Ultrasound guided onabotulinum injection in chronic migraine: a case series

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Key points
Chronic migraine is difficult to treat and requires a multidisciplinary approach. Several pharmacological treatments have been shown to be effective in placebo-controlled randomized trials and our patients therapy was between these: topiramate and local injection of botulinum toxin. Both therapies are reported to be effective in patients with chronic migraine with and without medication overuse. Ultrasound guidance provide many advantages and permits to visualize the spread of the drugs.

Abstract

Background
During the early years of Botulin Toxin type A (BoNT-A) treatment for motor conditions, investigators noted a significant benefit of BoNT-A on pain that often exceeded the improvement in muscle contractions. Recently BoNT-A received indication for the treatment of Chronic Migraine (CM). In this report we analyse how ultrasound-guided techniques, allowing the visualization of tissues, potentially improve the accuracy of the needle placement exemplifying BoNT-A procedures also in the treatment of untreatable CM with onabotulinumutoxin A.

Method
Patients with CM and inadequate response or intolerance to previous two prophylactic treatments and considered “untreatable Class I CM” patients were treated with pericranial injections of about 150 UI of BoNT-A every 3 months. The dose could be increased up to 200 U in case of no response. Patients reported headache diary, MIDAS score. effect of BTA on the frequency of disabling attacks, and consumption of analgesics.

Results
All meet the IHS criteria for analgesic overuse. The number of sessions studied with BTA were 4. Patients achieved reduction >70% in headache frequency and intensity. Those four patients reduced NSAIDs and analgesics consumption significantly.

Conclusions
US guidance provide clear advantages also in CM patients injections because it permits to visualize the spread of BTA from the needle and to validate procedure’s outcome. US guided BoNT-A injections could be a profitable option both clinically and pharmacoeconomically.

Introduction
Migraine is a common and disabling disorder, with 2 major subtypes primarily differentiated by headache attack frequency. Episodic migraine (EM) is characterized by headaches that occur on fewer than 15 days per month (1) Chronic migraine (CM) is defined as
headache occurs on \( \geq 15 \) days per month for at least 3 months (2). CM is difficult to treat and requires a multidisciplinary approach. Several pharmacological treatments have been shown to be effective in placebo-controlled randomized trials and our patients therapy was between these: topiramate and local injection of botulinum toxin (3,4). Both therapies are reported to be effective in patients with chronic migraine with and without medication overuse. Onabotulinumtoxin A (trade name Botox) received FDA approval for treatment of CM and recently BOTOX\(^\text{®}\) (botulinum toxin type A) has been further licensed, first Country in Europe, by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK for prophylaxis of headaches in adults who have chronic migraine. After UK several other European countries licensed Onabotulinumtoxin A for this indication. To be eligible for this treatment, according CM diagnostic criteria, individuals need to experience headaches for 15 or more days per month, with migraine on at least 8 of these days. Approval followed evidence presented to the agency from two studies funded by Botox maker Allergan Inc. showing a slight improvement in incidence of chronic migraines for migraine sufferers undergoing the Botox treatment (5,6). Initial treatment options for CM should focus on control of one or more factors shown to contribute to headache occurrence. These triggers would include changes in diet, sleep, exercise, and psychological well-being, in addition to many other potential influencing factors. Caffeine, alcohol, tobacco, and use of select over-the-counter (OTC) and prescription medications should be minimized due to their potential for increasing headache risk. Treatment options can further be subdivided into acute and preventive pharmacotherapy. Some of the acute treatment options include simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), triptans, and ergotamines. Use of these agents should be limited to 2 or fewer days per week to minimize risk for rebound headache that would complicate treatment and possibly require a detoxification treatment. Preventive pharmacotherapy focuses on several different classes of medications, including antidepressants, anticonvulsants, beta-blockers, calcium channel blockers and possibly Botox injections. Second line approach is worldwide considered to be topiramate (7). Topiramate study was evaluate to have a good efficacy and tolerability in the prevention of chronic migraine. Topiramate titrated according to patient need significantly reduced the mean number of monthly migraine days compared with placebo (P < 0.05) but treatment emergent adverse events (AE) were reported by 75% of topiramate-treated patients versus 37% of placebo. The most common AE were hand paraesthesia, nausea, dizziness, dyspepsia, fatigue, anorexia and disturbance in attention. The randomized, double-blind, placebo-controlled trial demonstrated that topiramate can be effective but best tolerated medication should be welcome (7). Onabotulinumtoxin A (trade name Botox): BoNT-A injection is an useful treatment that is advocates to enhance functional and motor abilities in upper motor neuronsyndrome with spasticity. Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on the cholinergic nerve terminals and decreasing the release of acetylcholine, causing a neuromuscular blocking effect. This mechanism laid the foundation for the development of the toxin as a therapeutic tool. Several authors had reported as during the early years of BoNT-A treatment for motor conditions such as dystonia, investigators noted a significant benefit of BoNT-A on pain that often exceeded the improvement in muscle contractions and did not strictly correspond to the region of neuromuscular effects. Its effectiveness is related not only to the amount injected but also to a precise muscle targeting therefore nowadays it has more and more injected under ultrasound guidance in several approaches (8-13). Results of the cited recent large, randomized, phase 3, placebo-controlled trials showed that onabotulinumtoxin A can be an effective, safe, and well-tolerated treatment for the prevention of
A diagnosis of migraine was assigned based on ICHD-2 criteria (2, 21). Assessment should include ascertaining the number of days per month without headache as well as the number of days with headache in order to accurately determine headache frequency. Four patients affected by intractable Class I Chronic Migraine according Silberstein’ Classification (16) and treated with mixed efficacy results where considered for BoNT-A injections. Patients characteristics are reported in tab 1. They were all CM patients proposed to be treated with BoNT-A because of side effects of ongoing therapies. Headache-related disability was assessed in 2 ways: using the MIDAS Score (22) and with questions about the impact of headache on functioning. All of them used to treat acute pain with simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and triptans, as needed (23). Preventive previous pharmacotherapy lastly has focused on topiramate (7). In all of four patients, topiramate were titrated according to patients need in order to significantly reduce migraine variables. BoNT-A treatment was considered because emergent topiramate-related AE were reported in all of four. The most common AE were hand paraesthesia, dizziness, dyspepsia, fatigue, and disturbance in attention. Because BoNT-A has already demonstrated good efficacy in several open-label studies of patients with migraine, involving either individualized or standardized protocols, we propose patients to consider a prophylaxis with BoNT-A for their CM. Our clinical goal was the reduction of number of migraine attacks and their intensity.

**Case series**

Di Lorenzo et al. Ultrasound and chronic migraine

Di Lorenzo et al. Ultrasound and chronic migraine

the risk of brow ptosis. There are several injection protocols commonly described and used, between those we followed that based on the PREEMPT clinical program (17). The overall objective is to inject toxin at multiple sites to ensure complete dispersal of toxin through the target regions. Bilateral symmetrical frontalis injections help to maintain visible cranial symmetry. Elsewhere, injections, when bilateral, need not to be symmetrical. In our cases, total doses of BotNT-A range from 100 to 200 U. Muscles typically injected include the frontalis, temporalis, occipitalis, splenius capitis, trapezius, and cervical paraspinal muscles, although the use of a range of muscle sites and doses has been reported in the literature (5,6,18).

Results
Patients in the active treatment group experienced a reduced frequency of headache days and episodes, fewer moderate or severe headache days, and a lower cumulative number of hours of headache on headache days (table 1). They also experienced a significant improvement in their functioning and less disability. Change in number of migraine attacks from pretreatment to weeks 12 was significantly different and there was a greater improvement in total intensity scores and a significantly different effectiveness (table 1) at weeks 12 with onabotulinum. Improvements in patient and global assessments between weeks 0-12 (effectiveness of pain relief and other not reported scores because beyond the paper aim) were reported to be more than 75% compared to the obtainable amelioration from all of 4 patients and considered a good result. Beneficial effect from toxin injection was apparent in few days as already reported in literature (18) and our patients experienced a sudden onset of pain relief even if we are aware that a potential bias could be the “dry-needling” effect (24) on the tension-type component of pain. Maximum response from the toxin was reached in approximately 1 week and last several weeks. Injections were suggested to be repeated every 4 months.

Discussion
Accurate neurological diagnosis is critical in developing an optimal treatment plan. Health care professionals have to be advised in order to take a thorough approach to CM. It can have significant effects on occupational, academic, social, and personal functioning and well-being. BotNT-A has been already proven effective in CM in many double-blind, placebo-controlled trials (2,3) and in our personal anecdotal experience BotNT-A injection benefits the highest percentage of patients in the shortest time. Moreover, BotNT-A has fewer side effects than do other pharmacological treatments. Average treatment dosage of BotNT-A in CM has been reported to be 150-200 U per patient. Researchers recommended the lowest starting dose according to profile’s effectiveness reported (18) and so, in our experiences, we used an average of hundred-fifty units of onabotulinumtoxin per mL of preservative-free normal saline. No general consensus exists among users of BotNT regarding the need for EMG guidance while injecting the compound for chronic migraine and PreEMPT results suggesting the rule “Follow the pain” (18). EMG guidance, however, in this case cannot be helpful and to identify the specific muscles involved in cervical pain and migraine prior to the injection is important. InPre e-empt2 study injections were administered as 31, fixed-site, fixed-intramuscular injections (minimum dose 155U) across seven specific head/neck muscle areas (corrugator, procerus, frontalis, temporalis, occipitalis, cervical, paraspinal and trapezius) every 12 weeks over 24 weeks (two cycles) (5,6). Authors adopted a “follow-the pain” strategy depending on the locations of the patient's predominant pain and severity of palpable muscle tenderness. Moreover, at the PreEempt investigators discretion, up to 40U additional onabotulinumtoxin A (maximum dose 195U) or placebo injections could be given to one or both sides in up to three muscles groups (occipitalis, temporalis and trapezium) (5,6). If we consider the procedure techniques available, the ultrasound-guided...
Ultrasound-guided techniques allow the visualization of a wide variety of tissues and it potentially improves the accuracy of the needle placement, as exemplified by various BoNT-A procedures (8-13). The method described for assessing the neck and cranial muscles is a potentially valuable tool in clinical practice (18,25). Ultrasound can be so used to assess abnormality of the deep neck muscle group providing useful views of the cross-sectional area of the deep neck muscles to be injected. Ultrasonographically, linear measurements can be used to better targeting the neck muscle, procerus and cranial muscles avoiding to inject deeply into the periostium or outside the muscle (optimising the amount of BT-A needed) (fig. 1,2) (18,25). Technical evident and reported advantages in migraine treatment are different, first of all the useful guidance for the whole cranial area (19,25). If the patient has posterior neck pain, then the occipital or cervical paraspinal areas should be evaluated. Pain is typically located in the cervical paraspinal area, below the nuchal ridge, where the trapezius, splenius capitis, and semispinalis capitis converge. Several authors suggest that it could be not necessary to differentiate the specific muscles injected. Rather, according recent trials (15,17,18) we should inject following the pain and the areas associated with pain and tenderness on palpation, So, typically, we can anecdotally report that injections are almost all located in the region of the splenius capitis injecting 1 or 2 sites on each side with the total dose varying between 5 to 15 U per side. A common “fixed sites” approach suggest to treat also trapezius muscle. Indeed, because Trapezius is innervated also by a cranial nerve, we prefer to treat it only if we localize “palpable trigger points” and its clear involvement injecting (1 to 3 sites per side; dose varying between 5 to 15 additional U); in three out of four our cases a clear trapezius tenderness was elicitable. Finally, we use to evaluate muscle belly with ultrasound before to perform injections, providing the chance to avoid trapezius (one out of four cases) and

Fig. 1 Facial Muscles
- **Corrugator** muscle draws the eyebrow downward and medially. Produce vertical wrinkles in the glabellar region. It is covered by thicker skin and subcutaneous tissue.
- **Procerus** pulls down the skin between the eyebrow. It produces horizontal wrinkles over the bridge of the nose and is covered by thick skin.

Fig. 2 Neck Muscles
Ultrasound permits to study posterior neck muscles and correctly target the chosen sites of BoNT-A injections.
Variable | All Subjects
---|---
Number | 4
Age [years] | 45.5
Age Range [years] | 32-56
Gender [male:female] | 0:1:03:00
Ethnicity [% caucasian] | 100
Migraine Days [mean] | 20.0
Range [days] | 10-30
MIDAS (Migraine Disability Assessment) Average Range | 13 Grade III Moderate disability (12-14)
Pain Intensity [Attacks] Range VAS | 9 8-10

Pain relief effectiveness

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<td>week 2 range [%]</td>
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<td>week 4 range [%]</td>
<td>74.86% (66.67-80)</td>
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<tr>
<td>week 12 range [%]</td>
<td>86.32% (80-88.89)</td>
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Table 1. Demographics and Pain Visual Analog Scores [PainVAS] in the study group.

Values are expressed as mean Pain Visual Analog Scale [PainVAS] scores ± standard deviation (SD) and [range] of the observed values. Effectiveness at discharge reflects the proportion of potential maximal improvement achieved during hospitalization. The proportion was calculated according to the following formula:

\[
PainVAS \text{ Effectiveness} = 100 \times \frac{\text{Discharge Scale score} - \text{Initial Scale score}}{\text{Maximum Scale score} - \text{Initial Scale score}}
\]

According to this formula, the PainVAS Effectiveness was 100 percent when a patient achieved the maximum scale score.

Abbreviations: PainVAS=Pain Visual Analog Scale, Av.=average, StDev=standard deviation, %=percent

The MIDAS (Migraine Disability Assessment) questionnaire measures the impact of headaches on life. The information on this questionnaire is also helpful for primary care provider to determine the level of pain and disability caused by headaches and to find the best treatment (Survey developed by Richard B. Lipton, MD, Professor of Neurology, Albert Einstein College of Medicine, New York, NY, and Walter F. Stewart, MPH, PhD, Associate Professor of Epidemiology, Johns Hopkins University, Baltimore).

Botulinum toxin appears in the headache armamentarium more than a decade ago and in the two recent trials (5,6) onabotulinumtoxin A (Botox) was found effective in CM. Performing BoNT-A cranial injections, the specific muscle location technique often allows a close approach, hopefully without the risk of muscle damage. Unfortunately, this is essentially a blind process, but modern imaging techniques might be used to overcome this. Ultrasound-aided muscle injections have been reported in literature since the mid-2000s (8-13), probably as a result of improvements in ultrasound equipment. Most of the studies of ultrasound in BoNT-A injections practice have looked at one or more of the various approaches to the spastic muscle, some using ultrasound to identify and mark the skin over nerves and blood vessels and others using it to guide the needle. In our CM case series patients were enthusiastic of outcomes achieved and ultrasound guidance gave both them and physicians the “feeling” that BoNT-A had been delivered precisely to the target cranial muscle, exactly targeting exactly only the underlying splenius capitis, that is always treated (fig.2). This approach seems to provide us “a sparing BoNT-A strategy” having used a total average amount of 150 (125-200) U.

Conclusion

Chronic migraine is one among the most disabling, often drug resistant and a serious public health problem, as it affects 1-2% of people in the general population (1) Within a recent large US-based population sample, it has been reported a CM prevalence rate of nearly 1% with CM representing 7.68% of all migraine cases (1) According to adjusted models, the highest prevalence rates were among females in midlife and in households with the lowest incomes. All Health care professionals should be therefore aware of the rates of CM in the population and recognize that they will likely see a much larger percentage of patients with CM in health care settings, especially specialty care settings (1).

Di Lorenzo et al. Ultrasound and chronic migraine
to the facial and neck muscles or its related structures. Knowledge of anatomy and US guidance addresses the needle to the general area of the muscle and helps avoid other structures. Ultrasound is normally used also to visualize the spread of BoNT from the needle and to validate procedure. Our antipodal experience and this case series could contribute to enforce the opportune practice of injecting BoNT in refractory chronic migraine using US guidance.

References

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