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# CIVAMIDE NASAL SPRAY: A BREATH OF FRESH AIR IN MIGRAINE AND CLUSTER HEADACHE THERAPY? INSIGHTS FROM A SYSTEMATIC REVIEW

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**ABSTRACT**

**Background:** Migraines and cluster headaches are severe neurological disorders characterized by complex pathophysiological mechanisms, particularly involving the trigeminal nerve and vascular inflammatory responses. Both conditions primarily affect the trigeminal nerve, a key pathway in pain transmission, and are closely associated with vascular inflammation. Migraines are typically characterized by recurrent, unilateral, and intense headaches, whereas cluster headaches are marked by excruciating pain, often localized around the eye. These disorders are multifactorial, with various mechanisms contributing to their initiation and persistence. Civamide nasal spray, which modulates neural pathways, has emerged as a promising therapeutic option for targeted pain relief. This study aims to evaluate the effectiveness of Civamide nasal spray in managing these debilitating headaches.
**Objective:** To assess the efficacy of civamide nasal spray in treating migraine and cluster headache attacks.
**Methods:** This study followed the Synthesis without Meta-analysis (SWiM) guideline. A systematic search was conducted using a predefined query in Medline, Google Scholar, and Cochrane Central Library. Eight independent reviewers screened studies for eligibility based inclusion criteria and assessed the risk of bias using the Cochrane RoB 2.0 tool.
**Results:** Two eligible studies were analyzed. Participants receiving civamide demonstrated a greater reduction in weekly headache frequency compared with those receiving a placebo. Additionally, civamide treatment was associated with decrease in pain intensity.
**Conclusion:** The findings suggest that civamide nasal spray effectively reduces both the frequency and severity of headaches. Nonetheless, further investigations, particularly evaluating its long-term preventive use, are required to establish its clinical role in migraine and cluster headache management.

**Keywords**: civamide, cluster headache, migraine, nasal spray



## Introduction

Headache, including migraine and cluster headaches, is a complex neurological disorder that often has a significant impact on the quality of life of sufferers. Migraine is characterised by recurrent headaches often accompanied by nausea, vomiting, and sensitivity to light and sound.[1,2] Cluster headaches, on the other hand, have a more distinctive pattern with intense, unilateral, and frequent pain attacks occurring

over time. Both conditions are closely related to trigeminal nerve dysfunction and neurovascular inflammatory mechanisms, resulting in an overreaction to painful stimuli. Headaches are divided into primary and secondary headaches.[3] Primary head pain comes from unknown causes, such as migraine, tension-type headache, cluster headache, and trigeminal pain. Secondary headaches often stem from underlying diseases, including organic structural disorders, metabolic problems, and infections.[4]

The World Health Organization (WHO) stated in 2012 that 90% of adults worldwide experience headaches at least once a year. A study conducted in Norway in 2007 by Stovner et al. found that the percentage of headaches in women was 78%, and in men, it was 22%. A study in New York found that the percentage of headaches in Caucasians was 22%. The fact that headache pain is so common worldwide and associated with many comorbidities makes it a common public health problem.[5] Headache pain is often associated with reduced productivity during daily activities and negatively impacts the quality of life for those who suffer from it.[4]

Currently, various pharmacological approaches have been developed to treat migraine and cluster headaches, including triptans, non-steroidal anti-inflammatory drugs (NSAIDs), and CGRP (Calcitonin Gene Related PEPTIDE) antagonists.[6] However, these therapies have limitations, including systemic side effects, variable effectiveness among individuals, and challenges in delivering drugs to specific targets in the central nervous system. Therefore, searching for more effective therapies with fewer side effects is the main focus of clinical research on treating primary headache pain.[7]

Civamide, a synthetic capsaicin analogue, has attracted attention as a new therapeutic candidate for managing headache pain.[8] As a TRPV1 (Transient Receptor Potential Vanilloid-1) receptor agonist**,** civamide works by inhibiting the release of pro-inflammatory neuropeptides and reducing trigeminal nerve activation**,** which plays a role in the pain mechanism of migraine and cluster headaches.[6,9] Using civamide as a nasal spray offers significant pharmacokinetic advantages, as it allows for rapid absorption through the nasal mucosa, with direct effects on the trigeminal system, bypassing first-pass metabolism.[10] Some preliminary studies suggest that civamide nasal spray may reduce the frequency and intensity of headache pain, but more robust scientific evidence is needed to evaluate its effectiveness more widely. This study aims to evaluate the efficacy of civamide nasal spray for migraine and cluster headache attacks.

## Methods

This systematic review was conducted in accordance with the guidelines of the Systematic Review without Meta-Analysis (SWiM) approach (Figure 1). A comprehensive literature search was conducted using three significant databases: Medline, Google Scholar, and Cochrane Central Library. The search strategy utilized the keywords “Civamide” and “Headache” along with other synonyms, all separated by the Boolean operator “AND”. The review included randomised controlled trials assessing the effects of civamide on headache pain. Data extraction was performed independently by the reviewers, with discrepancies resolved through discussion and negotiation. A risk of bias assessment was performed for all included studies using the Cochrane Risk of Bias Tool.

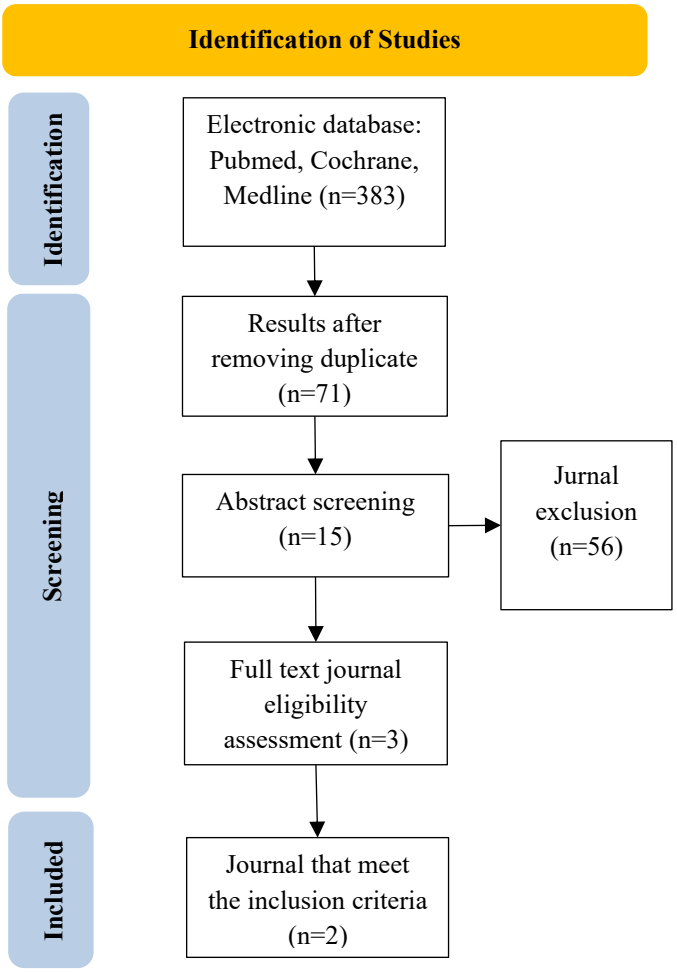


**Figure 1.** Identification of studies

### Eligibility Criteria

The inclusion and exclusion criteria were determined based on the objectives of this systematic review to ensure the relevance and quality of the included studies. Studies were included if they met the

following criteria: (1) randomized controlled trials involving adult participants diagnosed with headache, as defined by the International Headache Society (IHS) criteria; (2) studies that used intranasal civamide as the primary intervention; (3) studies that compared civamide to placebo or standard treatment; and (4) studies reporting clinical outcomes such as headache frequency, pain intensity, or adverse events related to treatment.

## Results

### Study Characteristics

The authors included two studies (Table 1) with 60 participants who had completed the research programme. Both studies used randomised controlled clinical trials with a double-masked, placebo-controlled method. The study subjects were divided into two groups: one receiving intranasal civamide and the other receiving a placebo. Specifically, 18 subjects received intranasal Civamide, and 10 subjects served as a placebo control (vehicle group).[11] Meanwhile, the second study by Diamond et al. was also grouped into two groups: the group that received civamide nasal spray and the placebo nasal spray control group (which has characteristics similar to civamide but without active ingredients).[12]

### Impact of Intranasal Civamide Usage on Headache

Based on two major studies related to the use of intranasal civamide for treating headache pain, the efficacy and effectiveness of intranasal civamide in reducing the intensity and frequency of headache pain are evident in the results of studies by Diamond et al. and Saper et al. In the study by Saper et al., patients with episodic cluster headache with headache intensity reduction parameters after administering 0.025% civamide solution (25 µg) per nostril with a total daily dose of 50 µg civamide and given 1 time per day for 7 days, while the placebo group (Vehicle Group) received vehicle solution (without civamide) in the same dose, the results of the group with civamide administration reported that civamide was effective in reducing the frequency of cluster headache, especially in the first 7 days after treatment.[13]

In the study by Diamond et al., the inclusion criteria were patients with migraine without aura who had been diagnosed according to the International Headache Society (IHS) criteria. The exclusion criteria included patients with other medical conditions that could interfere with the interpretation of the results, patients who used other medications that could interact with civamide, and patients with a history of allergy to civamide or any other component of the nasal spray.[14] The variables measured in the study conducted by Diamond et al. were headache pain intensity before and after civamide administration (using a pain scale), frequency of migraine attacks within a specific period, and side effects reported by study participants. The results obtained in this study were that Civamide effectively reduced migraine pain intensity within 3-4 hours after administering the Civamide nasal spray, with significant differences compared to placebo. Although intranasal civamide provides benefits to headache pain sufferers, some side effects have been found in its use. It is related to the mechanism of action of civamide, which is applied to the nasal mucosa. Civamide is thought to cause an initial release of neuropeptides from the trigeminal plexus, resulting in a burning sensation in the nose, lacrimation, and rhinorrhoea, which most patients in this study experience.[15]

### Safety and Tolerability of Civamide Intranasal

Civamide, a capsaicin analogue used as a nasal spray (intranasal), has demonstrated its safety and tolerability in studies by Saper et al. and Diamond et al. Studies show that civamide is safe for systemic use, causing no significant changes in blood pressure, heart rate, respiratory rate, or body temperature.[16] Additionally, no serious systemic side effects or clinically significant changes were detected on ECG, urine and blood tests, and nasal mucosa examination. The side effects reported were localised in the form of nasal mucosa irritation due to the activation of TRPV1 receptors, which is the main target of civamide. Reported side effects include a burning sensation in the nose, rhinorrhoea, lacrimation, and dry throat.[17] However, the study showed that the local side effects only lasted **for** less than 20 minutes after administration and decreased after several uses (mucosal desensitisation). Tolerability of civamide use is relatively high, with the majority of patients able to continue therapy despite experiencing initial irritation.[18] This balance between efficacy and safety underlines the advantage of using Civamide in treating headache pain.

The benefits of civamide stem from its ability to inhibit TRPV1 (Transient Receptor Potential Vanilloid-1) receptors that transmit neurogenic pain and inflammation. In addition, civamide plays a role in inhibiting the release of pro-inflammatory neuropeptides, such as Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP), which are involved in vasodilation and inflammation in migraine and cluster headache.[19] Civamide offers more specific capabilities than oral drugs; this ceramide directly targets the pain pathway, specifically the trigeminal nerve, which is the primary center of head pain, and is therefore considered to have a faster effect than oral drugs.

**Table 1.** Summary of Selected Studies

| Author (Year) | Study Design | Publications (Sample Size) | Intervention | Results | Headache Frequency Change | Headache Intensity Change |
|---|---|---|---|---|---|---|
| Saper et al. (2002). | Double-blind, Randomised, Placebo-Controlled Study | Patients with episodic cluster headache (28) | Administered **100 µL of Civamide 0.025% solution (25 µg) per nostril vs placebo** | Significant treatment difference in civamide vs. placebo ($p < 0.05$) | Significant reduction in attack frequency (esp. first 7 days) | Reduction in headache intensity observed |
| Diamond et al. (2000). | Double-blind, Randomised, Placebo-Controlled Study | Patients with migraine without aura (34) | Civamide nasal spray vs placebo | Patients who received the nasal spray experienced a reduction in acute headache pain compared with those who received the placebo. | Reduced frequency of migraine episodes | Significant reduction in acute pain within 3–4 hrs |

# Discussion

### Effect of Civamide on headache pain

The comparative analysis of the two randomized controlled trials reveals distinct yet complementary findings regarding the efficacy of intranasal civamide in treating primary headache disorders. Both studies employed double-masked and placebo-controlled methodologies, enhancing the validity and reliability of the reported outcomes. However, the therapeutic contexts of migraine without aura in the study by Diamond et al. and episodic cluster headache in the study by Saper et al. reflect the broad potential applicability of civamide across headache subtypes.[20]

In cluster headache patients, the administration of civamide demonstrated a measurable reduction in attack frequency during the first week of treatment. The rapid onset of this response supports the hypothesis that civamide acts directly on the trigeminal pain pathways, likely due to its targeted nasal delivery system. Moreover, the statistical significance reported ($p < 0.05$) underscores its potential for acute symptom relief in cluster headache, a condition notoriously resistant to standard therapies.[19]

In contrast, the Diamond et al. study highlights the role of civamide in managing migraine attacks. The observed decrease in headache intensity within 3 to 4 hours following administration suggests that civamide may exert a faster analgesic effect than conventional oral treatments. This timing is clinically meaningful, as early pain relief is critical to migraine therapy adherence and patient satisfaction. Additionally, the reduction in migraine frequency over the study period further indicates a possible prophylactic benefit, although this was not the primary endpoint.[20]

Despite differences in patient populations and headache characteristics, both studies converge on the therapeutic value of intranasal civamide. The shared findings of decreased pain intensity and frequency lend support to its mechanism of action involving TRPV1 receptor modulation and inhibition of pro-inflammatory neuropeptides such as CGRP and Substance P.[21]

Nevertheless, the discussion of efficacy must be balanced with considerations of tolerability. While systemic side effects were minimal, both studies reported local reactions, including nasal burning, lacrimation, and rhinorrhea, which were attributed to initial TRPV1 activation. These symptoms, although transient, could affect patient compliance, particularly in the longer term. Furthermore, the absence of head-to-head comparisons with established therapies such as triptans or CGRP antagonists limits the ability to define civamide's precise role in clinical practice.[22]

The results from Saper et al. and Diamond et al. provide preliminary yet promising evidence supporting civamide nasal spray as an acute treatment modality for both migraine and cluster headache. Future trials with larger samples and direct comparisons against standard therapies are needed to confirm its place in treatment guidelines and determine whether its benefits outweigh the short-term discomforts associated with nasal administration.

### Mechanism of action of civamide

The benefits of civamide stem from its ability to target the trigeminovascular system through the relative depletion of available neuropeptides, such as Substance P (SP) and Calcitonin Gene-Related Peptide

(CGRP). Inhibition of neuropeptide release to the central nervous system.[23] This is important because vasodilation prevents the activity of the dural blood vessels. Intranasal civamide offers additional benefits compared to oral drugs. Because civamide has more specific capabilities than oral drugs, it directly targets the pain pathway more precisely on the trigeminal nerve, which is the main center of head pain. Therefore, it is considered to have a faster effect than oral drugs.[24]

Civamide works by emptying neuropeptide reserves in the trigeminovascular system, preventing excessive release that can lead to dural vasodilation and neurogenic inflammation. This effect reduces migraine attacks gradually and prevents recurrence with repeated use.[25] The initial burning sensation indicates that civamide is working, but this symptom will diminish with regular use due to tachyphylaxis. With this mechanism, civamide can be an effective therapy for migraine headaches, especially for patients who do not respond well to standard therapies such as triptans or NSAIDs.[17]

### Variability across Studies

Variability across studies can arise from several factors, including differences in patient population, dosage, and timing of studies. Individual variations in response to civamide are observed in the onset of effect, the degree of pain reduction, local side effects, and adaptation to therapy.[24] Genetic differences, sensitivity to TRPV1 receptors, and metabolic variations play a role in patient response differences. Furthermore, not all patients experience the same pain reduction; some respond well, while others show minimal effects. Further studies with a larger sample size and a more extended monitoring period are needed to investigate the factors influencing the differences in response to civamide.[26]

### Limitations and Gaps in Current Research

One of the significant limitations in the current research on civamide is the lack of long-term studies; most studies have lasted only 7 to 20 days, so the long-term effectiveness and potential recurrent side effects remain unclear. Follow-up studies of longer duration are needed to determine if the effects of civamide remain consistent in repeated or chronic use. In addition, Civamide has not been compared directly with standard therapies such as triptans or CGRP antagonists, which are already commonly used in the treatment of migraine and cluster headaches, so studies comparing the effectiveness of Civamide with other treatments are needed to find out whether Civamide can be a first-line therapy or only as an adjunctive therapy.

Future research should prioritise more inclusive study designs that consider direct comparisons with standard therapies, such as triptans and CGRP antagonists, which have also not been widely conducted. Clinical studies comparing civamide with standard therapies will help determine whether civamide can be used as first-line therapy or only as adjunctive therapy for patients who do not respond to other drugs.

## Conclusion

This systematic review suggests that intranasal civamide significantly reduces headache pain in migraine and cluster headache, as measured by VAS score, indicating a substantial decrease in VAS score and reflecting the effectiveness of civamide in reducing headache pain intensity. Intranasal civamide is an innovative therapy that is effective in reducing cluster headache frequency and migraine pain intensity. Its advantages, including a rapid onset of action, direct targeting of the trigeminal nerve, and a good safety profile, make it a promising alternative for treating headache pain in the future. Further research is needed to evaluate the long-term effectiveness, improve the tolerability of civamide, and determine its role in treating headache pain compared to other standard therapies.

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