ARTIGO ORIGINAL/ORIGINAL ARTICLE

The Wearing-Off of OnabotulinumtoxinA in Patients with Chronic Migraine: Experience of a Tertiary Portuguese Centre

O Efeito "Wearing-Off" da Toxina Botulínica Tipo A em Doentes com Enxaqueca Crónica: Experiência de um Centro Terciário Português

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Abstract

Introduction: The onabotulinumtoxinA (onabotA) is an injectable preventive treatment of chronic migraine (CM), administered in 12 week's intervals. Some patients present a wearing-off (WO) effect in the last weeks before the next treatment. The aim of our study was to evaluate the WO phenomen in patients under onabotA treatment and to recognize possible predictive features of the phenomena.

Methods: We designed a cross-sectional study and proceeded to demographic and clinical characterization of a group of patients, and evaluation of onabotA therapeutic response and adverse events. WO effect was defined as the loss of therapeutic effect, that consists of reduction equal or greater than 50% in the number of headache days, before the 12-week interval. Statistical testing was carried out using a level of significance of $p<0.05$.

Results: We included 60 patients (95.1% female) with a mean age of 49.0±11.4 years. On average, before onaBotA treatment patients had around 15.0 attacks per month. In 45.3% we noticed a therapeutic response after the first treatment. The WO effect was noticed in 36 patients (66.7%) and the majority (50.9%) between the 10th to 12th week post treatment. Wearing-off was more reported by patients under 155 units PREEMPT protocol ($p=0.032$).

Conclusion: This study documents the high frequency of WO phenomen in patients with chronic migraine under onabotA. Therefore, the possibility of a different protocol in selected patients must be explore with larger observational and prospective studies as well as evaluation in clinical trials.

Resumo

Introdução: A toxina botulínica tipo A (onabotA) é um tratamento preventivo injetável da enxaqueca crónica (EC), administrado em intervalos de 12 semanas. Contudo, alguns doentes relatam uma perda de eficácia nas últimas semanas antes do próximo tratamento. O objetivo do nosso estudo foi avaliar esse efeito de *wearing-off* (WO) nos doentes sob tratamento com onabotA e reconhecer possíveis características preditivas desse fenómeno.

Métodos: Desenhámos um estudo transversal e procedemos à caracterização demográfica e clínica e à avaliação da resposta terapêutica e eventos adversos da onabotA. O efeito WO foi definido como a perda de efeito terapêutico, que consiste na redução superior ou igual a 50% no número de dias de cefaleia, antes do

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intervalo das 12 semanas. No estudo foi considerado um valor de significância estatística de $p<0,05$.

Resultados: Incluímos 60 doentes (95,1% mulheres) com idade média de 49,0±11,4 anos. Em média, antes do tratamento com onaBotA, os doentes apresentavam cerca de 15,0 crises de enxaqueca por mês. Em 45,3% verificámos resposta terapêutica após o primeiro tratamento. No entanto, o efeito de WO foi observado em 36 pacientes (66,7%) antes da próxima injeção de onabotA, na maioria (50,9%) entre a 10ª e a 12ª semana após o tratamento. O WO foi mais vezes reportado por doentes sob o protocolo PREEMPT de 155 unidades ($p=0,032$).

Conclusão: Este estudo documenta a elevada prevalência deste fenómeno em doentes com enxaqueca crónica sob onabotA. Sendo neste momento importante explorar a possibilidade de diferentes protocolos em doentes selecionados.

Introduction

Migraine is characterized by recurrent, pulsating headache attacks, usually associated to photophobia, phonophobia, nausea, vomiting and it is a neurological disorder with high impact in patient's quality of life.[1,2] According to the 2016 Global Burden of Disease study, migraine is the second leading cause of disability and is associated with significant absenteeism and reduced productivity related to the severity of headache attacks.[3,4]

Chronic migraine (CM) is defined by a headache present for at least 15 days per month for at least three months, with migrainous features for at least eight days.[5,6] This subtype of migraine occurs in around 2% of the population, therefrom effective preventive treatment is essential to reduce the number, duration and intensity of headache attacks.[7]

The onabotulinumtoxinA (onabotA), through PREEMPT (Phase 3 Research Evaluating Migraine Prophylaxis Therapy) protocol, is an injectable preventive treatment of CM, recommended in 12 week's intervals but real-life data shows that in most of the patients treatment interval is higher.[8] Randomized trials showed the efficacy of this treatment.[9,10] The mechanism of action results in an inhibition of peripherical sensibilization and, indirectly, a reduction of central sensibilization's progression.[11] However, this effect is temporary according to lifetime of the molecule and repetitive administrations are needed.

Some patients self-report fluctuations in botulinum toxin effect, as an increase of number of headaches attacks some days before the next treatment. In fact, WO effect has been previously described in the literature, usually in the two weeks before next treatment but systematic investigation is currently lacking.[12,13]

Most of the adverse events reported by patients under onabotA treatment are local, including injection site pain, eyelid ptosis, brow ptosis, neck pain, neck weakness and shoulder pain. Generally, these symptoms occur within the first few days following injection and are commonly transient.[14,15]

It is necessary to study the fluctuations of onabotA's response to predict factors of better response and to optimize the preventive treatment, with units and intervals of administration adapted to each patient.

The following objectives were defined:

[1] to characterize demographic and clinical patients with CM under onabotA treatment;

[2] to evaluate the wearing-off phenomen in patients under onabotA treatment;

[3] to recognize possible predictive features of better therapeutic response;

[4] to explore the adverse events of onabotA reported by our population.

Methods

Study population

Seventy patients were recruited consecutively at a headache outpatient clinic, during a follow-up visit after the second treatment with PREEMPT protocol and 60 were included. Inclusion criteria were a) age over 18 years old; b) diagnosis of CM with or without aura according to ICHD-III; c) under preventive treatment with onabotulinumA toxin and at least two treatment cycles completed; d) headache diary fulfilled; e) written or verbal informed consent to participate.

Exclusion criteria were a) diagnose of any other headache types, including tension-type headaches; b) language or intellectual barriers.

Study design

We designed a cross-sectional study of patients with CM and at least two treatments with onabotA from January 2021 until December 2021. The headache diagnosis was made according to ICHD-III. A questionnaire was provided and the patient's headache calendar were requested.

The questionnaire consisted of three parts: a) demographic data (gender, age, height and weight) and headache characterization: age of chronic migraine diagnosis, presence of aura, laterality of headache, date of first treatment with onabotA, number of units of PREEMPT protocol, medical report, current other preventive and abortive medication; b) the therapeutic effect of onabotA, the adverse events and the presence of WO, when they noticed it and total number of toxin treatment cycles. There were also applied and analyzed the Patient Global Impression of Change Scale (PGICS).

The number of headache days per month before, after the first and the second cycle of onabotA treatment were collected by the analysis of patient's headache diary.

According to our centre protocol, all the patients that fullfiled the criteria to onabotA treatment start with 155 units (U) protocol. After the first cycle, if the patient do not have therapeutic response defined by a reduction of 30% or more in number of headache days we increase the number units of PREEMPT protocol to 195 U.

The WO effect was defined as the loss of therapeutic effect, that consists of reduction equal or greater than 50% in the number of headache days, before the 12-week interval. We divided the population in two groups, patients with and without WO effect.

The study protocol was approved by the institution's ethics committee (OBS.SF.176-2021) and was conducted in accordance with ethical principles stated in the "Declaration of Helsinki".

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistics (version 26 for Windows®). Categorical variables were displayed as absolute value and percentage, and quantitative variables as mean and standard deviation, minimum and maximum. Under the assumption that our data had a normal distribution according to central limit theorem, Student's t-test were used for comparation of numeric data and Chi-square analysis for qualitative data. Multiple regression analysis was used to assess related factors with WO effect. Statistical testing was carried out using a level of significance of $p<0.05$.

Results

Population

Sixty patients were included in the study, 57 females (95.1%) and three males (4.9%), with an average age of 49.0±11.4 years, all diagnosed with chronic migraine and a mean age of migraine diagnosis of 31.8±14.2 years. Most of the patients did not show a laterality predominance of headache and half of them reported visual and/or sensitive aura in some of headache attacks. Medication overuse in present or history in the past were noticed in 12 patients (21.8%). Psychiatric disturbances, as depression and anxiety, were the more common comorbidities associated in our cohort. The mean of patient's body max index (BMI) was 26.8 ±4.3 kg/m^2 (**Table 1**).

Table 1. Sociodemographic and clinical data.

	All patients (n=60)
Age (y)	49±11.4 [23.0;67.0]
Sex	
Female	57 (95.1%)
Male	3 (4.9%)
Duration of chronic migraine diagnosis (y)	18.0±15.8
Migraine with aura (n)	30 (50.8%)
Laterality (n)	
Right	9 (15.0%)
Left	11 (18.3%
Indifferent	40 (55.7%)
Medication overuse (n)	12 (21.8%)
Comorbilities:	
Depression (n)	6 (14.2%)
Anxiety (n)	25 (55.6%)
Fibromyalgia (n)	7 (171%)

y,years; n, number

Onabotulinum toxin A treatment

We analyzed a mean of total number treatment cycles with onabotA of 4.7±2.0 and due to institutional issues the treatment interval was 13.9±2.0 weeks. Seven

patients (11.7%) were under PREEMPT protocol (155 units) and 54 under extended protocol (195 units).

The mean headache attacks per month before OnaBotA treatment was 15.0±7.8 and reduce to a mean of 3.0±3.9 attacks/month after six months of treatment. The therapeutic effect of onabotA was noticed in 24 patients (45.3%) after the first treatment, 11 (24.5%) after the second treatment, 15 (28.3%) after the third treatment and one patient (1.9%) only after the fourth treatment. Nine patients (15.0%) did not respond to onabotA (**Table 2**).

Table 2. Variability of number headache days and intensity of attacks pre and pos onabotulinum toxin type A treatment.

	Number of headache days	
	Before onabotA treatment	Pos onabotA treatment
Days/month	15	3
Standard deviation	±7.8	±3.9
	Intensity of headache attacks	
	Before onabotA treatment	Pos onabotA treatment
VAS pain	9	6
Standard deviation	±11	±23

VAS pain- visual analog scale for pain

Analyzing the WO, it was noticed in 36 patients (66.7%), the majority, 17 patients (47.2%) reported an increase in headache attacks between the 11-12th week post injection, 11 patients (30.6%) between 10-11th week and 8 patients (22.2%) after the 5th week (**Fig. 1**).

The patient's impression of therapeutic effect of onabotA were evaluate using the PGICS, 26.7% and 40% responded to be a great deal better and better, respectively. However, 6.7% responded moderately better, 16.7% somewhat better, 3.3% a little better and 6.7% felt almost the same.

Seven patients that reported WO also had history of medication overuse. The relation between the presence of WOand medication overuse was non-significant [(1,N=52)=0.041, p=0.840].

All the patients that do not reported WO were under the 195 units PREEMPT protocol (N=21) and had statistically significance (p=0.032). In five patients, the number of units protocol used was unknown. Regarding the number units of PREEMPT protocol, it remained unchanged during the follow-up of our study. No association was found between age, duration of disease, number of previous headache days or number of treatments and WO phenomena. The WO does not seem to influence the perception of onabotA therapeutic response according to PGICS (p=0.097) (**Table 3**).

Adverse events of onabotA

At least one adverse event was reported by 34 patients (56.7%), headache in the day of the administration were the more common (25.0%) and the second hypersensibility on injection site (24.6%). Other events mentioned were sleepiness, cervicalgia, nausea and vomiting, general weakness, fatigue and muscle weakness on injection in site and abdominal/articular/back pain (**Fig. 2**).

Other preventive and abortive treatment

Along with onabotA, 31 patients (52.5%) had concomitant other preventive treatment, the majority, 15 patients (48.4%) with topiramate, 10 (32.3%) with a beta-blocker, 11 (35.5%) with SSRI and seven (22.6%) with amitriptyline. Nine patients had prescribed concomitant to toxin administration two or more pharmacological

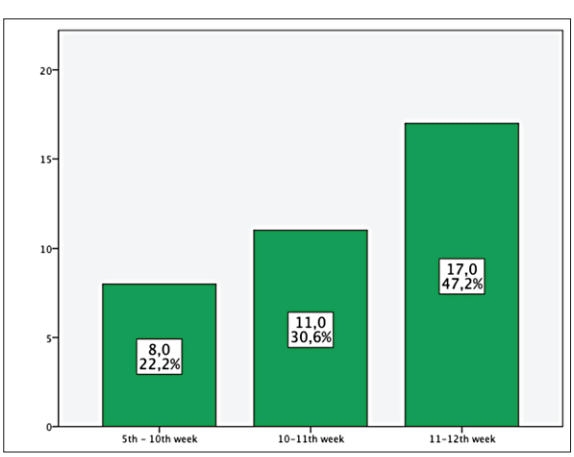

Figure 1. The wearing-off effect. When?

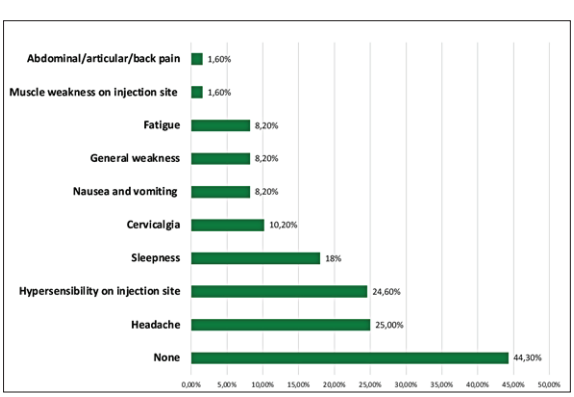

Figure 2. Adverse events of onabotulinum toxin A.

Table 3. Evaluation of possible influencing factors of wearing-off phenomena.

		With wearing-off effect	Without wearing-off effect	*P* value
Age (y)		49.0±11.6	49.6±11.9	0.855
Duration of disease (y)		17.3±15.9	20.1±14.7	0.499
Number of headache days before treatment (n)		16.3±9.0	13.8±8.8	0.324
Number of treatments (n)		4.8±2.0	4.6±2.0	0.798
		With wearing-off effect	**Without wearing-off effect**	**Pearson Chi square**
PREEMPT protocol (n)	**155 U**	6	0	0.032
	195 U	25	21	

y, years; n, number; PREEMPT, Phase 3 Research Evaluating Migraine Prophylaxis Therapy protocol; PGICS, Patient Global Impression of Change Scale.

preventive treatment. One of the patients included in our study were not possible to identify if there were other preventive treatment, it was considered missing data.

Beyond the prophylactic treatment, patients with migraine use abortive medication at the beginning and during headache attacks. In our sample, headache attacks seem to relief with first line abortive medication as acetaminophen, ibuprofen, naproxen and metamizole and only 23 patients (38.3%) had a regular use of triptanes.

Discussion

We studied the therapeutic response and adverse events of botulinum toxin. As expected, female sex predominated in our sample with a duration of the disease around 20 years. In the characterization of our population, a particularity was the average BMI over the normal limit and anxiety disorders were very prevalent, almost half of the patients.

According to the state of art, the efficacy of onabotA was proven by the reduction of headache days before and after the initiation of treatment of a mean of fifteen to three days per month, a decrease of 80%. Not only frequency, but also intensity of attacks, improved with this treatment, graded by a reduction of 3 points in VAS of pain. We verified that some patients respond to toxin after the first treatment cycle, although some patients, respond only after the second or third cycle. This supports the importance of perform three cycles before declare inefficacy.

Most of our population reported WO and most frequently between the 11-12th week post injection. These findings are in accordance with the previous literature published about this topic since 2019. Becker et al showed a tendency of WO in patients with more headache days and can be related with the severity of migraine.[14] Similarly, we found a higher average of previous headache days in the population that had WO, although without statistically difference.

However, we found that patients who do not reported WO were under the 195 units, this fact support the importance of patient's personalization of PREEMPT protocol units. Interesting the previous history of medication overuse and disease duration were not correlated with WO effect, in other words these factors that also contribute to the severity of migraine does not seem to influence this phenomenon. Other interesting fact was the patient global impression of change with this treatment were not influenced by the presence of WO.

As previous studies speculated, we must keep in mind that WO phenomen in clinical practice may not only include a loss of pharmacological OnabotA effects but also a possible loss of placebo effect related to injectable administrations.

Adverse events were reported by more than half of patients, in addition to the previous literature we found as more commons effects a headache and a hypersensibility on injection site in the day of the administration. Other events like cervicalgia, nausea and general weakness were also noticed and described in the literature.

An important fact was the other concomitant preventive and abortive treatment characterization of our population. Almost half of the patients, the onabotA were the unique preventive and usually the headache attacks improved with first line abortive medication as acetaminophen and anti-inflammatory agents, this also support the efficacy of this treatment

Our study had some limitations related to the study designed, single center, which can lead to selection bias in our sample. Some of data collected were patient-dependent, like headache diaries report of headache days, which could be a cause of bias in our study.

Conclusion

This study documents the high frequency of WO phenomen in patients with chronic migraine under onabotA as preventive treatment, particularly the patients under 155 units protocol. Most of patients with CM receiving onabotA experience a WO effect in the last two weeks before next treatment. The 12-week interval protocol does not provide a sustained effect in all patients, therefore the possibility a different protocol in selected patients must be explore with larger observational and prospective studies as well as evaluation in clinical trials. ■

Article Highlights

- Wearing-off was a common effect noticed in the last week before the next treatment, in patients under onabotulinumtoxinA 155 units protocol and with higher number of previous headache days.
- Medication overuse and disease duration did not influence the wearing-off phenomen in chronic migraine patients.
- There were more adverse events of onabotulinumtoxinA reported although there were generally mild.

Contributorship Statement / Declaração de Contribuição

CF: Design of the work, acquisition of the data, interpretation of the data, writing the manuscript, manuscript review and final approval.

BS: acquisition of the data, writing the manuscript and final approval.

JRL: acquisition of the data, writing the manuscript and final approval.

IL: Design of the work, interpretation of the data, manuscript review and final approval.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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