

The Use of Irinex in the Treatment of Cluster Headaches and Other Trigeminal Autonomic Cephalgias

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Abstract

To date, among the requests for medical help with headaches, a significant part of patients are people with paroxysmal headaches accompanied by pronounced autonomic disorders. This group of headaches belongs to terminal vegetative cephalgia and requires a new approach in therapy with the use of modern medications. The drug irinex (erenumab), used as a solution for subcutaneous administration, proved to be one of the most effective antimigrainous agents. Within the framework of this scientific work, the results of the use of the drug irinex in the treatment of cluster headaches and other trigeminal autonomic cephalgias were considered. The study used an indicator of the average monthly frequency of headaches in patients, as well as a subjective scale of severity of autonomic disorders. The drug Irinex is a modern anti-migraine drug, used as a solution for subcutaneous administration and contains the active substance - erenumab. As a result of the study, there was a general decrease in the frequency of painful paroxysms for 6 months with regular use of the drug at a dosage of 140 mg and an increase in the level of physical activity of patients. Thus, the use of the drug irinex has shown high efficacy and safety in the treatment of cluster headaches and other trigeminal autonomic cephalgias.

Keywords: Cephalgia, Autonomic disorders, Cluster headache, Anti-migraine drugs

INTRODUCTION

The prevalence of headaches in modern society is quite high, a significant part of patients with cephalgia are patients with cluster (bundle) headaches (0.5 – 0.8% of the total number of people) [1]. Trigeminal autonomic cephalgia combines headache and typical manifestations of cranial parasympathetic neuralgia [2]. At the same time, due to the difficulties of differential diagnosis of cephalgia, the correct diagnosis during the initial examination can be made only in 21% of cases [3]. However, patients suffering from cluster headaches with severe autonomic disorders require adequate, systematic, and effective treatment, which is possible only with the use of modern pharmacotherapy.

According to the ICGB-3 headache classification adopted in 2018 [4], cluster (bundle) headaches and other trigeminal headaches (autonomous) are included in the group of primary headaches (Part 1, Chapter 3). According to this classification, the group of the cluster (bundle) headaches includes:

1. Cluster headache;
2. Paroxysmal hemicrania;
3. Short-term unilateral neuralgic headaches with conjunctival injection and lacrimation (SUNCT);
4. Possible trigeminal autonomic cephalgia.

Previously, in the medical and scientific literature, we have met other names for cluster headaches – Horton syndrome, Harris ciliary neuralgia, and histamine cephalgia [5]. However, according to modern studies, the role of histamine in the pathogenesis of headaches of this type has not been proven [6]. At the same time, experimental and functional neuroimaging studies have shown that trigeminal autonomic cephalgia is accompanied by activation of the parasympathetic reflex, which provokes the formation of clinical signs of secondary sympathetic dysfunction [7].

The most characteristic symptoms of trigeminal vegetative cephalgia are relatively short-term intense and acute

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headache attacks, manifested in one part of the head and having a relatively clear localization in the orbital, supraorbital, or temporal region; unilateral (from the localization of headache) autonomic disorders in the form of conjunctivitis, ptosis and swelling of the eyelid, lacrimation, nasal congestion, increased sweating on one side of the face and some others [8].

However, it is not uncommon in clinical practice to encounter a masklike course of cluster headaches and other trigeminal autonomic cephalgias (**Figure 1**).

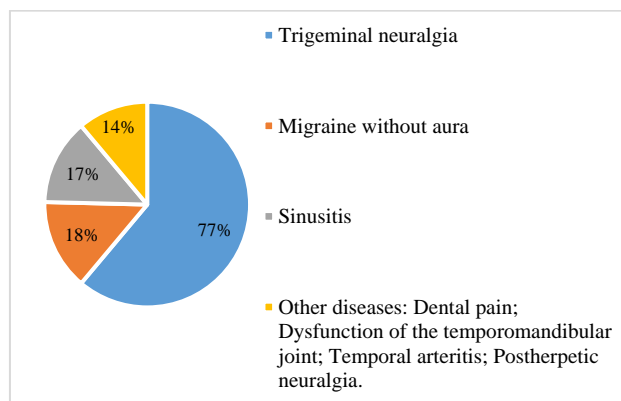


Figure 1. The most common masks of trigeminal vegetative cephalgia

Headaches of a short-term nature can be observed with a fairly wide range of disorders as secondary headaches resulting from other functional disorders [9]. Often, we also observe a pain syndrome similar in symptoms to bundle headache or trigeminal autonomic cephalgia with various lesions of facial structures, pathology of cranial vessels, pathology of the cavernous sinus, and other diseases.

It is important to carry out differential diagnostics of cluster headaches from migraine and tension headaches, which can occur with discirculatory encephalopathy, headache with arterial hypertension, osteochondrosis of the cervical spine with migraine-like paroxysms, vegetative-vascular dystonia with cephalgic syndrome, post-traumatic headache and vertebral-basilar insufficiency [10, 11].

Cluster headaches and other trigeminal vegetative cephalgias are primary headaches characterized by a pronounced cluster period during which painful paroxysms occur, lasting on average about 30 minutes each [12]. The duration of the cluster period is 1-2 months and is replaced by a period of remission, during which no externally provoking factors are capable of causing pain paroxysm [13]. The duration of remission is from several months to several years. The cluster period in some cases is characterized by seasonality, the suddenness of the onset, and the end of exacerbation [14].

Thus, if a headache accompanied by vegetative disorders and other similar symptoms has arisen for the first time, it is necessary to establish whether it is a primary or secondary headache. In the case of cephalgia in combination with another disease, it is necessary to consider headaches as a consequence of this disease [15, 16]. Therefore, when detecting clinical manifestations of cluster headaches and other trigeminal autonomic cephalgias, it is necessary to conduct a systematic and consistent differential diagnosis.

Cluster headaches and other trigeminal autonomic cephalgias require careful attention to diagnosis and therapy [17]. General recommendations for the treatment of cluster headaches have been developed and proposed by the European Federation of Neurological Societies [18]. Traditionally, the therapy of paroxysmal headaches is aimed at relieving pain paroxysms in the cluster period and preventing relapse during remission [19].

In the treatment of headaches in patients with cluster headaches and other trigeminal autonomic cephalgias, the use of the drug irinex has shown its effectiveness.

Irinex is a modern antimigrainous drug, used as a solution for subcutaneous administration and contains an active substance – erenumab [20]. Erenumab is a human monoclonal antibody of class G2 (IgG2) that binds with high affinity to the calcitonin-gene-related peptide receptor (CGRP). Erenumab consists of 2 heavy chains, each of which contains 456 amino acids, and 2 light chains of the lambda subclass, consisting of 216 amino acids [21]. Since erenumab is a human monoclonal antibody that is an antagonist of the CGRP receptor, it does not have significant pharmacological activity against the adrenomedulline, calcitonin, and amylin receptors, as well as agonistic activity against the CGRP receptor [22]. At the same time, CGRP is a neuropeptide that modulates the transmission of nociceptive signals, and a vasodilator associated with the pathophysiology of migraine. It has been shown that, unlike other neuropeptides, the concentration of CGRP increases significantly during a headache attack and returns to normal after its resolution [23, 24]. Intravenous administration of CGRP causes migraine-like headaches in patients, from which it can be assumed that CGRP may be the cause of various kinds of cephalgia.

The CGRP receptor is localized at sites related to the pathophysiology of headaches [25]. Erenumab is a powerful and specific competitor of CGRP for binding to the receptor and thereby suppresses its effect on the receptor. Thus, the use of the drug irinex leads to fairly rapid and effective relief of an attack of cephalgia.

MATERIALS AND METHODS

The study involved 548 patients of Vladikavkaz City polyclinics suffering from headaches. Of these, 167 people received the drug irinex subcutaneously at a dosage of 70

mg, and 128 people - at a dosage of 140 mg. Thus, the total number of patients receiving the drug was 295 people, the control group of the study was 253 patients receiving placebo.

The primary indicator that was recorded was the average monthly number of days with a headache for 6 months. Secondary indicators of effectiveness were a 50-100% decrease in the average number of days with headache relative to the baseline (response $\geq 50\%$), as well as a change in the average number of days relative to the baseline during the month in which patients used specific drugs to relieve an attack of cephalgia. To assess the degree of the headache's impact on the patient's quality of life and its changes relative to the baseline level, the MPFID questionnaire (Diary of the Effect of Migraine on Physical Activity) was used in the study, aimed at assessing headaches associated with deterioration of the physical condition and daily activity. Patients assessed daily the time during which they felt the effects of headaches or the level of difficulties associated with cephalgia. Indicators on the MPFID scale for the month are averaged over days with and without headaches. At the same time, the higher the indicator, the more headache affects the domains of daily activity and deterioration of physical condition.

RESULTS AND DISCUSSION

As a result, there was a general decrease in the average monthly number of days with headache (**Figure 2**) in patients taking the drug relative to the control group.

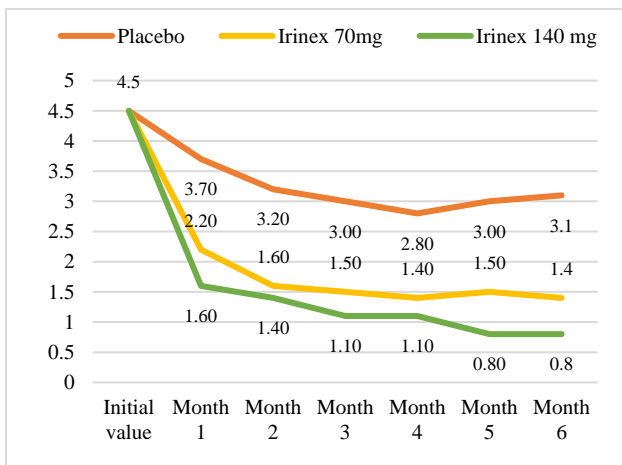


Figure 2. The level of average monthly indicators of headache in patients using the drug irinex and the control group.

At the same time, the analysis of the data obtained showed that in patients who did not achieve a clinical response to one or more methods of preventive treatment, the difference in the reduction of days with headache was observed between the dose of 140 mg and placebo was -2.5 (95% CI: -3.4; -1.7) and between the dose of 70 mg and placebo -2.0 (95% CI: -2.8; -1.2). Also, the proportion of patients who

achieved a 50% reduction in headache days was higher compared to the placebo group (39.7% for 140 mg and 38.6% for 70 mg, with an odds ratio of 3.1 (95% CI: 1.7; 5.5) and 2.9 (95% CI: 1.6; 5.3) respectively).

Focusing on the data indicating the effectiveness of the use of the drug irinex in the treatment of cluster headaches, we assumed the potential effectiveness of the use of the drug irinex in the treatment of cluster headaches and other trigeminal autonomic cephalgias. To this end, a study was conducted on 47 patients suffering from cluster headaches and other trigeminal autonomic cephalgias. All patients took the drug irinex subcutaneously for 6 months. The control group consisted of 21 patients. To assess the degree of effectiveness of the therapy used, we also used an indicator of the average monthly frequency of headaches in patients, as well as a subjective scale of severity of autonomic disorders.

Many patients throughout the study noted an overall improvement in physical condition, a significant decrease in the severity of vegetative manifestations, and an increase in vital activity.

As a result of the study, the data obtained indicate a high efficacy of the drug (**Figure 3**).

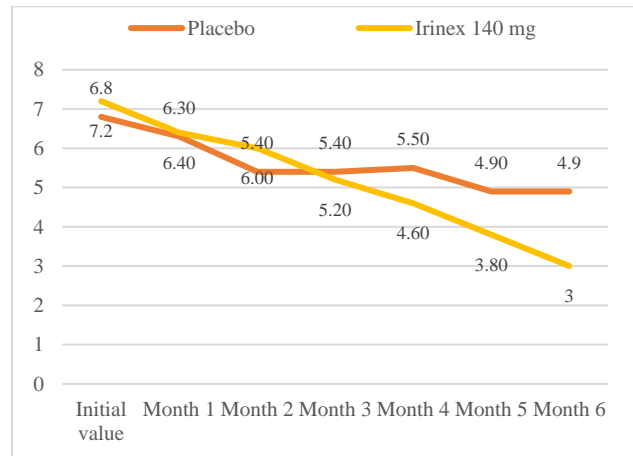


Figure 3. Indicators of changes in the average monthly level of headaches in patients with cluster headaches and other trigeminal autonomic cephalgias

Compared with the control group, patients taking irinex had a marked decrease in the number of days with headaches during the month and an overall improvement in physical performance and behavioral activity. At the same time, there was also a decrease in the severity of vegetative manifestations of trigeminal neuralgia.

To assess the safety of treatment, we analyzed data on the occurrence of side effects and undesirable effects when using the drug in the treatment of cluster headaches and other trigeminal autonomic cephalgias (**Table 1**).

Table 1. Indicator of adverse reactions among patients taking irinex

System-organ class	Side effects or undesirable reactions	Frequency of manifestation
Disorders of the immune system	Hypersensitivity reactions, including rash, swelling, urticaria	8.5%
General disorders and disorders at the injection site	Reactions at the injection site	12.8%
Disorders of the gastrointestinal tract	Constipation	4.3%
Disorders of the musculoskeletal system and connective tissue	Muscle spasm	2.1%
Disorders of the skin and subcutaneous tissues	Itching	2.1%

However, most of the observed adverse reactions when using the drug were mild or moderate, with symptomatic treatment they were quickly stopped. These and other data obtained indicate the safety and effectiveness of the use of irinex in the treatment of cluster headaches and other trigeminal autonomic cephalgias.

CONCLUSION

Headaches of various etiologies in the modern population are becoming more widespread. The general deterioration of the environment, constant stress, and unhealthy lifestyle contribute to the rejuvenation of this disease and an increase in the number of people suffering from cephalgia. A special group of patients is people suffering from cluster headaches and other trigeminal autonomic cephalgias. Diagnosis and therapy of this group of headaches require special attention. Often, the correct diagnosis is difficult. At the same time, the therapy of cluster headaches and other trigeminal autonomic cephalgias requires the use of new treatments.

One of the modern drugs showing the effectiveness of applied headache therapy is the drug irinex. Its active ingredient, erenumab, is a human monoclonal antibody of class G2 (IgG2) with high affinity binding to the calcitonin-gene-related peptide receptor (CGRP). The use of the drug irinex leads to a fairly rapid and effective relief of an attack of cephalgia.

The analysis of the conducted studies with the use of irinex in the treatment of headaches confirmed its high efficiency and safety of use. Thus, the use of irinex is advisable in the treatment of cluster headaches and other trigeminal autonomic cephalgias.

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ETHICS STATEMENT: All patients were informed of the details of the experiment and signed the agreement on volunteer participation. All additional data are available upon request from the corresponding author.

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