USE OF BOTULOTOXIN TYPE A IN THE TREATMENT OF PRIMARY HEADACHE

Anna Prokhorova, Nigora Kadyrkhodjayeva
Deparment of Neurology, 1st City Clinical Hospital
Farobi 2, Almazar District, Tashkent, Uzbekistan. 100109
anna-prohorova@yandex.com kadyrkhodjayeva@hotmail.com

Abstract
For the treatment of chronic daily headache (CDH) a Botulotoxin type A was used. After treatment, 34% of patients had no extravasal effect, and 66% had moderate. Normalization of venous outflow was noted in 58% of patients, of whom only 10% had changes in their severity after the procedure. The obtained results testify to an improvement in the cerebral blood flow indicators of patients with CDH against the background of injections of botulinum toxin type A. The purpose of the study was to determine the efficacy of botulotoxin type A influence on chronic daily headache (CDH) flow. The objectives were to assess the dynamics of the clinical signs of CDH, the chances of the effect of BTA on the activity of antinociceptive systems and cerebral blood flow.

INTRODUCTION

According to the International Classification of Headache (ICHA), headaches (HA) are divided into primary, secondary and mixed [1]. Primary HA includes a group of diseases not associated with structural damage or systemic disease of the nervous system. Primary HA are a serious medical and social problem, since the prognosis and outcome are

usually unpredictable (ICHA of 3rd version, 2014). A particular problem is the chronic forms of primary headaches, among which the most common is chronic migraine, chronic tension type headache (CTTH) and their frequent combination – chronic daily headache (CDH). Conditions are distinguished by severe course, frequent and prolonged disability. The large economic losses associated with this disease, and the significant costs of medicines stimulate a constant search for new treatments [2, 3].

At present, it is known that in the pathogenesis of CDH, peripheral and central mechanisms involving central sensing are of great importance, the essence of which is the reduction of thresholds of central sensory neurons to peripheral stimulation. This mechanism is not fully understood [4].

In CDH, which develops from CTTH, the peripheral mechanism is associated with a constant tension of pericranial muscles. When CDH develops from a transformed migraine, this factor is associated with extracranial arterial vasodilation, which activates the secondary mechanism - stretching of the nerve fibers involved in the process of pain transmission surrounding the blood vessels, which leads to neurogenic inflammation [5].

Stretching leads to the depolarization of nerve fibers. On the other hand, generates an active potential that goes to the central nervous system, besides that this leads to the release of inflammatory mediators such as substance P, calcitonin gene-related peptide, neurokinin A. Inflammatory mediators contribute to further expansion of arteries and reduce the threshold of pain sensitivity locally in peripheral tissues. Thus, a vicious circle appears in

which vasodilation leads to inflammation, which in turn intensifies vasodilation and makes it extremely painful. Constantly developing HA leads, probably, to the involuntary progression of the tension of the craniocervical muscles, which contributes to the chronization of the process. Regular migraine attacks lead to a progressive tension of the craniocerebral muscles, the frequency of attacks increases, and tension headaches join the migraine attacks. The increase in seizures, according to Egilius L.H. Spierings (2003), is a consequence of the fact that triggers for migraine attacks are formed in stressed muscles [6]. The muscle tension mechanically creates interference for its own circulation, stimulating the expansion of the feeding arteries. One of these is the frontal branch of the superficial temporal artery, which lies in the thickness of a powerful temporal muscle. In the end, migraine and tension headache merge into a daily or almost daily headache.

Treatment consists of arresting seizures for medicines, which are usually used to prevention of seizures. For preventive treatment, medicinal and non-drug therapy is used, most often biological feedback, back massage, acupuncture, hirudotherapy.

Of the drugs used β-blockers, calcium channel blockers, antidepressants, NSAIDs and antiepileptic drugs. The need to control the doses of drugs, the presence of side effects or lack of effectiveness limit the full use of these groups of drugs. For example, in recent studies of topiramate, 20% of patients refused to participate in the study because of the development of side effects [7, 8].

A new perspective direction in the treatment of chronic forms of headache is the use of BTA. Botulotoxin type A has been used in clinical practice since 1991 for the treatment of torticollis, hemifacial spasm, blepharospasm, equinoviral deformation of the foot in cerebral palsy and spasticity after stroke. Recently there has been a steady trend towards the expansion of both official and potential indications to therapy of BTA [9].

The aim of the study was to determine the effectiveness of BTA's influence on CDH flow. The objectives of the study were to determine the dynamics of the clinical picture of CDH, the possibilities of the effect of BTA on the activity of antinociceptive systems and cerebral blood flow.

MATERIAL AND METHODS

The study included 54 patients at the Department of Neurology, city Clinical hospital (Tashkent), of them 31 women and 23 men, with an average age of 42 years and a disease duration of 3 years.

The criteria for inclusion in the study was the presence of CDH with a frequency of attacks at least 4 hours a day, at least 12 days per month within 6 months. The primary headaches in the anamnesis corresponded to chronic migraine and chronic tension type headache in accordance with the ICHA of the 3rd version (2014).

The criteria for excluding patients from the study were the presence of skin inflammation at the injection site, an allergy to the injected drug or its components, patients with hemophilia.

Excluded patients with complicated forms of migraine (hemiplegic, ophthalmic or basilar migraine) and a high level of depression, receiving botulinum therapy less than 3 months before the study, patients abusing

alcohol. The study did not include pregnant, breastfeeding and women planning pregnancy in the next 3 months. The use of antibiotics, aminoglycosides and muscle relaxants was excluded.

The study was conducted prior to treatment and 10 days and 4 weeks after the administration of 155 ED of the Neuronax to the standard points and 45 ED to the muscles of the head and neck by the method of "following the pain." [3]. The number of points for injecting a particular muscle was determined by the localization of the pain, the patient's condition, the patient's constitution and the severity of the pain. The drug was administered in m. corrugator, m. procerus, m. frontalis, m.temporalis and m. ocipitalis.

An additional intake of analgesics was allowed with an insufficient analgesic effect of the drug, which was recorded in the diary of a headache.

Methods of the study include clinical-neurological examination, filling in the diaries of HA (recording frequency, duration, intensity on visual analog scale (VAS), the number of analgesic drugs taken), determining threshold of pain sensitivity and threshold of reflex (RIII); to study emotional sphere was carried out on the scale of self-assessment of anxiety and depression – HADS. The degree of muscle strain was assessed by skin EMG-monitoring of face and neck muscles (temporal muscles, frontal, cervical and trapezius), palpate oral determination of the state of muscles by verbal scale from 0 to 3 points. The state of cerebral blood flow was studied with the help of ultrasound dopplerography of extra- and intracranial vessels (velocity parameters of vertebral blood flow (V3

and V4 segments) and the main arteries, the presence of signs of extravasal influence on the blood flow vertebral arteries, as well as the state of venous outflow on vertebral plexuses).

Statistical processing of data was carried out using the computer program Statistica for Windows. Parametric and nonparametric methods of statistical analysis (Student, Wilcoxon, and Mann-Whitney) were used. When comparing the variational series, significant differences were taken into account ($p<0.05$).

RESULTS AND DISCUSSION

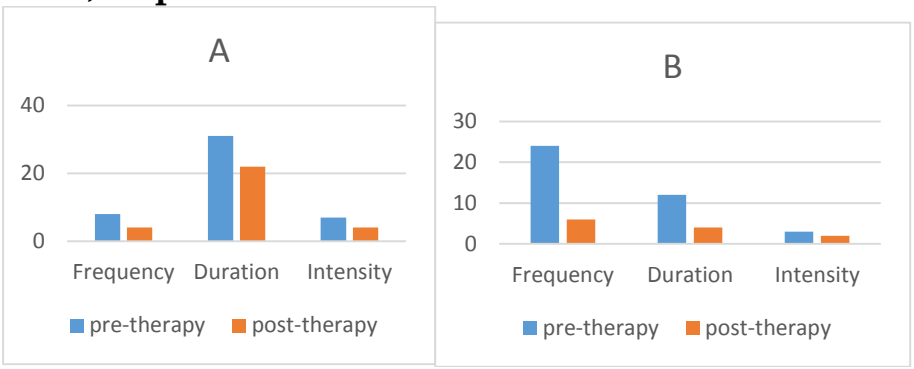
All patients had a history of episodes of migraine or tension headache. Transition HA from episodic to chronic daily occurred imperceptibly, and only in rare cases patients could name the exact date of the transformation.

All patients complained of a daily or almost daily headache, which was represented by background and paroxysmal pain. Background pain was long, bilateral, worn, sometimes pulsating, with fuzzy lateralization. They were noted on average during (25±4) days per month, the attack lasted on average (12.9±1.1) h. According to VAS, intensity was on average (3.1±0.2) points. Concomitant symptoms in the picture, nausea was noted in 20% of cases. Factors that provoke background pain could not be identified, as it pursued patients almost daily, regardless of the general condition, psycho-emotional overload and other factors. The paroxysmal pain was more intense, pulsating, sometimes pressing, with pronounced lateralization, the accent on the right and left was expressed in 12% of cases. Attacks of

paroxysmal pain were noted on average (7.7± 1.6) times a month for (35±4) h, intensity according to VAS reached (7.8±0.5) points (Fig. 1).

Concomitant symptoms more often were nausea, phonophobia and photophobia (39%) and vomiting (24%). Among the provoking factors, stress was noted more often than others, in 75% of cases, in 25% the cause of worsening was a change in the weather, in 22% of patients, the attack was provoked by turns of the head or uncomfortable posture. 51% of patients with CDH had a drug abuse – systematic intake of analgesic drugs. Patients with abuse took simple and combined analgesic drugs for the last 3 years (average for the group); average number of analgesic medications taken was 92 tablets per month.

Figure 1. Characteristics of the pain syndrome before and after treatment: A - paroxysmal headache; B - background headache; * - p <0.05



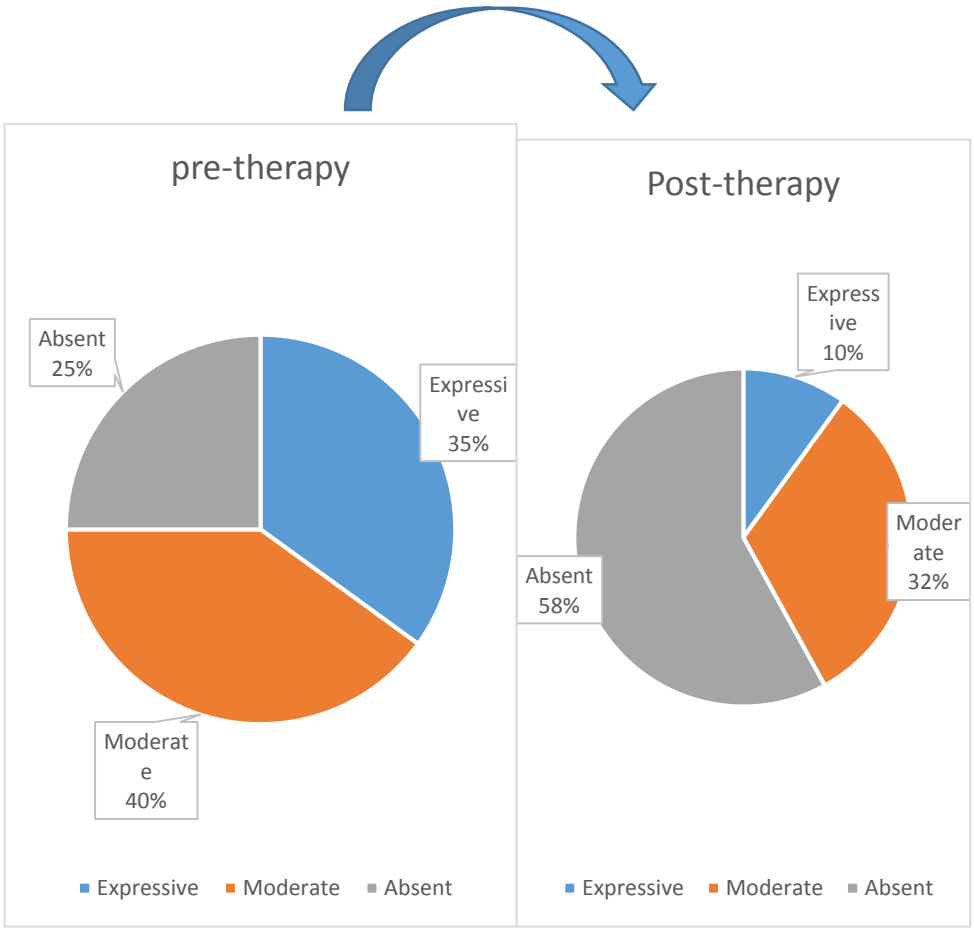
When investigating functional activity of nociceptive and antinociceptive systems utilizing nociceptive flexor reflex, significantly (p <0.05) decrease in the subjective pain threshold was revealed 5.4±1.2. Threshold of nociceptive flexor reflex was 6.4±1.4 and the ratio of the indices of the subjective pain threshold to the threshold of the nociceptive flexor reflex was 0.85±0.2 in all patients with CDH.

With neurologic examination during the Interictal period and during the attacks, there was a lack of focal symptomatology. Paraclinical research and neurological examination (examination of the fundus, magnetic resonance and computed tomography, electroencephalography) showed no signs of organic brain damage.

As a result of the treatment, a significant (p<0.05) decrease in the duration and intensity of paroxysmal pain to (11,0 ± 0,2) h and (6,5 ± 2,2) points in VAS, as well as frequencies up to (12,0 ± 1,2) of an attack and duration up to (6,0 ± 1,4) h of background pain. Significantly (p<0.05), the tension of pericranial and cervical muscles decreased

according to EMG and palpation study by verbal scale. Significantly, important changes in pain thresholds, both subjective and objective, were not obtained. When analyzing data of ultrasound imaging and TCD, the following results were revealed: Before treatment, all patients (100%) had an extravasal effect on the blood flow through the vertebral arteries: 75% expressed and 25% moderate. After treatment, 36% of patients had no extravasal effect, and 64% had moderate ($p<0.05$). Venous discirculation before treatment was noted in 73% of patients (in 44% severe violations of venous outflow, in 56% moderate disorders), after treatment, normalization of venous outflow was noted in 58% of patients ($p<0.05$), of which only 10% change retained their severity (Figure 2).

Fig. 2. Condition of venous outflow on vertebral plexuses before and after treatment



CONCLUSION

As a result of the therapy, a significant decrease in the duration and intensity of paroxysmal pain, as well as the frequency and duration of background pain, was obtained, which indicates the effectiveness of botulinum therapy in patients with HBH. There was no significant effect of BTA on antinociceptive systems in the study. Analysis of data of ultrasound imaging and TCD indicates an improvement in cerebral

blood flow in patients with chronic forms of primary HA with BTA injections. It is assumed that hemodynamic disorders of cerebral blood flow in the vertebral arteries and veins are more associated not with direct vertebral impact, but with the effect on the vessels of the pathologically enlarged posterior muscles of the neck due to muscular-tonic syndrome. Thus, the results of a pilot study indicate the effect of BTA injections on cerebral blood flow by optimizing both the arterial influx and venous outflow from the cranial cavity. The obtained data, possibly, will allow expanding the indications for the appointment of BTA and indicating the need for more extensive research.

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