ABSTRACT
Background: Botulinum toxin Type A (BoNTA) is a successful treatment for chronic migraine prophylaxis. Objective: We aimed to evaluate the monthly change of effectiveness of BoNTA treatment. Methods: A total of 80 patients (70 females and 10 males) with chronic migraine were included. In our study protocol, we applied to 155 U across 31 fixed-sites and if the patient had pain, 40 U dose injections were applied across 8 specific head/neck muscle areas. Headache days and analgesic intake were noted before the BoNTA injection and during the interviews at the first, second, and third months after the BoNTA injection. Results: The mean age was 37.59 ± 7.60 and 87.5% of the patients were female. The mean number of headache days/month before BoNTA was 18.95 ± 2.69, decreasing to 10.55 ± 3.15 days/month in the first month (p<0.001), 9.31 ± 2.43 days/month in the second month (p<0.001), and increased to 11.97 ± 3.27 days/month in the third month (p<0.001). The mean analgesic intake before BoNTA was 11.48 ± 4.68 tablets/month, while it decreased to 6.53 ± 2.72 tablets/month in the first month (p<0.001) and 5.40 ± 2.46 tablets/month in the second month (p<0.001). In the third month, it was 5.85 ± 2.59 tablets/month (p<0.001). There was a significant increase in pain medication use from the second to the third month (p<0.001). Conclusion: In our study, there was a significant reduction in analgesic intake and headache days in the first and second months after BoNTA injection, and an increase was observed in the third month. Keywords: Headache; Migraine Disorders; Botulinum Toxin, Type A.

RESUMO
Antecedentes: A toxina botulínica Tipo A (BoNTA) é um tratamento de sucesso para a profilaxia da migraña crônica. Objetivo: Nosso objetivo foi avaliar a mudança mensal da eficácia do tratamento com BoNTA. Métodos: Um total de 80 pacientes (70 mulheres e 10 homens) com migraña crônica foi incluído. Em nosso protocolo de estudo, aplicamos 155 U em 31 locais fixos e, se o paciente sentisse dor, injeções de dose de 40 U foram aplicadas em 8 áreas musculares específicas da cabeça/pescoço. Dias de cefaleia e ingestão de analgésicos foram anotados antes da injeção de BoNTA e durante as entrevistas no primeiro, segundo e terceiro meses após a injeção de BoNTA. Resultados: A média de idade foi 37,59 ± 7,60 e 87,5% dos pacientes eram do sexo feminino. O número médio de cefaleias dias/mês antes da BoNTA foi de 18,95 ± 2,69 dias/mês, diminuindo para 10,55 ± 3,15 dias/mês no primeiro mês (p<0,001), 9,31 ± 2,43 dias/mês no segundo mês (p<0,001), e aumentou para 11,97 ± 3,27 dias/mês no terceiro mês (p<0,001). A ingestão média de analgésicos antes da BoNTA foi de 11,48 ± 4,68 comprimidos/mês, enquanto diminuiu para 6,53 ± 2,72 comprimidos/mês no primeiro mês (p<0,001) e 5,40 ± 2,46 comprimidos/mês no segundo mês (p<0,001). No terceiro mês, era de 5,85 ± 2,59 comprimidos/mês (p<0,001). Quando comparados o segundo e o terceiro mês, observou-se aumento significativo do uso de analgésicos no terceiro mês p<0,001. Conclusão: Em nosso estudo, houve redução significativa da ingestão de analgésicos e dos dias de cefaleia no primeiro e segundo meses após a injeção de BoNTA, e aumento no terceiro mês. Palavras-chave: Cefaleia; Transtornos de Enxaqueca; Toxinas Botulínicas Tipo A.

ARTICLE
Botulinum toxin type A wear-off phenomenon in chronic migraine patients: how long does the maximum efficiency last?

O fenômeno do encurtamento do efeito da toxina botulínica tipo A em pacientes com migrañe crônica: quanto tempo dura a eficiência máxima?

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INTRODUCTION

Migraine is one of the most common neurological diseases. The prevalence of migraine for the adult population is between 3.3 and 21.9% for women and between 0.7 and 16.1% for men. Migraine is a neurological disorder characterized by recurrent, pulsating headache attacks, and symptoms such as aggravation by or avoidance of routine physical activity, photophobia, phonophobia, nausea, and vomiting. Most migraineurs have moderate or severe pain and 75% have a reduced ability to function normally during the headache attacks. Hence it often affects patients’ productivity and leads to loss of workdays. Migraine can have episodic and chronic forms. Chronic migraine is a migraine subtype in which a headache is present for at least 15 days per month for at least 3 months, with a migraine character for at least eight days. Chronic migraine occurs in around 2% of the population and chronicity rate of episodic migraine is around 3% per year. Therefore, effective treatment is very important for the quality of life of patients. In addition to avoiding migraine triggers, treatment includes medications and non-medication treatments to prevent and stop migraine attacks.

Botulinum toxin Type A (BoNTA) injection is a successful treatment for chronic migraine. Mediators such as glutamate, calcitonin gene-related peptide, and substance P released from the sensory nerve terminals cause pain in migraine pathophysiology. BoNTA is thought to reduce peripheral sensitization and neurogenic inflammation by reducing the secretion of these substances and indirectly suppressing central sensitization. BoNTA inhibits the release of acetylcholine in presynaptic vesicles, leading to dose-dependent reversible paralysis. The effect starts 2–3 days after application, reaches a maximum in 2 weeks and disappears within 2–4 months with axonal sprouting.

In this study, we aimed to determine the benefit of BoNTA on the monthly changes in headache days and analgesic intake in chronic migraine patients who underwent BoNTA for the first time.

METHODS

This study was designed as an observational prospective cohort study. The study protocol was conducted in accordance with the ethical principles stated in the 'Declaration of Helsinki' and was approved by the Ethical Committee of the Gaziosmanpasa Training and Research Hospital. Informed consent was obtained from the participants after the nature of the procedures had been fully explained.

A total of 80 patients (70 females, 10 males) with chronic migraine who were admitted to the neurology outpatient clinic of Bezmialem Foundation University Hospital were included in the study between 2017 and 2018. Inclusion criteria were being between 18 and 65 years old and diagnosed with chronic migraine according to the International Classification of Headache Disorder, ICHD-III-B classification. Exclusion criteria were prior BoNTA injection, pregnancy, additional headache types other than migraine. Analgesic overuse was defined as the use of headache medication on more than 15 days per month, for more than 3 months. Patients with headache analgesic overuse (n=27) were also included in the study. Prophylactic treatments of the patients were not changed during the study (Table 1). Patients were informed about the headache diary and were instructed on to fill them out. Before the procedure, monthly headache days and analgesic intake were recorded. A minimum of 155 and a maximum of 195 units of BoNTA across 31 fixed-sites were applied to the patients in the regions specified in the PREEMPT studies. If the patient had pain, 40 U additional doses across 8 head/neck muscle areas was administered. After the procedure, the number of headache days and analgesic intake were recorded monthly for 3 months. Visits were scheduled across intervals (before BoNTA injection — the first visit, after one month from BoNTA injection — second visit, after two months from BoNTA injection — the third visit, after three months from BoNTA injection — fourth visit). BoNTA response was obtained by calculating

![Image](https://example.com/table1.png)

Table 1. Sociodemographic and clinical data of all patients.

| Treatment                  | All patients |
|----------------------------|--------------|
| Age (years)                | 37.59±7.60   |
| Sex, % (n)                 |              |
| Female                     | 87.5% (n=70) |
| Male                       | 12.5% (n=10) |
| Duration of diagnosis (years) | 14.30±6.36 |
| Treatments                 |              |
| SSRI or SNRI               | 25% (n=20)   |
| Topiramat+SNRI             | 23.8% (n=19) |
| Topiramat                  | 18.8% (n=15) |
| SNRI+amitriptilin          | 7.5% (n=6)   |
| Propranolol+amitriptilin   | 5% (n=4)     |
| Valproicacid+Topiramat     | 5% (n=4)     |
| Flunarazin                 | 4% (n=2)     |
| Amitriptyline              | 2.5% (n=2)   |
| Flunarazin+propranolol     | 1.3% (n=1)   |
| No medication              | 3.8% (n=3)   |

Medication overuse

| Yes                        | 33.8% (n=27) |
| No                         | 66.3% (n=53) |

SNRI: selective norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitors.
separately for each patient according to the change in number of headache days by comparing to the second month (8 weeks — third visit) — with the first visit. Patients whose headaches did not decrease or increased compared to the previous month were considered unresponsive. We also looked for the patients whose headache days continued to decrease after three months (at the fourth visit — 12 weeks).

**Statistics**

The IBM SPSS Statistics Version 20.0 package program was used for statistical analysis. Categorical measurements were evaluated as numbers and percentages, and the numerical measurements as mean and standard deviation (median and minimum-maximum are provided) and descriptive statistical methods were used. Under the assumption that the data were distributed normally, one-sample Student's t-tests were utilized for the comparison of numeric data. Multiple regression analysis was used to assess related factors with BoNTA response. A p-value of less than 0.05 was considered statistically significant.

**RESULTS**

The mean age of the 80 patients included in the study was 37.59±7.60 years, and 87.5% (n=70) of the patients were female and 12.5% (n=10) were male. The most common treatments of the patients were as follows: 25% (n=20) was taking selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitor, 23.8% (n=19) was taking Topiramate+selective norepinephrine reuptake inhibitor, and 18.8% (n=15) was taking Topiramate. Medication overuse was present in 33.8% (n=27) of the patients (Table 1).

The mean number of headache days/month before BoNTA was 18.95±2.69, it decreased to 10.55±3.15 days/month in the first month, 9.31±2.43 days/month in the second month, and increased to 11.97±3.27 days/month in the third month. The number of headache days before BoNTA was significantly different than the number of headache days at each of the 1st (p<0.001), 2nd (p<0.001) and 3rd months after BoNTA (p<0.001). The number of headache days changed significantly (p<0.001) when the first and second months (p<0.001), 1st and 3rd months (p<0.001), and 2nd and 3rd months were compared (Table 2, Figure 1).

The mean monthly analgesic intake before BoNTA was 11.48±4.68 tablets, while it decreased to 6.53±2.72 tablets/month in the first month and 5.40±2.46 tablets/month in the second month. In the third month, it increased to 5.85±2.59 tablets/month. Parallel to the number of headache attacks, the analgesic intake prior to BoNTA administration was statistically significant when compared with each of the 1st (p<0.001), 2nd (p<0.001), 3rd months after BoNTA (p<0.001). When the second and third months (p<0.001) were compared, there was a significant increase in the analgesic intake at the third month (p<0.001), but it was still

| Table 2. Monthly change of the number of headache days and analgesic intake with Botulinum toxin Type A treatment. |
|----------------------------------------------------------|
| **Number of headache days**                                    | Before BoNTA | 1 month | 2 months | 3 months |
| Days/month                                               | 18.95        | 10.55    | 9.31     | 11.97    |
| Standard deviation                                      | 2.69         | 3.15     | 2.43     | 3.27     |
| p                                                       | p<0.001**    | p<0.001**| p<0.001**|         |
| **Analgesic intake**                                      | Before BoNTA | 1 month | 2 months | 3 months |
| Tablets/month                                            | 11.47        | 6.52     | 5.40     | 5.85     |
| Standard deviation                                      | 4.68         | 2.72     | 2.46     | 2.59     |
| p                                                       | p<0.001***   | p<0.001***| p<0.001***|         |

BoNTA: Botulinum toxin Type A; *one sample Student’s t-test; **the number of headache days before BoNTA was compared with the number of headache days at the 1st, 2nd, and 3rd month after BoNTA; ***the mean monthly analgesic intake before BoNTA was compared with the mean monthly analgesic intake at the 1st, 2nd, and 3rd month after BoNTA.
significantly lower than the analgesic intake before and at the first month after BoNTA (p<0.001) (Table 2, Figure 1).

The percentage of BoNTA responsive patients was 97.5%. The mean reduction rate in the number of headache days at the third visit was 50.49±14.47%. The reduction of headache days at the second visit continued in 53.8% of patients at the third visit, and 26.3% of the patients had an increase in the number of headache days compared to the second visit with the third visit; 20% of the patients had no change in the number of days with headache. Reduction of headache days was found to continue in 8.75% (n=7) of the patients in the 3rd month (fourth visit), indicating the headache days of these seven patients continued to decrease in each visit (second, third, and fourth visits). In the patients whose reduction of headache days continued at the forth visit compared with the rest, monthly intake of analgesic tablets (before BoNTA injections) was different between groups (p=0.038) (Table 3). This relationship was also present in the multiple regression analysis.

**DISCUSSION**

We investigated the effectiveness of BoNTA treatment in patients with chronic migraine who underwent BoNTA for the first time and determined the monthly variability of analgesic intake and number of headache days after the injections. Almost all of our patients were BoNTA-responsive, with a significant reduction of analgesic intake and headache days in the first and second months after BoNTA treatment. However, a decrease of the positive effect was observed at the third month (Figure 1). In addition, the reduction of headache days decreased month-to-month. The higher monthly analgesic intake was a negative factor for the continuation of the decrease in the number of headache days.

Zidan et al. studied 38 chronic migraine patients who underwent 155 to 195 U BoNTA treatment in the regions recommended in the PREEMPT study, similar to our study, and they monitored the number and severity of headache days and number of weekly painkiller intake. They observed that the number of headache days increased at the 8-week evaluation13. Markedly, that study had a very similar design and objective, and resulted in similar findings to our study.

Recently, in a retrospective study of 112 patients who had at least 30% BoNTA response, full BoNTA effect occurred in weeks 5 to 8. An increase in headache days was reported at the 12th and 13th weeks compared to the 5th and 8th weeks14. Our study was designed prospectively and follow-ups were done monthly, which allowed us to observe the monthly change in headache and analgesic intake. Unlike the aforementioned study, it was found that the wear-off effect appeared earlier. These results may be due to the difference in inclusion criteria, as they only included BoNTA-responsive patients.

In a previous retrospective study, authors accepted a 50% reduction in the number of headache days at week 12 as a complete response and reported that 47.1% (91/193) of their patients achieved a complete response. With these results, they emphasized that the treatment dose should be increased in patients with decreased BoNTA response15. In a study evaluating the BoNTA response in 143 patients, which considered wear-off as an increase in the number of headache days and use of painkillers during the 6-week follow-up, the authors found a wear-off rate of 62.9%16. These studies were retrospective and had different inclusion criteria, and the BoNTA response was handled differently in each study.

The interval for BoNTA injection in the management of chronic migraine is 12 weeks (78–84 days). Khan et al. studied 98 chronic migraine patients and their results also supported the notion that the 12-week injection protocol may not provide a sustained effect in all patients, explaining the failure in BoNTA response17.

In PREEMPT 1 and PREEMPT 2 studies of 1384 patients diagnosed with chronic migraine, BoNTA treatment and placebo groups were compared (24 weeks of double-blind assessment) and it was proven that BoNTA treatment was an effective, safe, and well-tolerated prophylactic agent for the treatment of chronic migraine. In these studies, which included headache patients with painkiller abuse, additional optional 40 U BoNTA injections were applied to 8 points in

| Table 3. Evaluation of possible related factors with continuation of reduction of headache days. |
|----------------------------------------|----------------------------------------|----------------------------------------|-----------------|
| BoNTA response | No BoNTA response |
| (n=7) (Mean rank) | (n=73) (Mean rank) | p-value* |
| Age (years) | 27.00 | 41.79 | 0.107 |
| Headache days before BoNTA (day/month) | 32.93 | 41.23 | 0.363 |
| Analgesic intake before BoNTA (pieces/month) | 23.00 | 42.18 | 0.036 |
| Duration of diagnosis (years) | 32.86 | 41.42 | 0.890 |
| Duration of prophylactic treatment (years) | 41.64 | 40.39 | 0.249 |

BoNTA: Botulinum toxin Type A; *Mann-Whitney U test.
head and neck muscles. Thus, a minimum dose of 155 U and a maximum dose of 195 U BoNTA was administered to each patient. At the end of 24 weeks, the number of headache attacks was assessed primarily in PREEMPT 1, and the number of headache days was assessed in PREEMPT 2, and a significant decrease in headache days was observed compared to those receiving placebo therapy \( (p=0.006; p<0.01) \). These results were very close to our study in which patients received 155 to 195 U BoNTA injections. There was a significant decrease in analgesic intake and headache days in the 1st and 2nd months. These results were very close to our study. However, in the PREEMPT study, the injection was repeated at the 12th week and the follow-up was continued, whereas, in our study, we stopped the follow-up at the 12th week.

This study should be considered within the context of several limitations. First, there was no placebo group. Therefore, as in all previous studies, the placebo effect could not be excluded.

Secondly, we did not evaluate the visual analog scale score and migraine-related disability. In addition, duration of follow up was relatively short. However, our study also has strong points, as it is one of the first studies that evaluated the duration of BoNTA efficiency over the course of three months.

In conclusion, BoNTA treatment was effective in pain control and reduction of analgesic use in chronic migraine patients. However, the efficiency duration was not as long as it is thought to be in clinical practice. From the 3rd month onwards, an increase in pain and painstaking use was seen. Therefore, future studies with additional doses or additional methods would shed light on the treatment of chronic migraine with BoNTA.

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