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Management of Chronic Daily Headache with Focus on Botulinum Toxin Type A

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Abstract

Aim: The purpose of the study was to review the efficacy, safety, and tolerability of botulinum toxin A (BTX-A) as a prophylactic treatment in adults with chronic daily headache (CDH).

Material and methods: The research participated in 100 patients with CDH comparing two groups of patients. Group I, 54 patients (31 women and 23 men) treated by BTX-A and group II, 46 patients (27 women and 21 men) treated with the classical method, with an average age of 35 ± 9 years. The patient's condition in group I was assessed on the third day, on the 7th day and the 15th day after the BTX-A injection and assessed every 15 days for 3 months, in group II the patients were evaluated every 15 days.

Results: After 3 months headache severity in group I: 2 (3,7%) patients had no changes, 7 (12,9%) patients with less than 50 percent reduction in pain, 23 (42,6%) reported 70 to 95 percent pain relief, and 22 (40,8%) had complete relief. Group II: 12 (26,1%) patients had no changes, 16 (34,8%) patients with less than 50 percent reduction in pain, 10 (21,7%) reported 70 to 95 percent pain relief, and 8 (17,4%) had complete relief. The mean change from baseline frequency of headaches ranged from 3 ± 1 headaches per 30-day periods in-group I and 7 ± 2 headaches in group II. The patient's in-group I used painkillers for an acute headache 4 ± 1 day, compared to 10 ± 2 days for the group II per 30-day period.

Conclusion: In this study, BTX-A injections are safe, well-tolerated, not any treatment-related serious adverse events reported. BTX-A injections recommended optimizing clinical outcomes for patients with CDH without using other prophylactic medications. Although, further observations are needed.

Keywords

BTX-A Injection; Daily Chronic Headache; Primary Headache

Abbreviations

BTX-A: Botulinum Toxin Type A; CDH: Chronic Daily Headache; CTTH: Chronic Tension-Type Headache; FSFD: Fixed-Site and Fixed-Dose; FTP: Follow-The-Pain; CM: Chronic Migraine

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Introduction

For more than two decades now, BTX-A injections have been used in cosmetic treatments to reduce wrinkles. The efficacy of BTX-A for the treatment of a headache discovered by an accident. Several patients who were using BTX-A injection for wrinkles reported an improvement in headaches, which they have for several years. This was the beginning of carrying out a multitude of studies to determine the efficacy of BTX-A for headache treatment. The U.S. Food and Drug Administration (FDA) approved BTX-A for the preventive treatment of CDH in October 2010.

BTX-A injections have their effect by binding to presynaptic nerve endings and interfering with the exocytosis of the neurotransmitter acetylcholine in the neuromuscular junction, which prevents muscle contraction and leads to muscle paralysis. Improvement of headache symptoms usually occurs within 1-14 days and the duration period is about 3 to 6 months. Some experimental studies showed that BTX-A could inhibit the release of nociceptive neuropeptides such as substance P from either cholinergic neurons or C or A-delta fibres. This would prevent the local sensitization of nociceptors and, thus, reduce the perception of the pain. Consequently, a reduction of nociceptive signals from the peripheral nervous system could then reduce the central sensitization associated with chronic pain [1-4].

CDH is one of the global problems, which affects around 4% of the general population [5]. The term Chronic Daily Headache is a descriptive that includes disorders with headaches. The primary chronic daily headache divided into short and long duration. The short duration headache lasting less than four hours includes various Trigeminal Autonomic Cephalalgias (TACs) that include: Cluster Headaches (CH), Paroxysmal Hemicrania (PH) and primary stabbing headache. In accordance with the ICHA of the 3rd version (2014), primary chronic daily headache subtypes of long duration are a Chronic Migraine (CM), chronic tension-type headache (CTTH), hemicrania continua, and new daily persistent headache [6]. For neurologists, the major challenge is the management of CDH, but with the right approach to treatment, the result will be successful. In our study, we will consider long-duration primary headaches, which occur on more than 15 days a month for more than three months and lasting for more than four hours per day.

CDH mechanism is not fully understood, but the sensitization of central nociceptive neurons is one possibility. This process can be caused by prolonged activation of peripheral nociceptors or any other factors that can change the endogenous pain control system. The development of CDH can result from the plasticity of a serotonin-dependent pain control system that affects sensitization [7,8].

Most researchers have reported the consequences of CDH on the quality of life of patients. The patients with CDH have complained to significant impairment with damage to their quality of life. Both during the attack and the interictal period of the CDH adversely affect the patient's quality of life [9]. CDH was consistently associated with loss of productivity and greater disability of the patients.

Material and Methods

The study involved 100 patients with primary CDH comparing between two groups of patients. Group I, 54 patients treated by BTX-A, where 31 women and 23 men and group II, 46 patients treated with the classical method, where 27 women and 21 men with an average age of 42 years and a minimum age of 18 years old.

The inclusion criteria were the presence of primary daily chronic headache lasting more than four hours duration, a frequency of minimum 15 days monthly, in the last three months. The criteria for excluding patients from this study where pregnant (category C-safety for use during pregnancy), breastfeeding, patients abusing alcohol, a patient with the prior allergic reaction for BTX- A, a patient with infection or inflammation in areas of injection, pre-exciting cardiovascular diseases, and age under 18 years old.

They were prevented from taking the analgesics that were currently used before the beginning of the

study. In this study, the group I, 54 patients received a dose of 155 U of BTX-A by using a fixed-site and fixed-dose (FSFD) (each injection was 5 -10 U) and 40 U of BTX-A with additional specific follow-the-pain (FTP) sites, which considered depending on individual symptoms. Each muscle was palpated prior to injection to verify muscle delineation, determined muscle tenderness and areas of pain that required additional treatment by using the "follow the pain" method. Totally 195 U BTX-A was administered to the patients with CDH (**Table-1**).

Table-1: Recommended Dose for FSFD

Head and Neck area	Total Dosage (dose distributed bilateral)
Frontalis	20 U
Corrugator	10 U
Procerus	5 U
Occipitalis	30 U
Temporalis	40 U
Trapezius	30 U
Cervical paraspinal muscle group	20 U
FTP	40 U

In group II, 46 patients were treated with the use of standard preventive medication such as tricyclic, β blockers, at a low dose to minimize the possibility of developing side effects. The dose of the medicines steadily and regularly increased until the medication works, intolerable side effects occur, or a maximum dose is reached, and anticonvulsants were added if no response [10-12].

The patient's condition in group I was evaluated on the third day, on the 7th day and the 15th day after the BTX-A injection and assessed every 15 days for 3 months, in group II the patients were assessed every 15 days.

Health Outcome Measures and Efficacy Measures:

The efficacy of BTX-A and quality of life of the patients was evaluated by several measurements such asVAS (Visual Analog Scale), Headache Intake Questionnaire: HSQoLQ (Headache Specific Quality of Life Questionnaire), HMQ (Headache Management Questionnaire), HDQ (Headache Disability Questionnaire), Psychology Questionnaire – Headache Program (PQHP) and patients are filling Headache Diaries (day occurrence, frequency of headache days and number of headache-free days, duration of headache attacks, the severity of pain, medication intake, functional capacity, quality of life and associated headache symptoms).

Safety Measures:

From the beginning until the end of the 3rd month were recorded and documented any new adverse events. The investigator-assessed the relationship between the adverse event and study treatment as none, possible, probable, or definite.

Statistical Analyses:

Statistical processing of data was carried out using the computer program Statistica for Windows. Parametric and nonparametric methods of statistical analysis (Student, Wilcoxon) were used.

There was no statistically significant difference between groups I and II concerning age, sex, headache frequency, the severity of pain, analgesic intake, headache diagnosis, headache questionnaires and life quality in the baseline. All patients had a normal neurological examination, investigations and normal brain MRI.

Results

Baseline Characteristics and Demographics: Group I, 54 patients (31 women and 23 men) and group II, 46 patients (27 women and 21 men).

After the 3-months of study, there was a statistically significant decrease for the frequency and

the severity of headaches, analgesics intake, increase numbers of headache-free days and improved quality of life for the group I, as compared with group II.

The number of Headache - free days: The mean number of headache-free days per month was no statistical differences for the two groups before treatment (group I: 5.77 headaches free days; group II: 5.54 headaches free days; P=0.124).

The frequency of Headaches: The mean frequency of headaches per month was no statistical differences for the two groups before treatment (group I: 24.22; group II: 24.45; P=0.125).

The frequency of headaches and numbers of headache-free days significantly decreased from the baseline after treatment (**Table-2**).

Headache Severity: At baseline, the degree of headache severity was no big difference between the two groups before treatment. The change from baseline in headache severity based on a scale of 0 to 10 (with 0 = no pain and 10 = pain as bad as it can get) per 30-day periods (Headache Disability Questionnaire). After 3 months of headache severity in group I significantly decreased as compared to group II (**Table-3**).

Analgesics intake: No statistical difference between the two groups for analgesics intake (15 ± 3 days per month). Significantly changes of painkillers intake for an acute headache during the study. The patient's in-group I used painkiller for an acute headache 4 ± 1 day, compared to 10 ± 2 days for the group II per 30 days. Significantly changes from the baseline.

Safety and Tolerability: During the study, BTX-A was well-tolerated and no notable adverse events by the patients.

Conclusion

The obtained results testify BTX-A is effective and well-tolerated by the patients. Because of the BTX-A therapy, a significant decreased in the frequency of headache days, analgesic medications intake, duration of headache attacks, the severity of pain and, increased numbers of headache-free days, functional

Table-2: Numbers of headache-free days and frequency of headaches before and after treatment

	Symptoms	Groups	Mean	Std. deviation	P value
Baseline	Number of headache -free days	Group I	5.777	0.785	P = 0.124
		Group II	5.543	0.713	
	Frequency of headaches	Group I	24.222	0.785	P = 0.125
		Group II	24.456	0.713	
After 3 months	Number of headache -free days	Group I	27.703	0.852	P = <0.0001
		Group II	20.847	1.102	
	Frequency of headaches	Group I	2.333	0.838	P = <0.0001
		Group II	9.13	1.075	

Table-3: Compared results of headache severity in the two groups after treatment

Pain score (0-10)	Group I		Group II	
No changes	2	3,7%	12	26,1%
Less than 50% reduction in pain	7	12,9%	16	34,8%
70 to 95% pain relief	23	42,6%	10	21,7%
Complete relief	22	40,8%	8	17,4%

capacity and quality of life of the patients compared to the background and with the patients in group II. BTX-A has been the best option in the prophylactic treatment of CDH. The work presented here has profound implications for future studies of BTX-A injections for patients with CDH.

Conflict of Interest

We have no conflict interest to declare.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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