# Low-dosed Botulinum Toxin A in the Prophylactic Management of Unilateral Migraine: A Randomized Double-blind Placebo-Controlled Crossover Study

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**Abstract:** Botulinum toxin is a therapeutic option in chronic migraine. No dose-finding studies have been conducted so far. Some authors maintain that one injection into the corrugator muscle will do.

*Objective*: We studied the effect of Botulinum toxin (BTX) injections in patients with strictly unilateral migraine.

*Methods*: We treated 22 patients (ITT) in a crossover design for 4 months with 2 x 5 units Onabotulinum toxin (in the corrugator and occipitalis muscle ipsilaterally). Aside from patient data, we also gathered information on undesired drug effects, besides IQOLA SF36, SF-MPQ SADP, OLBPDQ, VAS (pain intensity and daily living skills), PPI, frequency of attacks and application of medication. The statistical evaluation was guided by SPSS (V.13).

*Results*: Assessed were 19 patients (PP) aged 45.2 ± 11.1 years, thereof 17 women. In both injection intervals there were no clinically relevant and/or statistically significant differences as to the target parameters (for example: VAS pain intensity p=0.702), with a notably evident placebo effect (VAS in placebo prior to the injection was 61.4, after 6 weeks 45.1; good or excellent improvement (TOQ) was quoted by 36.8% after 6 weeks in the placebo group). BTX merely proved superior in two aspects: Regarding the pain quality "throbbing" (SF-MPQ SADP), 11 patients initially indicated a pronounced intensity; after BTX only 4 of them did. As to the severity of the pain felt, (PPI) 42.2 of the subjects described "limiting" or "horrible" pain prior to the injection versus 26.3% six weeks after the injection and 21.1% 4 months later. The placebo group started out with 31.6%, that figure remaining the same (31.6%) 6 weeks later, rising to 42.2% after 4 months. 84.2% of the BTX-group and 63.2% in the placebo group requested a reinjection when the study was completed.

*Conclusion*: The injection of low-dosed Botulinumtoxin A did not show any relevant or significant effects in patients with unilateral migraine without aura. One injection into the corrugator muscle alone must be considered as ineffective. The place-value of the two injection sites remains in the open.

**Keywords:** Chronic migraine, Botulinum toxin, Onabotulinum toxin A, corrugator muscle.

## INTRODUCTION

For years, Botulinum toxin (BTX) has been considered an option in the management of chronic migraine [1]. The data published represent contradictory results. Based on current research [2-4], the intermediate approval for treatment of chronic migraine is obtained in USA and UK and expected in continental Europe. There is no evidence for a beneficial effect of BTX in patients with episodic migraine [5].

Standardized doses and injection schemes have most commonly been used. A dose-finding study has not yet been conducted. In many studies high doses were preferred, without any justification. Some authors maintain that one injection into the corrugator muscle will suffice; surgical sectioning is recommended if there is response to treatment [6, 7].

With this study we therefore wanted to elucidate whether or not a small dose of botulinum toxin injected at only two sites would do to produce a significantly marked and more prolonged pain reduction than placebo.

## PATIENTS AND METHODS

This was a randomized double-blind placebo-controlled crossover study.

Enrolled were 22 patients between the age of 18 and 70 with the clinically confirmed diagnosis of migraine without aura – only unilateral that is. The duration of this illness, so far refractory to conservative treatment (physiotherapy, massages, stretching exercises, peroral medication) was supposed to come to at least 2 years.

## INCLUSION CRITERIA:

| |
|---|
| Age 18-75 years |
| Confirmed diagnosis of migraine without aura (according to IHS) |
| Refractory to treatment by conservative approaches |
| Duration of disease > 2 years |
| Submission of written consent |

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## EXCLUSION CRITERIA:

| |
|---|
| Participation in another clinical trial within the past 3 months |
| Specific pain in neck/shoulder region in need of different specific treatment (i.e. acute nerve irritation with disk prolapse, manifest inflammatory processes etc.) |
| Contraindication of treatment with botulinum toxin (ascertained sensitivity to clostridial toxin or to one of the other ingredients and generalized disorders of muscular activity, e.g. myasthenia gravis or Lambert-Eaton syndrome) |
| Pregnancy or breastfeeding, inadequate or no contraception in women of childbearing age |
| Serious concomitant illnesses involving the internal organs in particular, and systemic diseases and serious neurologic disorders |
| Abuse of alcohol, drugs and narcotics |
| Medication with anticoagulants and heparin preparation (topically applied heparin unguents excluded), thrombocyte aggregation inhibitors, aminoglycoside antibiotics, spectinomycin or muscle relaxants of the tubocurarine type |

The patients gave their written consent to participate in the study. The study was also endorsed by the local Ethics Commission.

Pain reduction was the primary target parameter at any time of set examinations, as determined by the visual analog scale.

The changes in pertinent scores to rate pain and to assess the state of health (SF-McGill Pain Questionnaire, Northwick Park Neck Pain Questionnaire, IQOLA SF 36, SADP, OLBPDQ,) were defined as secondary target parameters. Additional focus was on undesired drug effects, the number and duration of headache attacks and adjuvant medication.

The statistical evaluation was done by SPSS (V.13). An injection was administered with 5 MU Onabotulinum toxin A (0.1 ml Botox®) /injection site vs. 0.1 ml 0.9% NaCl-solution in crossover design into the corrugator muscle and the occipitalis muscle of the side affected – thus a total of 10 U Botox®. Four months later, a reinjection was applied with the alternative injection scheme (Table **1**). At the end of phase 2, the patients were offered free-of-charge further treatment with the true preparation.

## RESULTS

Evaluated were 19 patients (PP), 45.2 ± 11.1 years old, 17 of them were females.

We found no clinically relevant or statistically significant differences regarding the target parameters in both injection intervals (for example: VAS pain intensity p=0.702), with a notable placebo effect (Table **2**); good or excellent improvement (TOQ) 36.8% after 6 weeks in the placebo group. BTX proved to be superior in merely two aspects. The pain quality "throbbing" (SF-MPQ SADP) was initially rated by 11 patients as very intense, after BTX only 4 of them claimed that this had not changed. As far as the perception of pain intensity (PPI) was concerned, 42.2% of the subjects described their pain as „limiting" or "horrible" before receiving the injection; this held true for 26.3% 6 weeks later, and for 21.1% after 4 months. In the placebo group, this initially pertained to 31.6%, after 6 weeks to 31.6% again, and after 4 months to 42.2%. 84.2% in the Onabotulinum toxin A - group and 63.2% in the placebo group requested a reinjection upon completion of the study.

## DISCUSSION

Meanwhile dozens of studies have been published on the efficacy of botulinum toxin in various pain syndromes. Noteworthy among them is the research done in the field of chronic headache; the results, however, are unfortunately

**Table 1. Schedule of Examinations and Injections**

| Week /month | -1 W. | 0 | +6 W. | +4 M. | +5 ½ M. | +6-7 M. |
|---|---|---|---|---|---|---|
| | | | | | | |
| Personal contact with physician | X | X | X | X | X | X |
| Consent form | X | | | | | |
| History | X | | | | | |
| Medical examination | X | | | | | |
| Neurological examination | X | | | | | |
| Pain diary - handover | X | | | | | |
| Control of pain diary | | X | X | X | X | X |
| Scoring | X | X | X | X | X | X |
| Evaluation of therapeutic response | | | X | X | X | X |
| Injection | | X | | X | | |
| Review of side-effects | | | X | X | X | X |
| Optional reinjection | | | | | | X |

**Table 2. VAS (Visual Analogue Scale), Pain Intensity in mm (0 = no Pain, 100 mm = Worst Imaginable Pain, p=0.702)**

| | Prior to Injection | 6 Weeks After Injection | 4 Months After Injection |
|---|---|---|---|
| Onabotulinum toxin | 57.3 | 42.1 | 53.7 |
| Placebo | 61.4 | 45.1 | 53.0 |

rather contradictory [8-11]. Most of the open studies related positive results, whilst most of the controlled studies reported negative findings [8, 10, 12, 13]. The type of headache is certainly playing a key role; current findings corroborate the effect on chronic migraine rather than on tension-type headache [10]. The criterion "chronic" proved to be decisive, meaning patients have headaches more than half of the time. Whereas good results had first and foremost been obtained for patients with chronic daily headache [9, 11, 14], positive outcomes have in the mean time been verified in chronic migraine as well [2-4].

By direct comparison with topiramate, a similar action was revealed in the presence of considerably less undesirable effects [15]. In another study BTX was as effective as amitriptyline [16].

We set out to study the effect of injections at 2 sites unilaterally (in the corrugator and occipitalis muscle ipsilaterally) with a low dose of BTX (total 10 U Onabotulinum toxin A). This study hasn't been adequately powered, its validity is therefore limited. We terminated the inclusion of patients after not seeing any clinical improvement. A statistically reliable conclusion would have required a much larger group of patients.

There were no appreciable differences in both groups. One injection only administered to these two sites would thus qualify as inefficient. Of course, this also applies to one injection into the corrugator muscle alone. The surgical section of the corrugator muscle after the alleged response to a BTX injection must not be regarded as a therapeutic option for migraine [6, 7].

In the assessment of effects we always distinguish strictly between episodic and chronic migraine. However, we are not dealing with 2 entities of disease. The classification is solely based on the time factor. We presently have no evidence that BTX is efficient in episodic migraine, but there is sufficient evidence as to its efficacy in chronic migraine. Of course, and by reversal conclusion, this doesn't mean that BTX won't work in episodic migraine. There is merely no statistical significance.

## CONCLUSION

From the data published so far, the injection of BTX may be considered a promising approach in the management of chronic migraine. Optimum injection sites and appropriate doses, however, still need more exploration. One injection into the corrugator muscle alone must be considered as ineffective

## CONFLICT OF INTEREST

The study was not at all sponsored by manufacturers of botulinum toxin. The statistical analysis was funded by the Botulinum toxin work group of the Deutsche Gesellschaft für Neurologie (German Society of Neurology).The author is a lecturer and counseler to the companies Allergan, Ipsen and Merz.

## ABBREVATIONS

BTX = Botulinum toxin

IQOLA = International quality of life assessment

ITT = Intention to treat

OLBPDQ = Oswestry low back pain disability questionnaire

PP = Per protocol

PPI = Present pain intensity

SADP = Scale of attitudes toward disabled persons

SF36 = Short form (36) health survey

SF-MPQ = Short-form McGill pain questionnaire

SPSS = Statistical package for the social sciences

TOQ = Treatment optimization questionnaire

VAS = Visual analog scale

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