicogenic headache

Reference	Indication to treatment	N	Methods	Results
Freund and Schwartz (2000) [40]	Cervicogenic headache	26	r, db, pc	4 weeks after injection, significant pain reduction and improvement of range of motion; no significant reduction of headache days
Schnider <i>et al.</i> (2001) [41]	Cervicogenic headache	33	r, db, pc	No significant results
Hobson and Gladish (1997) [42]	Cervicogenic headache	1	Case report	Within 3 months > 50% reduction of attacks

r, randomized; db, double blind; pc, placebo controlled.

headache frequency was not reduced significantly by botulinum toxin. One study of patients with coexisting migraine and tension-type headache was positive also in headache frequency [47].

In the open studies on these patient groups, mostly positive results can be observed. In several studies, more than 50% of the patients had a significant improvement of their headache intensity or frequency [43,49,52–56]. Interestingly, one of these studies was performed in children [54]. However, even a few open studies did not result in a significant efficacy of botulinum toxin in the prophylaxis of chronic daily headache [50,51].

Pathophysiologic aspects

For the explanation of successful treatment of idiopathic headache with botulinum toxin, different hypotheses with different pathophysiologic concepts can be found. Various authors discuss peripheral myogenic as well as central antinociceptive mechanisms [1,57,58].

A direct myotonic effect of botulinum toxin as the underlying mechanism of a potential pain relief seems obvious and is based on the experience that in dystonia the substance can offer a pain-decreasing effect independent from the antispastic effect in adults [59,60] and in children [61]. However, this hypothesis might not be a sufficient explanation because, to date, there is no evidence that pathologically increased muscle tonus is the only reason for primary headache. In contrast, most experimental studies are not in accord with this hypothesis [62]. The concept of a peripheral mode of action is supported by the effect of botulinum toxin on muscle spindles in experimental animal studies [63,64]. A direct affection of intra- and extrafusal γ -fibers was demonstrated, resulting in reduced activity of α -motor neurons and decreased muscle tonus.

Experimental studies of the central effect of botulinum toxin were able to show that the substance is internalized in neurons and can be transported afferently, and that an uptake in cultures of hippocampal neurons and astrocytes is possible [65,66]. This uptake in nociceptive neurons leads to a decreased release of neuropeptides (*e.g.*, substance P) in cell or animal models [67,68••] and to a blockade of glutamate release in an *in vivo* model [58]. An increased release of neuropeptides as well as sensitization of trigeminal nociceptors of the first branch are well-known mechanisms in idiopathic headache [69]. An attenuation of peripheral neuropeptide release by botulinum toxin has also been shown in human *in vivo* studies [70•]. This attenuation, however, was without any analgesic effect. Cutaneous nociception in humans was also unaffected by botulinum toxin in another experimental study [71•].

Conclusion

In this review, the current published data on botulinum toxin in headache treatment was analyzed, showing that general efficacy of this therapy cannot be postulated to date. According to the guidelines of the International Headache Society, reduction of headache frequency is the most important aim of prophylactic treatment and should be the primary outcome parameter [13,14]. However, with respect to the often insufficient design of the trials, an inverse statement of a general inefficacy in idiopathic headache is not possible.

For tension-type headache, nearly all randomized, double-blind, placebo-controlled trials showed negative results. Within the open or uncontrolled studies, the number of positive and negative studies is about the same. It is necessary to take into consideration that the probability of publishing negative results or case reports is poorer. Concerning the prophylactic treatment of migraine, one

Table 4. Studies of botulinum toxin in the prophylactic treatment of trigemino-autonomic headache

Reference	Indication to treatment	N	Methods	Results
Robbins (2001) [44]	Chronic and episodic cluster headache	6	Case reports	Two cases, no effect; one case, moderate effect; three cases, immediate effect
Freund and Schwartz (2000) [45]	Chronic cluster headache	2	Case reports	Both cases abruptly pain free within 9 days
Göbel <i>et al.</i> (2001) [46]	Chronic paroxysmal hemicrania	1	Case report	Pain free after 6 days

r, randomized; db, double blind; pc, placebo controlled.

Table 5. Studies of botulinum toxin in the prophylactic treatment of miscellaneous headache and chronic daily headache

Reference	Indication to treatment	N	Methods	Results
Klapper <i>et al.</i> (2000) [30]	Miscellaneous chronic headache	56	r, db, pc	Significant reduction of headache intensity and duration in month 2 compared with placebo; no significant reduction in headache frequency
Göbel <i>et al.</i> (2003) [47]	Coexisting migraine and chronic tension-type headache	40	r, db, pc	Both migraine and tension-type headache days significantly reduced compared with placebo
Ondo <i>et al.</i> (2004) [48•]	Chronic daily headache	60	r, db, pc	No significant reduction but a trend ($P=0.07$) in primary end point (days with headache)
Wheeler (1998) [49]	Chronic daily headache	4	Case reports	2 patients with remission, 2 patients with pain reduction
Mauskop (1999) [50]	Chronic daily headache	12	Open, not randomized, not controlled	1 patient with pain reduction
Smuts and Barnard (2000) [43]	Tension-type headache, migraine, cluster headache, cervicogenic headache	79	Open, not randomized, not controlled	“Positive” results for 30 of 50 patients with tension-type headache, for 13 of 19 patients with migraine, for 2 of 4 patients with cluster headache, for 1 with cervicogenic headache
Robbins (2001) [51]	Chronic daily headache	79	Open, not randomized, not controlled	30% of patients with “moderate” or “good” effect, 70% with “mild” or no effect
Borodic and Acquadro (2002) [52]	Different types of facial pain	44	Open, not randomized, not controlled	75% of patients with more than 50% pain reduction (frequency or intensity)
Porta and Maggioni (2002) [53]	Chronic daily headache	60	r, open, parallel group (no placebo)	45–80% reduction of headache days in three different treatment groups
Berweck <i>et al.</i> (2003) [54]	Chronic daily headache	6 (children)	Open, not randomized, not controlled	Reduction of headache days in all 6 children
Erdemoglu and Varlibas (2003) [55]	Chronic daily headache	28	Open, not randomized, not controlled	64% of patients with complete headache relief
Blumenfeld (2003) [56]	All primary chronic and episodic headaches	256	Retrospective study	56% of patients with reduction of days with headache

r, randomized; db, double blind; pc, placebo controlled.

both positive and negative study (dependent on the dose) and two negative studies with a high level of evidence can be found. Beside these studies, the open case series and prospective studies suggest an efficacy of botulinum toxin in migraine prophylaxis. For cervicogenic headache, the two randomized, double-blind, placebo-controlled studies did not show a significant reduction of headache frequency by botulinum toxin. For patients with cluster headache, only case reports have been published to date. Approximately half the patients experienced proper relief. Notably, the phenomenon that some patients with cluster headache were pain free directly after the injection cannot easily be explained by the known pharmacologic characteristics of botulinum toxin. For chronic daily headache, no consistent picture can be obtained both from the randomized, double-blind, placebo-controlled trials and from the open studies.

In conclusion, botulinum toxin might be sufficient therapy for defined subgroups of patients with idiopathic headache, but well-designed, controlled studies with a large number of patients are needed for a valid evaluation. To date, no sufficient and consistent evidence by randomized, double-blind, placebo-controlled studies is given for idiopathic headache disorder, for cervicogenic

headache, or for chronic daily headache. There is a big discrepancy between the large number of negative blinded trials in contrast to the large number of positive open trials.

Furthermore, the known standard therapies in headache treatment need to be compared with botulinum toxin. This can be performed in blinded, double-dummy studies, which are, however, difficult to design. It is nevertheless important for the development of treatment recommendations to discuss the advantages and disadvantages of this particular prophylactic procedure in comparison with oral medication.

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