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Evaluation of the effect of botulinum neurotoxin type A (BoNT/A) on daily activity performance in chronic migraine patients using VAS, MIDAS AND HIT-6 tests

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Abstract

Background & Objectives: According to ICHD-III beta 2013 criteria, chronic migraine is defined as having headaches more than 15 times a month, for a period of more than 3 months, at least 8 must have migrainous features or good response to migraine-specific treatment; there must also be a history of 5 or more migraine attacks. The aim of the present study was to evaluate the effect of Botulinum Neurotoxin A (BONT/A) on headache and daily activities in chronic migraine patients using VAS, MIDAS and HIT-6 tests. *Methods:* Twenty five patients admitted to Hospital Department of Neurology were reviewed retrospectively. In order to evaluate the severity of headache and effects on daily performance, MIDAS (Migraine Disability Assessment Test), VAS (Visual Analogue Scale for Pain) and HIT-6 results after the baseline assessment, first and second administration of (BONT/A) were examined retrospectively from patients' records. *Results:* VAS, MIDAS and HIT-6 scores were compared after baseline assessment and the first and second administrations. Results showed that VAS, MIDAS and HIT-6 scores decreased. This difference was statistically significant ($p<0.05$). Correlation analysis was conducted and significant correlations between scores on these three tests were found. *Conclusions:* The results showed that BoNT/A is an important and effective treatment option for chronic migraine patients not responding to migraine-specific prophylactic treatment and having alterations in daily life due to frequency and severity of pain.

Keywords: Chronic migraine, MIDAS, VAS, HIT-6, botulinum neurotoxin, headache

INTRODUCTION

Migraine is a primary headache disorder which is frequently seen in the population and often causes disability. Diagnostic criteria have been determined by the International Headache Society (IHS).[1] Migraine is defined as a usually familial, periodic, often one-sided, throbbing headache. It starts in childhood, adolescence or adulthood and usually decreases with age.[1,2]

According to ICHD-3 Beta criteria, chronic migraine is defined as having headaches more than 15 days a month, for a period of more than 3 months, without overuse of drugs, which cannot be related to other disorders; of these headaches, at least 8 must have migrainous features or good response to migraine-specific treatment; there must also be a history of 5 or more migraine attacks. It is important to query and possibly rule out drug overuse.[1,3-4]

Although varying worldwide in various studies, the incidence of chronic migraine is about 1-3%.[2-5] In Turkey, prevalence of migraine was found to be 16.4% in a large epidemiological, population- based study. Of these patients, about 10% have chronic migraine, mostly seen between the ages of 20-50.[6]

Pathogenesis of migraine

To understand the mechanisms of migraine and other primary headaches, it is necessary to review the relationship between the brain's vascular structure and the trigeminal nerve that transmits the pain.[7,8] Periaqueductal grey matter (PAG), the rostral ventromedial medulla, brainstem nuclei such as dorsal raphe and the locus ceruleus, and various structures of the brain including the hypothalamus and cortex all play role in regulation of trigeminovascular nociception.[9]

With activation of the trigeminal nerve, neuropeptides such as CGRP (calcitonin gene-

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related peptide), SP (substance P) and NKA (neurokinin A) are released into the perivascular space. This causes vasodilatation of blood vessels, increase in blood flow and extravasation of protein, resulting in "neurogenic inflammation".[10,11]

5-HT1D receptors, which are mainly located in trigeminal axon ends, play an important role in headache, by inhibiting trigeminal activation that leads to inhibition of neuropeptide release and neurogenic inflammation.[12]

Beta-blockers, anticonvulsants such as valproate and topiramate, antidepressants such as amitriptyline, selective serotonin and selective serotonin-norepinephrine reuptake inhibitors, calcium channel antagonists and botulinum toxin are drugs used in treatment of chronic migraine.[13-15]

Mechanism of botulinum neurotoxin type A in chronic migraine

Botulinum neurotoxin (BoNT) is produced by an anaerobic gram-positive bacteria called Clostridium Botulinum and it prevents neurotransmission by blocking acetylcholine release at the presynaptic terminals of peripheral cholinergic nerves.[16-19] Its effect peaks two weeks after administration and ends due to increased axonal sprouting after 2-4 months, depending on the toxin.[19,20]

Recent studies have demonstrated that BoNT/A has a direct influence on pain receptors, which is independent from the effects on neuromuscular activity.[21]

It is thought that the toxin inhibits the peripheral sensitization of the nocciceptive fibers and thus reduces central sensitization.[22] Many animal and human studies have revealed that BoNT/A inhibits glutamate A, calcitonin-gene related peptide and substance P, which are released from the activated sensory nerve terminals and are important mediators for inflammatory pain.[23-27]

Studies on preventive treatment of chronic daily headache using BoNT/Ainjections with different doses and at different injection points have shown that BoNT/A is efficient in the treatment of chronic migraine.[28-30]

METHODS

Twenty five patients admitted to Celal Bayar University Medical Faculty Hospital Department of Neurology were reviewed retrospectively. Celal Bayar University Clinical Research Ethics Committee on Drugs Decision Form approved the current study. All patients were informed on drug action, possible side effects and procedures to be applied; and their written consent was obtained.

Criteria for inclusion were having a diagnosis of migraine being diagnosed in follow-ups as having chronic migraine according to International Headache Society ICHD-3 Beta criteria and administration of botulinum neurotoxin. Patients included in the study had received more than 2 prophylactic medications for at least 2 months each. The average duration for trials of prophylaxis was 6 months. Our patients had failed prophylactic medication, as defined by the lack of reduction of migraine attack frequency by 50% with their treatment.

The exclusion criteria were being under 18 years of age, pregnancy, lactation, diagnosis of neuromuscular disease, mental retardation and hypersensitivity to Botulinum Neurotoxin type A or any other substance within it.

The VAS, MIDAS and HIT-6 scores of patients were evaluated retrospectively after the baseline assessment, and after the first and second administrations of botulinum toxin and the results were compared statistically.

After obtaining a detailed history and physical examination of all the patients, brain imaging studies (cranial magnetic resonance) and blood tests (complete blood count, biochemical analysis) were done and patient history form for botulinum toxin administration and application forms were filled.

As in the PREEMPT 1 and 2 studies on chronic migraine, intramuscular injections with a fixed total amount of 155 U BoNT/A were given to 31 points in 7 specific head and neck muscles at intervals of 12 weeks (16,18,27,28). At the first assessment and after each injection, VAS, MIDAS and HIT-6 test scores were determined. Patients were asked to come again for follow up and treatment after 12 weeks and in the meantime, they were asked to keep a headache diary. Test results at baseline, first and second injections were compared.

Tests used

In the literature, many different tests have been administered to the patients with chronic migraine in order to evaluate the effects on their lives. Since the effect of botulinum toxin administration can take 3 weeks to develop, the tests were done 1 month after each treatment

Visual Analogue Scale for Pain (VAS)

The first test administered was VAS (Visual Analogue Scale for Pain). It is a scale which allows

measurable objective assessment. This scale is 10 cm long, lies vertically or horizontally on a line and both ends are named differently (0=no pain, 10=worst possible pain).[31]

Migraine Disability Test (MIDAS)

Migraine Disability Test (MIDAS) was developed to measure the level of disability associated with headache and to improve patient-doctor communication about functional consequences of migraine. The test helps patients to express the severity of the headache in an objective and quantitative way.[50]

MIDAS has been translated into Turkish and its Turkish version has been found to be valid and reliable. It is filled by patients and used to determine disability caused by migraine in all activity domains over the last three months.[32] In the literature, factors affecting disability have been examined by using MIDAS.[33]

MIDAS scores are interpreted as follows: 0-5 points (Grade I) little or no disability, 6-10 points (Grade II) mild disability, 11-20 points (Grade III) moderate disability, and 21 and above (Grade IV) severe disability.

Headache Impact Test (HIT)-6

The Headache Impact Test (HIT)-6 is a measurement of quality of life with six questions. It was designed for the patient to identify and describe his feelings and disabilities relating to headache.[34-37]

HIT-6 scores are interpreted as follows: 60 or more points indicate severe headache, 56-59 points moderate, 50-55 points mild, and 49 or less points indicate minimal or no impact.[55,56] Reliability and validity studies have not yet been conducted in Turkey. Its Turkish version was published in 2000.

Statistical methods

Statistical analysis of the data was performed using SPSS (Statistical Package for Social Sciences) v.16.00. The mean, standard deviation, median, minimum and maximum values of continuous variables were presented. The normality of the distribution of these variables was investigated. Based on both graphical research and normality tests regarding the size of the sample, it was decided that none of the variables met the requirements for normal distribution. Non-parametric methods were chosen for comparisons of these variables. The Friedman Test method was used in comparisons investigating the differences between dependent variables on different administrations. The Wilcoxon Signed Rank Test was used in binary comparison of dependent groups. For graphical representation, the "box-pilot" graphical method was used to show changes in median, minimum and maximum values in the form of quarters between the applications. Relationships between the variables were assessed with non-parametric correlation methods. For all statistical comparison tests, type 1 error margin was set at $\alpha = 0.05$ and tested bidirectionally; p values lower than 0.05 between the groups were considered statistically significant.

RESULTS

Of the 25 patients who participated in the study, 22 (88%) were female and 3 (12%) were male; their mean age was 43 ± 6years (range: 33 to 52 years).

VAS, MIDAS and HIT-6 values were evaluated 3 times: At baseline and after the first and second injections of BoNT/A. Average VAS scores were 9±1, 5±1 and 4±2 respectively. Average MIDAS scores were 92±41, 36±21 and 30±21 respectively. Average HIT-6 scores were 74±5, 54±9 and 50±10 respectively. The results were listed in Table 1.

The p values of the test scores differences by MIDAS, VAS, HIT-6 scores at baseline and first administration of BoNT/A, baseline and second administration of BoNT/A, and first and second administrations of BoNT/A were: MIDAS: p<0.001, <0.001, <0.001; VAS: p<0.001, <0.001, <0.001; HIT-6: 0.010, p=0.005, p=0.023. Therefore, the decrease in average scores of MIDAS, VAS and HIT-6 were all statistically significant.

All 25 patients assessed initially were found to have MIDAS grade IV. MIDAS grades after the first and second administrations are indicated in Table 2.

Correlation analysis

The relationships between VAS, MIDAS and HIT-6 scores were compared with each other; after the first administration (Table 3), and after the second administration (Table 4) There were strongly significant correlations between these scores.

Before the administration, the patient's average monthly headache days over three months were 21.00 ±5 days (range: 15.00-30.00). After the first administration, average monthly headache days were 8.83±4.82 (0.67-20.00). After the second administration, the patient's average monthly

Table 1: Scores of MIDAS, VAS, HIT-6 at baseline, after first and second administration of botulinum neurotoxin type A

	Number of patients	Average	Standard deviation	Median	Minimum	Maximum	Distribution interval
MIDAS (baseline)	25	91.72	41.43	84.00	35.00	204.00	169.00
MIDAS (1st administration)	25	35.64	21.00	32.00	2.00	72.00	70.00
MIDAS (2nd administration)	25	30.00	20.79	24.00	0.00	72.00	72.00
VAS (baseline)	25	9.12	1.13	9.00	6.00	10.00	4.00
VAS (1st administration)	25	5.24	1.45	5.00	2.00	8.00	6.00
VAS (2nd administration)	25	4.28	1.70	4.00	1.00	9.00	8.00
HIT-6 (baseline)	25	73.64	4.96	76.00	64.00	78.00	14.00
HIT-6 (1st administration)	25	53.56	8.63	54.00	36.00	70.00	34.00
HIT-6 (2nd administration)	25	49.96	9.94	48.00	36.00	66.00	30.00

MIDAS, Migraine Disability Test; VAS, Visual Analogue Scale for Pain; HIT-6, Headache Impact Test-6

headache days declined further to 5±4.75 days (0-20.00). There was correlations between average monthly headache days after the first and second administrations and VAS, MIDAS and HIT-6 test scores (Table 5).

Table 2: MIDAS grades after the first and second administration of botulinum neurotoxin type A

		Number of patients	Percentage (%)	Total percent (%)
MIDAS grade after the first administration	Grade I	2	8.0	8.0
	Grade II	1	4.0	12.0
	Grade III	2	8.0	20.0
	Grade IV	20	80.0	100.0
MIDAS grade after the second administration	Grade I	*3*	*12.0*	*12.0*
	Grade II	*1*	*4.0*	*16.0*
	Grade III	*8*	*32.0*	*48.0*
	Grade IV	*13*	*52.0*	*100.0*

MIDAS, Migraine Disability Test

Table 3: Relationships between VAS, MIDAS and HIT-6 scores after the first administration

		VAS (first administration)	MIDAS (first administration)	HIT-6 (first administration)
VAS (first administration)	r	1.000		
	p	.		
MIDAS (first administration)	r	.672(**)	1.000	
	p	<0.001	.	
HIT-6 (first administration)	r	.624(**)	.620(**)	1.000
	p	0.001	0.001	.

VAS, Visual Analogue Scale for Pain; MIDAS, Migraine Disability Test; HIT-6, Headache Impact Test-6

DISCUSSION

Migraine is a common chronic neurological syndrome in the population, which is characterized by attacks of headache and often causes disability.[2] According to the ICHD 3 Beta criteria, chronic migraine is defined as a migraine complication that is distinguished from the episodic migraine by the frequency of headache.[1,3-4] It is important to look for and exclude drug overuse when chronic migraine is suspected.[4] Studies have shown that only 3-13% of chronic migraine patients use prophylactic medication.[3,4]

Recent studies have shown that BoNT/A directly inhibits pain receptors independently of its effects on neuromuscular activities.[21] Botulinum toxin indirectly blocks central sensitization, which is seen in migraine and other painful conditions.[38-40] BoNT/A has become one of the acceptable treatment options in chronic migraine due to its prolonged but reversible effect, ease of application, appropriate safety and side effect profile.[41]

The results obtained in the PREEMPT studies showed that BoNT/A was an effective prophylactic treatment for chronic migraine, including patients who overuse acute painkillers.[38-40] Freitag *et al*. used a fixed dose of 100 U BoNT/A. The number of migraine attacks ($p<0.01$), number of headache days ($p = 0.041$ at 4 weeks; $p = 0.046$ at 16 weeks) and headache index ($p = 0.003$, in 16 weeks) were evaluated. BoNT/A was found to be statistically superior to placebo.[42]

PREEMPT 1 and PREEMPT 2, published in 2010, were multicentered phase 3 trials. BoNT/A was compared with a placebo group. The class 1 studies enrolled 1,384 chronic migraine patients and were double-blind for 24 weeks and open for 32 weeks. As a result, BoNT/A was confirmed to be a safe and well-tolerated prophylactic agent in treatment of chronic migraine.[38,39]

In PREEMPT 1 the number of headache episodes and in PREEMPT 2 the number of days with headache were evaluated for 24 weeks. In both studies, there was a significant decrease in the number of days with headache compared to the placebo ($p=0.006$; $p<0.01$).[38,39] Another study

Table 4: Relationships between VAS, MIDAS and HIT-6 scores after the second administration

		VAS (second administration)	MIDAS (second administration)	HIT-6 (second administration)
VAS (second administration)	r	1.000		
	p	.		
MIDAS (second administration)	r	.678(**)	1.000	
	p	<0.001	.	
HIT-6 (second administration)	r	.736(**)	.750(**)	1.000
	p	<0.001	<0.001	.

VAS, Visual Analogue Scale for Pain; MIDAS, Migraine Disability Test; HIT-6, Headache Impact Test-6

Table 5: **Correlations between average monthly headache days after the first and second administrations and VAS, MIDAS and HIT-6 test scores**

		VAS After first administration	VAS After second administration	MIDAS After first administration	MIDAS After second administration	HIT-6 After first administration	HIT-6 After second administration
Average monthly headache days in the 3 month interval after the first administration	r	0.555	0.319	0.961	0.571	0.541	0.377
Average monthly headache days in the 3 month interval after the second administration	r	0.261	0.626	0.525	0.947	0.309	0.629

VAS, Visual Analogue Scale for Pain; MIDAS, Migraine Disability Test; HIT-6, Headache Impact Test-6

that evaluated the data from PREEMPT 1 and 2 was also published in 2010.[40] Studies on the patients with chronic migraine have shown that BoNT/A is well tolerated and has low termination percentage of treatment due to side effects (from 1.4 to 3.8%).[40]

Alvaro *et al*. evaluated number of attacks and migrainous days before and after treatment, pain intensity, MIDAS scores indicating disability, and drug intake. Decrease in headache severity indicated by the VAS scale (VAS scale $p < 0.001$), reduction in the number of days leading to disability (3.2 vs. 0.4, $p < 0.001$), reduction in the number of monthly headache days (19.8 vs. 13.8, $p < 0.05$), and reduction in the excessive use of analgesics (69% vs. 13%, $p < 0.01$) were shown. This study indicated decreases in headache severity and analgesic overuse.[14]

Aydinlar *et al*. evaluated effects of BoNT/A therapeutic effect on headache in 30 patients diagnosed with chronic migraine. Patients' MIDAS scores improved significantly from the time of first injection; pain intensity and frequency also decreased.[15] In a study by Kuen *et al*., 12 weeks after the BoNT/A administration, reduction of more than 30% in headache frequency was observed in 40% of the patients with chronic migraine and treatment-related side effects were found to be transient and acceptable.[43]

In our study, pain severity was determined using the VAS scale. This was administered at 0, 3 and 6 months. The administrations at the months 3 and 6 were regarded as controls. These applications were analysed both numerically and statistically and a decrease in pain intensity was shown. VAS scores were 9 ± 1, 5 ± 1 and 4 ± 2 at baseline and after the first and second administrations, respectively. The decline in VAS scores after the first and second administrations compared to baseline VAS scores was statistically significant. The p-values of comparisons of VAS scores between the baseline and 1st administration, between the baseline and 2nd administration, and between the 1st and 2nd administration were <0.001, <0.001, and 0.05 respectively. Pain is an important symptom which affects the patient's quality of life; eliminating the pain will contribute positively to the daily activities of patients. In binary comparisons in the our study, the p values of differences for the MIDAS scores between the baseline and 1st administration, between the baseline and 2nd administration, and between the 1st and 2nd administration were <0.001, <0.001 and 0.010 respectively. Therefore, the reduction in average MIDAS scores in all three comparisons was found to be statistically significant. Consistent with the literature, the present study showed that statistically significant differences were detected

between the MIDAS scores (baseline, 1st and 2nd administration).

In binary comparisons in the our study, the p values of differences for the HIT-6 scores between the baseline and 1st administration, between the baseline and 2nd administration, and between the 1st and 2nd administration were <0.001, <0.001 and 0.023, respectively. All three decreases in average HIT-6 scores were statistically significant. In our study, as in PREEMPT, HIT-6 score changes between baseline assessment and after 1st and 2nd administrations were statistically significant.

The CHORD (Canadian Headache Outpatient Registry and Database) study compared the HIT-6 and MIDAS, which were the clinical scales used to measure the disability associated with headache. A total of 798 patients were enrolled and total HIT-6 and MIDAS scores were used to determine the relationship between headache frequency and severity using correlation and regression analysis. A positive correlation was found between HIT-6 and MIDAS results (r=0.52). A stronger correlation was found between headache severity (VAS) and HIT-6 scores (r=0.46) than between VAS and MIDAS scores (r=0.26). As a result, HIT-6 and MIDAS scores were generally found to be similar in the evaluation of headache associated disability. It has been shown that for headache severity, HIT-6 scores are more informative than MIDAS scores. However, MIDAS scores are more related to headache frequency. Using these two scales together, more accurate and precise assessments can be made of disability associated with headache.[44]

Ghorbani *et al*. showed that MIDAS and HIT-6 scales were both reliable and valid; however, the HIT-6 scale was found to be more simple and practical for the patients. A high correlation was found between the two tests (r = 0.94).[45]

In episodic headaches, there is a weak correlation between MIDAS and HIT-6. However, in chronic headaches there is a high correlation (r = 0.59) According to Magnoux *et al*., HIT-6 is more sensitive than MIDAS, but has a ceiling effect. That is why when given the choice between these two questionnaires for the purpose of following patients in a migraine clinic, MIDAS is more useful than HIT-6.[46]

Different studies on workplace disability caused by migraine have concluded that the most important factor in disability is severity of pain.[47] In most studies, a relationship has been found between headache frequency and MIDAS; it has also been shown that pain frequency is an important factor influencing migraine disability.[48] In the present study, there was a significant relationship between the frequency of attacks and MIDAS scores; as attacks became more frequent, disability also increased.[48]

In our study, correlations between the three scales following the first and the second administrations were analysed. After the first administration, significant positive correlations were found between the scores of VAS-MIDAS (r = 0.672), VAS-HIT-6 (r = 0.624) and MIDAS-HIT 6 (r = 0.624). After the second administration, significant positive correlations were found between the scores of VAS-MIDAS (r = 0.678), VAS-HIT-6 (r = 0.736) and MIDAS-HIT-6 (r= 0.750).

In the evaluation of headache diaries, migrainous headache days were calculated monthly for periods of three months**.** The average number of days per month with migraine headache in the 3 month periods prior to administration and after the 1st and 2nd administrations were 21 ± 5, 8 ± 4 and 7 ± 5, respectively. These values were compared and the difference between the baseline values and those after the 1st and 2nd administrations was found to be statistically significant ($p < 0.001$).

After the 1st and 2nd BoNT/A administrations, VAS, MIDAS and HIT-6 test results were compared with numbers of monthly migraine headache days and significant positive correlations were found.

In studies on the effect of BoNT/A in the treatment of chronic migraine, number of days with headache, headache episode count, HIT-6, health-related quality of life (HRQoL), VAS, MIDAS and intake of acute headache medication have been used in the overall assessment. However in our study, the VAS, MIDAS and HIT 6 scales were used together. Based on these scales, an assessment was made of whether the severity and disability of migraine decreased. The data collected showed that BoNT/A had a positive effect on daily life activities.

DISCLOSURE

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