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The Effect of Abobotulinum Toxin A in the Prophylactic Treatment of Refractory Migraine

Dirençli Migrenin Profilaktik Tedavisinde Abobotulinum Toksin A Etkisi

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Summary

Objective: Some patients with migraine headache still experience severe migraine attacks despite use of proper prophylactic treatments. There are several treatments for refractory migraine (RM), one of which is abobotulinum toxin A (Dysport). This study aimed to investigate the efficacy of abobotulinum toxin A in the prophylactic treatment of RM.

Materials and Methods: In this prospective single-arm clinical trial, 18 patients with RM were included. Patients completed a questionnaire including migraine characteristics one month before the study. Each patient received an injection of 150 U abobotulinum toxin A in the specific head and neck regions. Before and 3 months after treatment, migraine severity was evaluated.

Results: The average number of attacks per month before injection was 7.56±4.06, which decreased to 1.89±1.32 3 months after injection ($p<0.0001$). The average duration of attacks also decreased significantly after 3 months of injection (from 20.33 hrs to 2.56 hrs per month) ($p=0.0001$). Three patients (16.6%) had no attacks during the follow-up period. Eleven patients (61.1%) reported mild attacks and four patients (22.2%) reported moderate pain.

Conclusion: Abobotulinum toxin A (Dysport) can reduce frequency, duration, and severity of migraine attacks in patients with RM and it can be used as a prophylactic treatment in this group of patients.

Keywords: Refractory migraine, abobotulinum toxin A, headache

Öz

Amaç: Migren hastalarının bir kısmı uygun profilaktik tedavi kullanımına rağmen ciddi migren atakları yaşamaya devam etmektedirler. Dirençli migrende kullanılan çeşitli tedaviler vardır ve bunlardan birisi abobotulinum toksin A'dır (Dysport). Bu çalışmada dirençli migrenin profilaktik tedavisinde abobotulinum toksin A'nın etkinliğinin araştırılması hedeflenmiştir.

Gereç ve Yöntem: Bu prospektif tek kollu klinik çalışmaya 18 dirençli migren hastası dahil edildi. Hastalar çalışmadan 1 ay önce migren karakteristiklerini içeren bir anketi tamamladılar. Her hastanın spesifik baş ve boyun bölgelerine 150 U abobotulinum toksin A enjeksiyonu uygulandı. Tedavi öncesi ve 3 ay sonrasında migren şiddeti değerlendirildi.

Bulgular: Enjeksiyon öncesi aylık ortalama atak sayısı 7,56±4,06 iken, enjeksiyondan 3 ay sonra bu sayı 1,89±1,32'ye geriledi ($p<0,0001$). Ortalama atak süresinin de enjeksiyondan 3 ay sonra anlamlı olarak azaldığı görüldü (ayda 20,33 saatten 2,56 saate) ($p=0,0001$). İzlem süresince üç hastada (%16,6) hiç atak gözlenmezken, 11 hasta (%61,1) hafif, dört hasta ise (%22,2) orta şiddette ataklar bildirdi.

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Sonuç: Abobotulinum toksin A (Dysport) dirençli migren hastalarının atak sıklığı, süresi ve ciddiyetini azaltabilir ve bu hasta grubunda profilaktik tedavi olarak kullanılabilir.

Anahtar Kelimeler: Dirençli migren, abobotulinum toksin A, baş ağrısı

Introduction

Migraine is a complex debilitating neurologic disease that reduces patients' quality of life (1). The current worldwide prevalence of migraine and its lifetime prevalence have been estimated by the World Health Organization as 10% and 14%, respectively (2).

To date, various prophylactic drugs including anticonvulsants, ß blockers, calcium channel blockers, serotonin reuptake inhibitors, and tricyclic antidepressants have been used to reduce migraine pain (3). Despite timely and appropriate application of prophylactic medications, some patients develop refractory migraine (RM) that is resistant to treatment (4). RM is a relatively common and very disabling condition but its epidemiology is unknown (5).

Various treatments have been suggested for the RM, one of which is botulinum toxin type A (6). Botulinum toxin type A has been used so far for reducing pain in conditions such as cervical dystonia, achalasia, anal fissure, and myofacial pain syndromes (7). In the recent decade, botulinum toxin type A injection has been used in many studies for tension-type and migraine headaches (8). Botulinum toxin type A injection was approved by the United States Food and Drug Administration (FDA) for prophylactic treatment of migraine in 2010.

This study was designed to investigate the effect of abobotulinum toxin A injection in the prophylactic treatment of migraine headache in patients with RM because our knowledge is limited about the effect of botulinum toxin type A in Iranian patients with RM.

Materials and Methods

This single-arm open-label clinical trial was conducted on 18 patients with RM from May 2011 to May 2012 in our Neurology Clinic. The study protocol was approved by ethics committee at Islamic Azad University, Medical Branch, Mashad.

Patients aged above 18 years who were confirmed as having migraine with no appropriate response to treatment, or RM with or without aura (classic and common migraine), were included in the study (Table 1). The diagnosis of migraine was made based on International Headache Society-2 criteria (9) and the diagnosis of RM was made based on the criteria proposed by Schulman et al. (Table 1) (10).

Patients with types of headaches other than migraine, pregnancy or breastfeeding, previous history of other injections in the injection sites within the previous month, or who were unavailable for follow-up or non-cooperative were excluded from the study.

The study objective, the drug safety of abobotulinum toxin A and its possible adverse effects, such as temporary ptosis or diplopia following injection, were explained to the patients who signed written informed consent forms before enrollment.

Information about sex, age, jobs, family history for migraine, and other diseases, imaging findings, drugs, and the characteristics of migraine attacks a month before injection including the number, duration and severity of attacks were collected in a questionnaire at the beginning of study. Each patient kept a headache diary during the trial to report events and migraine headache changes.

Severity of migraine disease was defined as mild: a single attack in a month, moderate: two attacks in a month, severe: more than two attacks monthly for at least three consecutive months.

Severity of headache pain was assessed using the visual analogue scale (VAS) pain score. VAS is a numeric scale of 0-10, where zero indicates no pain at all and 10 shows unbearable pain. According to this scale, severity of headache was categorized into 5 groups: none (score 0-1), mild (score 2-3), moderate (score 4-5), severe (score 6-7), and very severe (score 8-9) and unbearable pain (score 10).

Abobotulinum toxin A is another type of botulinum toxin type A; however, its therapeutic dose is somewhat different from botulinum toxin A (Botox). A conversion ratio of 3:1 (abobotulinum toxin A: botulinum toxin type A) has been suggested (11). By this consideration, a triple-fold dose of Botox should have been considered in our study, but because we did not know the adverse

Table 1. Inclusion criteria of study based on criteria proposed by Schulman et al. (10) for the diagnosis of refractory migraine

Inclusion criteria
A. Diagnosis of migraine based on ICHD-2
B. Headaches cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy
Failed adequate treatment with acute and preventive drugs, alone or in combination from at least 2 of 4 drug classes:
Beta-blockers,
Anticonvulsants,
Tricyclics,
Calcium channel blockers.
Failed abortive medicines from the following classes, unless contraindicated:
Both a triptan and DHE,
Either NSAIDs or combination analgesics.
There may be modifiers: With or without medication overuse, With significant disability (MIDAS >11).

DHE: Dihydroergotamine, ICHD: International Classification of Headache Disorders, MIDAS: Migraine disability assessment, NSAIDs: Nonsteroidal anti-inflammatory drugs

effect of high doses of Dysport, we used the same dose used in the study of Sikaroudi et al. (12).

The patients were receiving preventive drugs including beta-blockers, anticonvulsants, tricyclic drugs and calcium channel blockers prior to the study. All prophylactic drugs were discontinued during the trial and a washout period of four weeks was considered prior to abobotulinum toxin treatment. The patients were only allowed to take painkillers during the trial for acute migraine attacks if required.

One hundred fifty units of abobotulinum toxin A (Dysport) (IPSEN, France) with divided doses was injected intramuscularly for each patient with insulin syringes in related sites according to Table 2. Injection sites were selected according to the Robertson and Garza (13) study.

The patients were assessed again after three months and the frequency, severity, and duration of migraine attacks were recorded. A placebo group was not approved by ethical committee because the treatment was invasive, as such we did not include a control group in the study.

The data were then analyzed using SPSS software version 18.00 for Windows with chi-square test and paired t-test. The nonparametric Wilcoxon signed-rank test was used to compare attack numbers and severity before and after treatment because of the non-normal distribution of data. P values less than 0.05 were considered significant.

Results

In this clinical trial, 18 patients with RM were included; 27.8% (n=5) were men and 72.2% (n=13) were female. The mean age of men and women was 37.6±7.23 years and 32.38±6.83 years (range, 18-45 years), respectively, with no significant difference between the sexes (p=0.17). There was a family history of intractable migraine in 13 (72.2%) patients. None of the patients had medication overuse.

Table 3 shows the characteristics of the migraine headaches in the study participants a month before and three months after treatment. Data analysis using the Wilcoxon signed-rank test and paired t-test showed that the number of migraine attacks per month and duration of migraine headaches reduced significantly three months after abobotulinum toxin A injections (Table 3) (p<0.0001). No drug adverse effects were reported by the patients.

A month before injection, all patients had severe or very severe headache but pain severity reduced after 3 months of treatment; 3 patients (16.6 percent) had no attacks during the 3-month follow-up, 11 patients (61.1 percent) experienced mild, and four patients (22.2 percent) had moderate headache pain (Table 4). At the beginning of the study, headache in all patients was severe or very severe, but no patients reported severe and very severe headache after three months of injections.

Table 2. Dose and location of botulinum toxin injections used in this study (13)

• 5.0 U into each corrugator muscle and into the procerus muscle One injection site per muscle (15.0 U total)
• 5.0 U into the right and left superior frontalis muscle Two injection sites per muscle (10 U total)
• 12.5 U into each temporalis muscle Two injection sites per muscle (25 U total)
• 12.5 U into each splenius capitis muscle Two injection sites per muscle administered as two-thirds of 12.5 U (8.3 U) at superior injection site (near muscle insertion) and one third (4.2 U) at mid-belly of muscle to minimize neck weakness (25 U total)
• 12.5 U into each occipitalis muscle Two injection sites per muscle (25 U total)
• 25 U into each trapezius muscle Three injection sites per muscle (50 U total)

Discussion

This study results showed that abobotulinum toxin A injection is effective in the improvement of pain severity, number, and duration of migraine episodes.

Botulinum toxin type A has been approved by United States FDA for prevention of migraine headaches. Different mechanisms have been described for the effect of Botox in migraine headache. The simple mechanism of the analgesic effects of botulinum toxin type A on migraine headache works by reducing the muscles spasms and contractions around the skull by inhibiting acetylcholine release and consequently reducing the frequency and severity of migraine headaches (7). Other mechanisms have been suggested for botulinum toxin type A action, such as reducing the production of calcitonin gene-related peptide by cultured trigeminal ganglion neurons (14); inhibiting release of glutamate and other pain neurotransmitters (15,16); blockade of substance p (17); inhibition of acetylcholine release from Schwann cells (18), which affects neurotransmission

Table 3. Comparison of characteristics of migraine attacks a month before and three months after injection

Characteristics of migraine attacks	A month before injection	3 months after injection	p value
Frequency of migraine days/month (mean ± SD)	7.56±4.06	1.89±1.32	<0.001*
Duration of migraine (hour) (mean ± SD)	20.33±6.83	2.56±2.03	<0.001†

*Wilcoxon signed-rank test, p<0.05 significant, †Paired t-test, p<0.05 significant, SD: Standard deviation

Table 4. Comparison of the severity of migraine pain a month before and three months after injection

Severity of migraine pain	A month before injection	3 months after injection
Very severe, n (%)	5 (27.7)	0
Severe, n (%)	13 (72.2)	0
Moderate, n (%)	0	4 (22.2)
Mild, n (%)	0	11 (61.1)
None, n (%)	0	3 (16.6)

at distal central nervous system sites (19); inhibiting release of acetylcholine in terminal neuromuscular junctions (16), suppression of c-fos expression; and finally, blocking peripheral sensitization and reducing central sensitization (20). Botulinum toxin type A may also exert its antinociceptive properties through affecting pain carrying C and A delta fibers, and by reducing cholinergic transmission at perivascular nerve endings (21).

Sikaroudi et al. (12), treated patients with 125 U Dysport or saline (as placebo) and found no significant difference between the two groups after 3 months. When they considered a subgroup of patients with moderate and severe migraine they found a significant difference between the two study groups after 3 months (20). Our study findings in patients with RM with severe to very severe pain at baseline confirm the findings of Sikaroudi et al. (12) In the present study, the intensity of migraine attacks decreased after 3 months. In similar studies, including those of Sikaroudi et al. (12) and Silberstein et al. (7), the same results were obtained in patients with moderate to severe migraine (7,12).

In German study in 2009 by Petri et al. (22), 127 patients received placebo and two different doses of BoNT-A (Dysport). The results showed a reduction in the number of attacks in the Dysport group but with no significant difference (22). They concluded that although BoNT-A seemed to be effective in reducing the number of attacks to some extent, its efficacy in the prophylactic treatment of migraine was not significant (22).

In a clinical trial on patients with episodic migraine without aura, the efficacy of two different dosages (120 vs. 240 units) of Dysport vs. placebo was evaluated for migraine prophylaxis (23). The authors found no changes in the number of migraine attacks after 3 months of therapy; however, pain intensity and mean duration of headache decreased with Dysport-240 at weeks 8-12 (not significantly) and 0-4, respectively (23).

In a meta-analysis by Shuhendler et al. (24), eight clinical trials with 1601 patients with episodic migraine were included and the efficacy of high and low doses of botulinum toxin type A versus placebo was assessed. That study again found no statistically significant differences between high or low dose Botox and placebo in reducing the frequency of episodic migraine attacks at 30, 60, and 90 days after injection.

In a recent large meta-analysis in America, 27 placebo-controlled randomized trials were included. In these 27 trials, a total of 1938 patients with episodic and 1544 with chronic migraines participated. The study concluded that Botox had no greater beneficial effects than placebo in prophylactic treatment of episodic migraine but it had beneficial effects in prophylaxis of chronic migraine headaches (25).

Study Limitations

The small sample size and having no placebo arm are the main limitations of the present study, which limits generalization of the results. However, despite these limitations, our study showed good results with such a small dose of abobotulinum toxin A, which usually requires a 2-3 times higher relative dose compared with other botulinum toxin type A formulations, with no adverse effects in preventing migraine attacks in RM.

Future controlled clinical trials with greater sample size, multiple doses of abobotulinum toxin A, and longer follow-up in patients with RM are warranted to confirm our findings.

Conclusion

Considering the results, it seems that low-dose abobotulinum toxin A injections are effective in the prophylactic treatment of RM and could reduce the frequency, duration, and severity of migraine episodes, and it can be used in patients with RM.

Ethics

Ethics Committee Approval: The study protocol was approved by Ethics Committee at Islamic Azad University, Medical Branch, Mashad, Informed Consent: All patients gave signed written informed consent before enrollment.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Seyed Mehran Homam, Concept: Seyed Mehran Homam, Design: Seyed Mehran Homam, Data Collection or Processing: Afrouz Alipour, Mostafa Khorashadizadeh, Maedeh Beheshti Saadat, Analysis or Interpretation: Afrouz Alipour, Morteza Mazloum Farsi Baf, Literature Search: Maedeh Beheshti Saadat, Morteza Mazloum Farsi Baf, Writing: Morteza Mazloum Farsi Baf.

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