



# Warfarin in the treatment of refractory chronic cluster headache: a case report and review in therapeutic options

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## Abstract

Cluster headache is the most common of trigeminal autonomic cephalalgia, with variable prevalence. It can be episodic or chronic, with few remission and high therapeutic failure. The case refers to a 55-year-old female patient, hypertensive and diabetic, with a history of migraine without aura with pain management. In 2014, the patient began to present a new headache pattern, with a diagnosis of Chronic Cluster Headache. Pain management to nasal sumatriptan as an acute treatment. For the prophylactic treatment, she presented therapeutic failure to several medications, with pain management with the use of warfarin. Associated with valproic acid to control migraine. There are few cases described in the literature about the use of warfarin, and its mechanism is still unclear. Warfarin was a key drug, with more than a 50% reduction in attack control. There is a need for more clinical trials randomly that support it. Cluster headache has peculiar clinical diagnosis, being increasingly well recognized and diagnosed. Knowledge and institution of treatment can significantly improve the quality of life of patients, helping to recover the functionality of patients affected by treatment failure.

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## Introduction

Cluster headache is the most common of the trigeminoautonomic headaches, with variable prevalence, with an average of 279:100,000 population, especially young adult males.<sup>1</sup> It can be episodic or chronic, with little remission and high therapeutic refractoriness, leading to significant functional disability and, in some cases, suicidal ideation.<sup>2</sup>

## Case Report

This case is a 55-year-old female patient, hypertensive and diabetic, with a history of migraine without aura since childhood, with good pain control. She presented a change in the crisis pattern in 2014, described as headache strictly in left hemi cranium, strong intensity, duration 60-120 minutes, recurrent, three to four episodes a day, associated with conjunctival hyperemia and ipsilateral nasal congestion, occurring daily for 18 months, with no remission period. Neurological examination and magnetic resonance imaging of the brain showed no alterations.

Although the duration of pain of 60-120 minutes was very suggestive of cluster headache, it was initially chosen to perform a test with indomethacin at a dose of 150 mg/day. With no response to the medication, the diagnosis of continuous hemicrania, an important differential diagnosis in headaches of short duration and restricted to one hemi cranium, was unlikely.

In view of these clinical data, the results of complementary exams and the test with indomethacin, according to the criteria of the International Classification of Headaches, the diagnosis of chronic cluster headache was established.<sup>2</sup>

The therapeutic strategy is divided into two approaches: acute treatment for attacks, which aims at immediate pain relief; and prophylactic treatment, which aims at reducing the frequency and intensity of attacks. For the acute treatment, a good response was obtained with nasal sumatriptan.

For prophylactic treatment, the use of prednisone 60 mg/day and occipital nerve block ipsilateral to pain (two blocks 21 days apart in February/2018) were initially proposed with good response, however for a short period of time. Associated with prophylactic treatment, several lines of preventive treatment were proposed in the course of the disease, with variable response. Verapamil 480 mg/day was used, with good response, and the patient started presenting 8 crises per month. However, in December 2018, the frequency and intensity of the

condition worsened, and lithium carbonate 300 mg/day was initiated, with progression to 600 mg/day.

In February/2019 without any clinical improvement, therapeutic failure was considered, and lithium carbonate was discontinued. Then, melatonin 10 mg/day (partial remission) and clomiphene 50 mg/day (partial remission) were proposed. Supported by some case reports in the literature, the treatment with warfarin at a dose of 2.5 mg/day was chosen. The patient had a significant improvement in crises, starting to have 2 crises a day and remain up to 1 week crisis-free, a pattern not seen before. In February 2020 warfarin was adjusted to 5 mg/day and verapamil was reduced to 240 mg/day.

Finally, in April/2021, the initiation of valproic acid 1,000 mg/day was proposed, with the goal of improving comorbid migraine. Currently, the patient maintains an attack of "mild" cluster headache every two months. Neurological examination is unchanged. The patient is currently taking propranolol 80 mg/day, amitriptyline 75 mg/day and valproic acid 1,000 mg/day (chronic migraine without aura); verapamil 240 mg/day and warfarin 5 mg/day (cluster headache). Non-pharmacological measures with good control.

## Discussion

The first case described in the literature about remission of cluster headache with warfarin was in 2004 by Souza et al.<sup>2</sup>, the authors describe the case of a patient who took warfarin for anticoagulation purposes due to thrombotic events, which incidentally resulted in complete remission of the cluster headache attacks.<sup>2</sup>

In 2005, Kowacs et al.<sup>3</sup> based on this published case-chose to administer warfarin to three patients as a therapeutic option for control of refractory cluster headache and were successful. In 2011 the first randomized trial by Hakim<sup>4</sup>, in which it was shown that the use of low strength warfarin anticoagulation (INR 1.5 to 1.9) in patients with refractory chronic cluster headache was associated with greater remission at 4 weeks compared with placebo.

Regarding the proposed treatment line, the use of nasal sumatriptan as treatment in the acute phase has recommendation level B of evidence, similar to the use of oral zolmitriptan and sphenopalatine ganglion stimulation. Treatment with established efficacy recommendation (level



A) include subcutaneous sumatriptan, nasal zolmitriptan, and oxygen. Nasal lidocaine and subcutaneous octreotide are level C.<sup>5</sup>

Regarding the prophylactic treatment, only occipital nerve block is established as effective (level A), however, as in this case, the response is for a short period of time. Civamide (nasal spray) is considered level B recommendation. The other medications used by the patient in this case (lithium, verapamil, melatonin, and warfarin) are considered level C, although the patient had an excellent and sustained response to warfarin. It is important to note that there are no serious adverse events described in the literature associated with the use of warfarin. Moreover, this positive recommendation is new, being based on reports of incidental benefits in cluster headache and from the conclusions of a randomized clinical trial.<sup>1,3</sup>

Valproic acid has negative evidence (level B: probably ineffective), with randomized studies speaking against its benefit in the treatment of cluster headache. Thus, we note that the improved pain control response presented by the patient is due to the previous migraine pain control.<sup>6</sup>

There is not enough evidence for the efficacy of prednisone use, and it is a level U recommendation. Generally used as bridging therapy until definitive prophylactic treatment.<sup>7</sup> No consensus on mode of administration, dose, and duration.<sup>8</sup>

The mechanism by which warfarin induces pain remission is still unclear, there is the hypothesis that its action may be related to the suppression of neurogenic inflammation caused by nitric oxide, besides the action as an antagonist of vitamin K in the metabolism of dendrites and neurons and in the circadian rhythm of the hypothalamus.<sup>1,3,4</sup>

## Conclusion

In the case presented, in agreement with the literature, there was a need for combined therapy with several drugs, warfarin being a key drug, with a reduction of more than 50% in the control of the attacks.

Currently, the treatments described for refractory chronic cluster headache include more invasive measures such as sphenopalatine ganglion stimulation and occipital nerve stimulation.<sup>9</sup>

There is a need for more randomized clinical trials that support the recommendation of warfarin use and its efficacy, and also for the ideal dose and the determination

of the time of use. In addition, close follow-up of these patients is necessary given the potential risk of hemorrhagic adverse events.

Cluster headache has a peculiar clinical diagnosis, and it is increasingly well recognized and diagnosed. The knowledge and institution of early treatment can significantly improve the quality of life of patients, assisting in the recovery of functionality of patients affected by refractory treatment.

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