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Original Article

Botulinum toxin applications at doses appropriate for aesthetic procedures: Effect on tension type headache

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Abstract

Aim: Prophylactic treatment options for tension-type headache are limited. Studies have demonstrated beneficial effects of botulinum toxin-A in headache suffers. This study aimed to evaluate the effect of application of Btx-A at normal aesthetic procedure doseage in the treatment of tension-type headache.

Material and Methods: Forty-six patients (37 females; 80.4%), were included in the study, sub-divided by type of head-ache; chronic or episodic. All patients received 55 UI botulinum toxin-A. Pain frequency and severi-ty were evaluated by neurological examination and visual analog scale, before application, three and six months after application. Results were compared at time points and between the groups.

Results: Mean±standard deviation age of the patients was 41.80±8.36 years. Episodic and chronic tension-type headache was present in 54.3% (n = 25) and 45.7% (n = 21), respectively. In both episodic and chronic tension-type headache there was a significant reduction in visual analog score score at both the third (p=0.001) and sixth (p=0.001) months post-application compared with pre-application. However, visual analog score scores significantly worsened by the sixth month compared to the third month (p=0.01 and p=0.007 for episodic and chronic tension-type headache, respectively) while remaining improved compared to baseline. In episodic tension-type headache, frequency of occurrence decreased significantly at the third (p=0.025) but not at the sixth (p=0.16) months com-pared to baseline. In chronic tension-type headache there was no difference in the frequency of ten-sion-type headache at any time point (p>0.05).

Conclusion: We believe that there may be a role for low dose botulinum toxin-A in the prophylactic treatment of tension-type headache but further larger studies are required to confirm this and identify the optimal dose.

Keywords: Botulinum toxin; headache; tension-type; treatment

INTRODUCTION

Headache is a symptom that is common in society, impairs a person's quality of life and is non-specific (1). Tension-type headache (TTH) is the most common type. TTH manifests as a recurring pain that is in the form of a circle, accompanied by contractions, lasting from 30 minutes to a week with low-moderate severity in the forehead. Factors such as stress, anxiety, depression, and fatigue increase the frequency and severity of symptoms. It is more common in females than in males and can be seen at any age. Sometimes TTH is accompanied by nausea; however, vomiting does not oc-cur often. Treatment of TTH is very important because it is seen frequently, is a serious source of stress and impairs individual, social and professional functionality (2). Bringing psychological fac-tors, such as underlying depression and anxiety disorder under control, myorelaxant-analgesic medi-cation, relaxation, hot showers, exercise, and massage are frequently used treatment methods (2,3).

As prophylactic treatment options are limited, new treatment strategies need to be developed. The revelation that botulinum toxin-A (Btx-A) applications reduce symptoms in migraine patients has increased the tendency for Btx-A to be used in TTH treatment (4). An incidental finding was that Btx-A applications for aesthetic purposes also reduced the symptoms of TTH (5).

In this study, we aimed to evaluate the details and results of Btx-A application as an alternative method in the treatment of TTH.

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MATERIAL and METHODS

For this study, the appropriate ones were selected from the patients who were applied Btx-A for aesthetic purposes in Kocaeli University Medical Faculty Hospital and informed consent form was obtained from all of the patients. Among patients who had Btx-A application for aesthetic purposes, patients with a diagnosis of TTH diagnosis were included in the study. Patients who received regular myorelaxant and analgesic ther apy and/or who received additional doses of Btx-A were excluded from the study. The diagnosis of TTH was made by the neurology consultant, according to theInternational Classification of Head-ache Disorders(ICHD-III) (6) criteria.

A total of 55 IU Btx-A was given to all study patients, with the following distribution: frontal total 5-8 injections / 20 IU; procerus total 1 injection / 5 IU; corrugator total 4 injections / 10 IU ; orbicu-laris oculi total 6 injections/ 10 IU; nasal total 4 injections / 10 IU (Figure 1). Pain frequency and pain severity were evaluated by routine neurological examinations of the patients, before and after the application and at the third and sixth months post-application, and by use of the visual analog scale (VAS) and results were subsequently compared statistically. The VAS assessment was marked on the paper chart. All these evaluations were made by the neurologist.

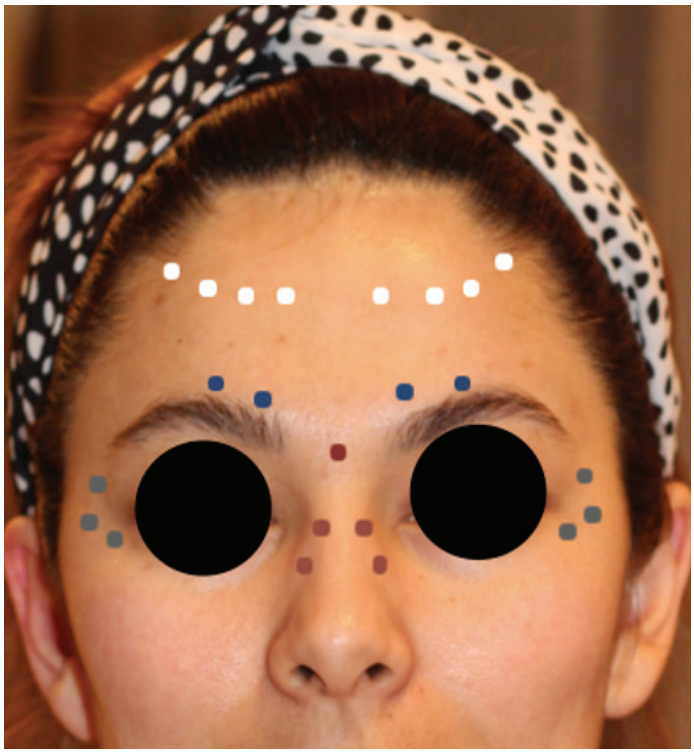

Figure 1. Illustration of botulinum toxin-A injection points: frontal total 5-8 injections / 20 IU; procerus total 1 injection / 5 IU; corrugator total 4 injections / 10 IU ; orbicularis oculi total 6 injections/ 10 IU; nasal total 4 injections / 10 IU

Statistical Examination

Study data were evaluated by Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program using descriptive statistical methods including mean, standard deviation, median, frequency, percentage, minimum, and maximum.

The normality of distribution of the quantitative data was evaluated using the Shapiro-Wilk test and graphical examinations, and comparison of the non-parametric quantitative variables was evaluated by Mann-Whitney U test. Additionally, the Friedman test was used to evaluate VAS severities, and Dunn Bonferroni and Wilcoxon Signed Ranks test were used in pair comparisons. Lastly, the Pear-son correlation analysis was used to evaluate the frequency of headaches. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 46 patients with a mean±standard deviation (SD) age of 41.80 ± 8.36 (range 28-62) years, including nine males (19.6%) and 37 females (80.4%), were included in the study. Episodic type TTH was present in 54.3% (n = 25) of the cases and chronic type TTH was present in 45.7% (n = 21). The descriptive characteristics of the patients are given in Table 1.

Table 1. Characteristics of The Patients

Age	Min_Max	28-62
	mean±SD	41.80±8.36
Gender	Male	9 (19.6)
	Female	37 (80.4)
Working Status	Unemployed	17 (37.0)
	Under 8 hours/day	18 (39.1)
	Over 8 hours/day	11 (23.9)
Education	Primary	22 (47.8)
	High School-University	24 (52.2)
Smoke	No	30 (65.2)
	Yes	16 (34.8)
Alcohol	No	36 (78.3)
	1-2 glass/month	8 (17.4)
	3 glass/month	2 (4.3)
Type of headache	Episodic	25 (54.3)
	Chronic	21 (45.7)

Assessment of Pain Frequency

In episodic TTH there was a statistically significant difference between the frequency of pain before the application compared with during the third month after the application, and during the sixth month after the application ($p<0.05$). In bilateral comparisons the decrease in pain frequency was statistically significant in the third month post-application compared to pre-application ($p<0.05$). However, it was not statistically significant in the sixth month post-application compared to pre-

application (p>0.05). The change in the frequency of pain was not statistically significant between the third month post-application and the sixth month post-application (p>0.05). The change in the frequency of pain in chronic TTH cases before the application, three months after and six months after the application was not statistically significant (p>0.05) (Table 2).

Assessment of Pain Severity

In episodic TTH the reported change in VAS score before the application, in the third month and in the sixth month after the application was statistically significant (p<0.01). In bilateral comparisons, the decrease between pre-application and in the third month after the application was significant (p<0.01), and the decrease in the sixth month

Table 2. Type of TTH; Evaluation of Pain Frequencies

Pain Frequencies			Type of TTH		[a]p
			Episodic; n(%)	Choronic; n(%)	
Before Application	under 3/months- over15 day/month		10 (40.0)	15 (71.4)	**0,033***
	4 and over/month- everyday		15 (60.0)	6 (28.6)	
After Applicaton/3.months	under 3/months- over15 day/month		15 (60.0)	16 (76.2)	**0,243**
	4 and over/month- everyday		10 (40.0)	5 (23.8)	
After Appli-caton/6.months	under 3/months- over15 day/month		12 (48.0)	15 (71.4)	**0,180**
	4 and over/month- everyday		13 (52.0)	6 (28.6)	
		[b]p	**0.022***	**0.607**	
Before application- After application 3.months			[c]**0.025***	[c]**0.317**	
Before application- 6.months after application			[c]**0.157**	[c]**1.000**	
3.months after application- 6.months after application			[c]**0.083**	[c]**0.317**	

Table 3. VAS Evaluation according to the types of TTH

VAS			Episodic	Chronic	[d]p
Before Application	Mean±SD		6.60±1.47	5.76±1.64	**0.078**
	Median		7.00	6.00	
	Min-Max		4-9	3-9	
3. months after Btx-A application	Mean±SD		4.48±1.73	3.52±1.60	**0.143**
	Median		4.00	4.00	
	Min-Max		2-8	1-7	
6. months after Btx-A application	Mean±SD		5.20±1.58	4.52±1.63	**0.124**
	Median		5.00	4.00	
	Min-Max		3-8	2-9	
		p	[b]**0.001****	[b]**0.001****	
Before application- 3.months after application			[e]**0.001****	[e]**0.001****	
Before application- 6.months after application			[e]**0.001****	[e]**0.001****	
3.months after application- 6.months after application			[e]**0.010***	[e]**0.007****	

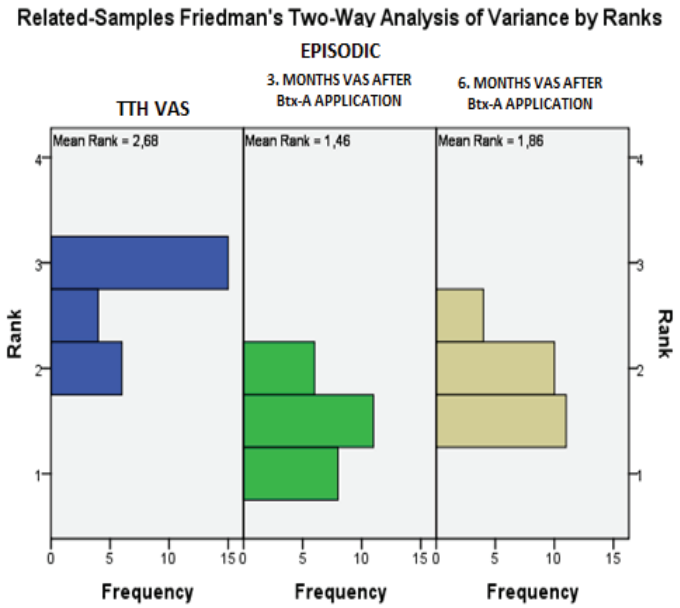

Figure 2. VAS evaluation according to follow-ups in the type of chronic TTH

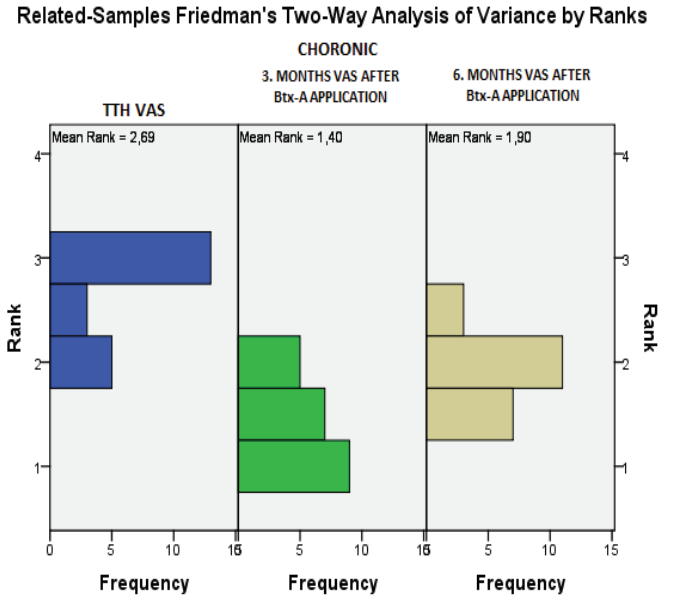

Figure 3. VAS evaluation according to follow-ups in the type of chronic TTH

remained significant (p<0.05; see Figure 2). The change in VAS between the third month after the application and the sixth month after the applica-tion was not significant (p>0.05). In Chronic TTH the detected change in VAS score between be-fore the application, in the third month after application and in the sixth month after application were statistically significant (p<0.01). In bilateral comparisons, the decrease between pre-application and in the third month after the application was found to be significant (p<0.01) whereas, the con-tinuing decline in the sixth month was remained significant but less so (p<0.05; see Figure 3). The change in VAS score in patients with chronic TTH between the third and sixth months after the application was not significant (p>0.05; see Table 3).

DISCUSSION

The worldwide prevalence of TTH is 21.75% and is the second most common chronic disease (7). It is more common in females than in males. In a study conducted in our country, it was reported that 65.9% of patients who applied to the neurology polyclinic reported having headache and of these were 26.2% male and 73.8% of females (8). The proportion of males to females in our cohort was somewhat different at 19.6% male and the remainder (80.4%) were female but was broadly in line with previous reports.

TTH pathogenesis is still unclear. Peripheral myofascial (myofascial nociception) and central (sensi-tization and inadequate endogenous pain control) mechanisms are thought to have a potential role (9, 10). Analgesic drugs are often used in the treatment although there is no guideline showing when the prophylaxis should start. If the frequency of headaches is two days or more per week, prophylactic treatment options should be considered, but there is no accepted standard treatment protocol. In cases where analgesic treatment is unsuccessful, methods with proven efficacy in mi-graine can be tried. The effectiveness of Btx-A has been proven in the prophylactic treatment of chronic migraine patients [11]. Although the results obtained from reviews and meta-analyses on the effectiveness of Btx-A in TTH seem complex (4), they are similar to previous studies on its use in migraine (12).

Btx-A and -B are used for medical purposes. It's most obvious effect is that it blocks the release of acetylcholine in the neuromuscular junction and causes paralysis in the muscle. Its effect on head-ache was initially thought to be due to muscular relaxation (13). Indeed, muscle relaxation can indi-rectly contribute to analgesic effects, but the mechanisms behind chronic muscle pain are known not to be related to an increase in muscle activity. It is suggested that the etiology of TTH is not entirely muscular and botulinum toxin probably acts on several levels (5). In support of this hypothesis, ani-mal studies have shown that subcutaneous injections of Btx-A in rats significantly reduced forma-lin-induced nociceptive behavior, inhibited inflammation-induced pain through glutamate and acted directly at the peripheral level on nociceptive neurons (14, 15). It has been suggested that Btx-A indirectly inhibits central sensitization and inhibits environmental signals in the central nervous sys-tem (16). Some studies have shown the pain modulating effects of Btx-A, and this report empha-sized that it is worth paying attention even in cosmetic procedures, as Btx-A application has a po-tentially beneficial effect on the quality of life (8). Btx-A applications have been used in facial aes-thetics for more than 20 years and are a preferred method for dynamic wrinkles on the upper 1/3 of the face (17). There

are publications showing that headache also improved in patients in whom botu-linum toxin was applied for aesthetic purposes (5).

In a study where 100 UI Btx-A was applied to 82 patients, 71 of whom had chronic migraine and 11 of whom had chronic TTH, 76.1% (54/71) of the migraine group and 36.4% (4/11) of the TTH group reported some degree of improvement with Btx-A. In addition, at least 50% reduction in pain frequency was detected (18). In a further study, a reduction of 25% in 12 weeks and 64% in one year was reported in the frequency of pain in TTH patients who received Btx-A (19). In a double-blind study conducted by Harden et al (20), a statistically significant decrease in the frequency of pain at a maximum of 5-8 weeks (p=0.013) was detected. In should be noted that in earlier studies there were some limitations and methodological differences, such as short follow-up time and insuf-ficient treatment repetition. For example one study reported that Btx-A did not provide benefit up to three months after treatment, a different study stated that the frequency and severity of head-ache continued to be reduced from 30 days to 90 days (21, 22). In our study, in both episodic- and chronic-type TTH patients when compared to the pre-application period, both reduction in the fre-quency of pain and a statistically significant decrease in pain severity were found in the third and sixth months after the application. In a meta-analysis analyzing 22 studies related to this subject, it was emphasized that injection protocols had no role in treatment effectiveness, only one study re-ported that a pre-determined protocol was beneficial. As a result, following the paradigm applied in migraine is recommended. The same comment applies to dosing. Although some studies suggest higher doses, doses used for migraine are recommended (4). The dosages recommended in migraine prophylaxis by PREEMPT 1 and 2 studies are: frontal 4 injections / 20 IU; procerus 1 injection / 5 IU; corrugator total bilateral 2 injections / 10 IU; temporal 8 injections / 40 IU; occipital 6 injections / 30 IU; cervical paraspinal total bilateral 4 injections / 20 IU; and trapezius total bilateral 6 injec-tions / 30 IU (23, 24). In our study, Btx-A dosages were: frontal 5-8 injections / 20 IU; procerus 1 injection / 5 IU; corrugator total bilateral 2 injections / 10 IU; orbicularis oculi total bilateral 10 injec-tions / 10 IU; and nasal total bilateral 4 injection / 10 IU. Compared to migraine prophylaxis, the same dose was applied at three similar points (frontal, corrugator and procerus) (total 35 IU). The dose of Btx-A applied in aesthetic applications is slightly more than one third of that in migraine (55 IU compared with 155 IU).

Many studies have shown that additional treatments may affect the outcome (23). To prevent this confusion, patients were recommended to use non-pharmacological treatment methods during fol-low-up. Our study has shown that Btx-A application at aesthetic application doses had a positive effect on the frequency and severity of pain in TTHs, even at low doses and limited application are-as.

CONCLUSION

In this study a significant decrease in both pain frequency and pain intensity in the third and sixth months after botulinum toxin application for aesthetic purposes was found. Even though the study was not specifically planned for TTH, there were limited application sites and the dose used was at aesthetic levels this may be an advantage of our study as these latter two features are well known. At the same time, patients were followed up for six months and re-evaluated at the third and sixth months after initial Btx-A application. The study has produced robust results as none of the patients took regular pharmacological treatment during their follow-up, thus avoiding one possible con-founding variable. We believe that the results obtained are encouraging for the usage of Btx-A as an option in the prophylactic treatment of TTHs. These initial findings should be supported by further studies involving larger cohorts and should also investigate the effect of alternative injection sites and variation in dosages.

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