▪ Headache Medicine 2024, 15(4): 304-310 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2024.50

Original

Treatment of refractory migraine in the emergency department

Sara Luiza Ronzani da Cunha[1], Mauro Eduardo Jurno[1,2]

[1]Hospital Foundation of the State of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[2]Barbacena Faculty of Medicine, Barbacena, Minas Gerais, Brazil

Sara Luiza Ronzani da Cunha
sara.ronzani@gmail.com

Edited by:
Marcelo Moraes Valença

Background
Headaches are among the most common neurological complaints in emergency care, predominantly affecting young women of childbearing age. Migraines, as a subtype, are particularly disabling, significantly reducing quality of life and posing a burden on healthcare systems. When standard preventive and acute treatments fail, migraines are classified as refractory, requiring alternative therapeutic strategies.
Objective
This study aimed to evaluate the therapeutic response to a treatment protocol for refractory migraine in the Emergency Unit of the Barbacena Hospital Complex.
Methods
A prospective observational study was conducted from August 1, 2023, to July 31, 2024, involving 16 patients (15 females, 1 male, mean age: 32 years) classified as refractory due to non-response to at least three adequately dosed migraine medications. After obtaining informed consent, demographic and medical history data were collected, and pain intensity was measured using the Visual Analog Scale (VAS). Patients received 5 mg of haloperidol and 4 mg of dexamethasone, either orally or intravenously. The pain was reassessed two hours post-treatment.
Results
All patients demonstrated a reduction of at least 2 points on the VAS two hours after treatment. The combination of haloperidol and dexamethasone proved effective, providing significant pain relief in this refractory population.
Conclusion
The study highlights the potential of haloperidol and dexamethasone as a promising treatment strategy for refractory migraine, offering meaningful pain reduction in patients unresponsive to conventional therapies. Further studies are warranted to validate these findings in larger populations.

Keywords:
Refractory migraine
Migraine treatment
Haloperidol
Dexamethasone

Submited: December 5, 2024
Accepted: December 29, 2024
Publish online: December 31, 2024

Introduction

Headache is one of the leading conditions prompting visits to emergency departments, with the majority of cases involving young women, primarily due to the debilitating nature of the pain. Headaches account for up to a quarter of all neurological cases treated in these settings. However, they can affect individuals of all ages, ethnicities, and genders (1–5). According to the Global Burden of Disease study conducted by the Institute for Health Metrics and Evaluation (IHME) in 2016, migraine substantially impacts quality of life. It ranks among the leading causes of years lived with disability (YLDs) worldwide (4,6).

Migraine stands out as one of the most prevalent and disabling headache disorders, significantly impairing normal activities and quality of life while also placing a burden on healthcare systems (1,4,5,7). This condition is divided into two groups: migraine without aura and migraine with aura. Aura refers to a state characterized by focal neurological symptoms—such as visual, sensory, or motor disturbances, or a combination—that precede or accompany the headache. Both types are characterized by unilateral, pulsatile pain of moderate to severe intensity, which is often disabling, exacerbated by physical activity, and accompanied by systemic symptoms such as nausea and/or vomiting, photophobia, and phonophobia. These episodes typically last between 4 and 72 hours (1,5,7,8).

The exact mechanism of migraine is not yet fully understood, but it is believed to involve a combination of environmental, genetic, and neurovascular factors. Key mechanisms implicated in migraine pathogenesis include activation of the trigeminovascular system, the release of vasoactive substances, and neurogenic inflammation, which contribute to central and peripheral pain sensitization (9,10).

As individuals experience recurrent or chronic headache pain, psychiatric comorbidities such as depression and anxiety often arise (3). The increasing frequency of migraine attacks in the general population escalates the disease burden, healthcare utilization, and associated costs, which usually include inadequate assessments and the overuse of emergency department resources (1). Compared to typical migraine attacks treated at home, refractory cases are more challenging to manage and tend to worsen over time (11).

Patients with migraines unrelieved by adequate acute and preventive treatments may be classified as having "resistant" or "refractory" headaches (1). Resistant migraine is defined as the failure of treatment with at least two to four medication classes, with debilitating headache lasting at least eight days per month over three consecutive months. Refractory migraine is defined by inadequate response to both two to four preventive medications and acute treatment options (12,13).

Research on the optimal treatment of migraines in emergency departments remains limited. Initial management typically involves intravenous fluid therapy, antidopaminergic agents combined with diphenhydramine, corticosteroids such as intravenous (IV) or oral (PO) dexamethasone, and nonsteroidal anti-inflammatory drugs (NSAIDs). In Brazil, dipyrone (IV) is often used as a first-line treatment despite limited international evidence supporting its efficacy as an analgesic. Another cornerstone of therapy is the administration of antidopaminergic drugs such as metoclopramide, chlorpromazine, haloperidol, and triptans (1,14,15).

The use of neuroleptics in the acute and emergency treatment of migraine crises has shown promising results. Their efficacy has been demonstrated in studies evaluating their standalone use and clinical trials comparing them with other drug classes (1,11,14,16,17).

Corticosteroids reduce pain by inhibiting prostaglandin synthesis, leading to inflammation and decreasing vascular permeability, which results in tissue edema. The exogenous administration of corticosteroids suppresses the hypothalamic-pituitary axis's excessive stress and inflammatory responses (18). Short courses of corticosteroids not only acutely reduce migraine attacks but also decrease the risk of headache recurrence after discharge from the emergency department (1,11,18).

Given the importance of this topic, the present study aimed to evaluate the therapeutic response two hours after administering a combination of 5 mg of haloperidol (IV or PO) and dexamethasone (IV or PO) to patients classified as refractory to initial treatment. The evaluation focused on pain reduction and consequent improvement in disability.

Method

A prospective observational study evaluated the therapeutic response of patients classified as refractory to initial treatment. Refractory migraine was defined as any form of migraine that does not respond to two to four classes of indicated preventive medications or adequately dosed acute-phase therapies (19). For this study, refractory patients were defined as those who had used at least three adequately dosed acute-phase medications without relief.

After consenting to participate, demographic data were collected, followed by a targeted anamnesis to define the type of migraine according to ICHD-III criteria (7). Additional information was obtained from electronic medical records, and the patient completed a Visual Analog Scale (VAS) to quantify their pain.

Patients received 5 mg of haloperidol orally or intravenously (diluted in 10 ml of distilled water) combined with 4 mg of dexamethasone administered either intravenously (diluted in 10 ml of distilled water) or orally. Two hours after receiving the above-mentioned therapy, patients were asked to describe the intensity of their pain and complete the VAS again.

Inclusion Criteria

a) Patients who consented to participate in the study;
b) Patients of both sexes, aged over 18 years;
c) Patients diagnosed with refractory migraine.

Exclusion Criteria

a) Patients with any condition that would prevent them from understanding the study;
b) Patients who refused to participate.

The study was conducted at the Emergency Department of the Regional Hospital of Barbacena Dr. José Américo, part of the Barbacena Hospital Center (FHEMIG Network). The hospital provides care for individuals aged 13 and older from Barbacena and surrounding health micro-regions. It attends 89 to 120 patients daily, with a monthly average of 3,000 to 4,000 visits. The average patient age is approximately 45 years, with a slight predominance of females.

The study period extended from August 1, 2023, to July 31, 2024. During this time, there were 833 visits classified under ICD-10 codes "R51" (headache) and "G43" (migraine), including subdivisions such as G43.0 (migraine without aura), G43.1 (migraine with aura), G43.2 (status migrainosus), G43.3 (complicated migraine), G43.8 (other forms of migraine), and G43.9 (unspecified migraine). Of these cases, 16 patients met the inclusion criteria and were eligible for the study, resulting in a prevalence of 1.92% for refractory migraine among all migraine patients seen in the emergency department.

Results

A total of 16 patients were evaluated, but one patient required treatment on two separate occasions, 48 hours apart, for the same migraine episode. Consequently, the sample consisted of 17 records, including 16 women and one man. Due to the small sample size, no sex distinction was made. The average age of the patients was 32.47 ± 10.16 years.

Regarding marital status, 9 (52.9%) individuals were single, 7 (41.2%) were married, and 1 (5.9%) was divorced.

Comorbidities were reported in 5 participants, while 12 (70.6%) had no comorbidities. Among those with comorbidities, 2 (11.8%) had systemic arterial hypertension (SAH), 1 (5.9%) had generalized anxiety disorder (GAD) and depression, 1 (5.9%) was a smoker and alcohol consumer, and 1 (5.9%) had asthma.

Educational attainment data showed that 10 (58%) participants had completed high school, 5 (29.4%) had higher education, 1 (5.9%) had incomplete high school education, and 1 (5.9%) had completed elementary school. The most common occupation among the participants was sales associate.

Lastly, racial demographics revealed that 14 (82.4%) were White, 2 (11.8%) were Mixed-race, and 1 (5.9%) did not disclose their race.

All statistical data are summarized in Table 1.

Table 1. Sociodemographic and Clinical Characteristics

Variable	N	%
Sex		
Female	15	
Male	1	
Marital status		
Single	9	52.9
Married	7	41.2
Divorced	1	5.9
Comorbidities		
No comorbidities	12	70.6
Hypertension (HAS)	2	11.8
GAD and depression	1	5.9
Alcoholism/smoking	1	5.9
Asthma	1	5.9
Education level		
High school	10	58
Higher education	5	29.4
Incompl. high school	1	5.9
Elementary school	1	5.9
Race		
White	14	82.4
Brown	2	11.8
Black	0	-
Not declared	1	5.9

Pain Assessment

Regarding the pain evaluation of patients before administering "haloperidol and dexamethasone," the VAS (Visual Analog Scale) scores ranged from 6 to 10 points. This distribution of values is represented in Figure 1 below.

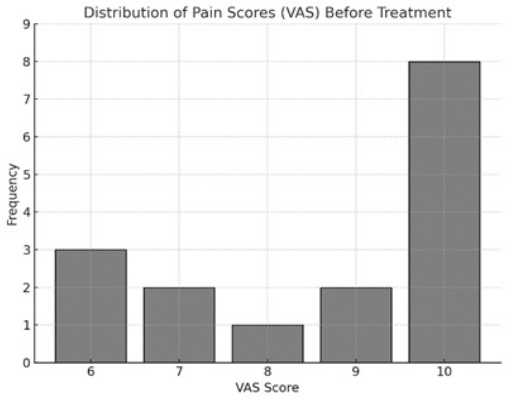

Figure 1. Distribution of Visual Analogue Scale (VAS) pain scores patients reported before treatment. Scores range from 6 to 10, with the highest frequency observed at a score of 10.

Post-Treatment Pain Assessment

Two hours after administering the treatment, a completely different pattern was observed. There was an improvement compared to the initial VAS scores, with values ranging from 0 to 8 points. This is represented in Figure 2, showing that none of the patients experienced the same intensity of maximum pain (10 on the scale) after treatment.

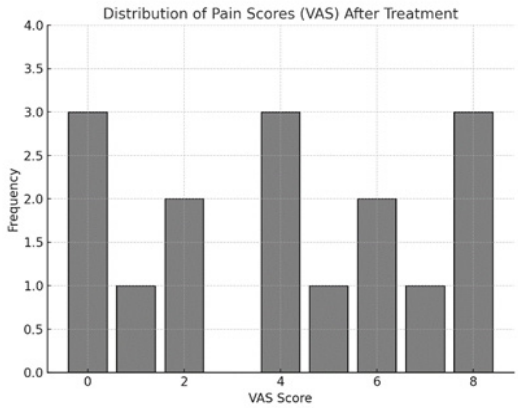

Figure 2. Distribution of Visual Analogue Scale (VAS) pain scores reported by patients two hours after treatment. The scores range from 0 to 8, showing a significant reduction in pain intensity compared to pre-treatment levels, with no reports of maximum pain (score of 10).

Pain Evolution

The progression of VAS scores can also be visualized in Figure 3, which highlights the reduction in pain levels for each patient in the study two hours after the administration of the medication.

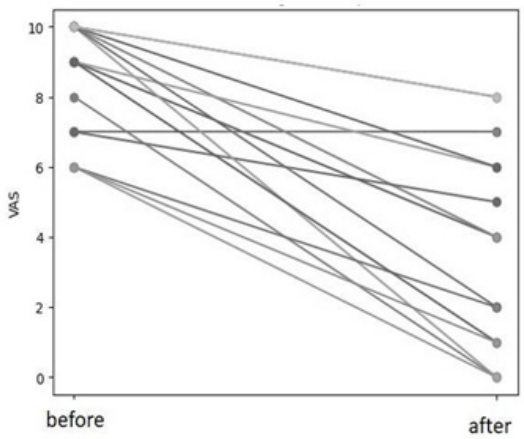

Figure 3. Visualization of the evolution of VAS (Visual Analogue Scale) values. The graph illustrates the reduction in pain levels for each study participant two hours after the administration of the medication.

Statistical Analysis of Pain Scores

The VAS pain scores showed a significant difference between the pre- and post-treatment measurements with "haloperidol and dexamethasone." Before the intervention, the mean pain score was 8.64 ± 1.62; post-intervention, it decreased to 3.88 ± 2.96.

Given that the VAS data distribution cannot be assumed to be normal, a non-parametric statistical test was employed to validate the significance of the difference between the pre- and post-intervention scores. Using the Wilcoxon test (a non-parametric, designed to measure differences between two groups), a p-value < 0.001 was obtained.

This result allows us to reject the null hypothesis that the two distributions (pre- and post-intervention) are equivalent. Consequently, we can affirm a significant trend of improvement following the pharmacological intervention.

Discussion

Migraine is a debilitating neurological condition affecting millions worldwide, accounting for approximately 25% of neurological complaints in emergency departments (1). Each year, it leads 3 million individuals to seek medical care (19). The International Headache Society (IHS) defines migraine as a condition characterized by recurrent attacks of severe headache, often accompanied by autonomic and neurological symptoms such as nausea, vomiting, photophobia, and phonophobia (7). It remains one of the primary causes of emergency visits, with studies indicating that up to 60% of headache-related emergency department visits are due to migraine (20).

As defined by the European Headache Federation, refractory migraine occurs when at least two first-line preventive treatments fail, are poorly tolerated, or are contraindicated (12). This condition significantly impacts patients' quality of life and imposes a substantial economic burden due to absenteeism and reduced productivity, posing a challenge for healthcare professionals (6).

Initial evaluation of refractory migraine patients in emergency settings must be thorough to rule out secondary causes of headache, such as subarachnoid hemorrhage, meningitis, or vascular conditions. History-taking should include headache frequency, duration, characteristics, triggers, and responses to previous treatments. A complete neurological examination is essential to identify warning signs of underlying severe pathology (20).

Acute treatments for refractory migraine often involve a combination of medications to alleviate pain and associated symptoms. Standard options include nonsteroidal anti-inflammatory drugs (NSAIDs), frequently used as first-line treatments due to their pain-reducing efficacy (21). Triptans are effective for many migraine cases but may be contraindicated in patients with cardiovascular conditions due to the risk of coronary vasoconstriction and are often unavailable in emergency settings (9). Antiemetics are used to control nausea and vomiting associated with migraines (4).

For refractory cases, more potent therapies such as corticosteroids, including dexamethasone, may be required. Studies have shown that intravenous dexamethasone can reduce migraine recurrence rates after emergency department discharge (18). A single dose of dexamethasone provides prolonged relief and prevents headache recurrence within 24 to 72 hours.

Antipsychotics, such as haloperidol, a typical antipsychotic, have demonstrated efficacy in reducing pain in refractory migraine patients. Research by Honkaniemi et al. (17) showed that intravenous haloperidol effectively alleviates migraine pain. A randomized, double-blind, placebo-controlled study revealed that 80% of patients treated with intravenous haloperidol experienced significant pain relief compared to only 15% in the placebo group (17). Combining haloperidol with other medications, such as ondansetron and dexamethasone, may enhance both analgesic and antiemetic effects (4).

The combination of different drug classes may be necessary for effectively managing refractory migraine (22). Combined therapy aims to maximize analgesic efficacy while minimizing the side effects associated with high doses of a single medication (1).

In severe cases of refractory migraine, hospitalization may be required for intensive management (16). Hospital care should be individualized, considering patient comorbidities and previous treatment responses. Continuous monitoring and therapeutic adjustments are essential to ensure effectiveness and minimize adverse drug effects. The combination of haloperidol and dexamethasone has shown particular efficacy in managing refractory migraine, offering synergistic benefits (16–18).

In our study, 1.92% of all patients treated for headache in the emergency department were diagnosed with refractory migraine and deemed eligible for the proposed therapeutic approach. A trend toward improvement was observed following pharmacological intervention. No side effects related to the neuroleptic or corticosteroid treatments were reported during the observation period. There was no recurrence of pain or return to the emergency department within 48 hours among patients treated with haloperidol and dexamethasone. These findings align with studies by Monzillo et al. (14) and Woldeamanuel, Rapoport, and Cowan (18).

Conclusion

Refractory migraine represents a significant challenge in the management of headaches in emergency settings. A multifaceted approach incorporating pharmacological and non-pharmacological therapies is essential for effective pain relief and improved patient quality of life.

Haloperidol, while effective, is underutilized in emergency medicine due to significant side effects such as sedation and akathisia, which can limit its use. Corticosteroids, on the other hand, are frequently employed to prevent relapses and reduce inflammation, particularly in patients with status migrainosus. The combination of haloperidol and dexamethasone offers a powerful option for treating refractory headaches in the emergency department, especially when other treatments have failed.

Thus, the use of haloperidol and dexamethasone in the treatment of refractory migraine offers a promising approach, particularly for patients who do not respond to conventional treatments. However, it is essential to consider potential adverse effects and closely monitor patients during treatment. Further studies are needed to optimize the dosages and combinations of these medications, aiming to maximize efficacy and minimize risks.

References

1. Robblee J, Grimsrud KW. Emergency Department and Inpatient Management of Headache in Adults. Curr Neurol Neurosci Rep. 2020 Apr 18;20(4):7. Doi: 10.1007/s11910-020-01030-w
2. Minen MT, Tanev K, Friedman BW. Evaluation and Treatment of Migraine in the Emergency Department: A Review. Headache: The Journal of Head and Face Pain. 2014 Jul 4;54(7):1131–45. Doi: 10.1111/head.12399
3. Silva AV da, Kiy LMC, Alves C de A, Kirylko GC, Bello VA, Poli-Frederico RC. Impact of headache on a supplemental healthcare emergency unit and on use of opioids. Arq Neuropsiquiatr. 2021 Jul;79(7):579–83. Doi: 10.1590/0004-282x-anp-2020-0188
4. Benevides ML, Oliveira S de S, Aguilar-Nascimento JE. A Associação de Haloperidol, Dexametasona e Ondansetrona Reduz a Intensidade de Náusea, Dor e Consumo de Morfina após Gastrectomia Vertical Laparoscópica. Brazilian Journal of Anesthesiology. 2013 Sep;63(5):404–9. Doi: 10.1016/j.bjan.2012.07.011
5. Melhado EM, Santos PSF, Kaup AO, Costa ATNM da, Roesler CA de P, Piovesan ÉJ, et al. Consensus of the Brazilian Headache Society (SBCe) for the Prophylactic Treatment of Episodic Migraine: part I. Arq Neuropsiquiatr. 2022 Aug 17;80(08):845–61. Doi: 10.1055/s-0042-1756441
6. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov;392(10159):1789–858. Doi: 10.1016/S0140-6736(18)32279-7
7. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan 25;38(1):1–211. Doi: 10.1177/0333102417738202
8. Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. 2018 Feb;17(2):174–82. Doi: 10.1016/S1474-4422(17)30435-0
9. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev. 2017 Apr;97(2):553–622. Doi: 10.1152/physrev.00034.2015
10. Noseda R, Burstein R. Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain. 2013 Dec;154(Supplement 1):S44–53. Doi: 10.1016/j.pain.2013.07.021
11. Gelfand AA, Goadsby PJ. A Neurologist's Guide to Acute Migraine Therapy in the Emergency Room. Neurohospitalist. 2012 Apr 16;2(2):51–9. Doi: 10.1177/1941874412439583
12. Sacco S, Braschinsky M, Ducros A, Lampl C, Little P, van den Brink AM, et al. European headache federation consensus on the definition of resistant and refractory migraine. J Headache Pain. 2020 Dec 16;21(1):76. Doi: 10.1186/s10194-020-01130-5
13. Martins IP, Sousa L, Monteiro PJM. Enxaqueca crônica, refratária e cefaleias por uso excessivo de medicamentos: Revisão clínica e terapêutica. Sinapse. 2018;18(2):1–12.
14. Monzillo PH, Nemoto PH, Costa AR, Sanvito WL. Tratamento agudo da crise de enxaqueca refratária na emergência: estudo comparativo entre dexametasona e haloperidol. Resultados preliminares. Arq Neuropsiquiatr. 2004 Jun;62(2b):513–8. Doi: 10.1590/S0004-282X2004000300025
15. Steiner TJ, Birbeck GL, Jensen R, Katsarava Z, Martelletti P, Stovner LJ. The Global Campaign, World Health Organization and Lifting The Burden: collaboration in action. J Headache Pain. 2011 Jun 22;12(3):273–4. Doi: 10.1007/s10194-011-0342-4
16. Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the Emergency Department treatment of migraines: a randomized controlled trial. J Emerg Med. 2002 Aug;23(2):141–8. Doi: 10.1016/S0736-4679(02)00502-4
17. Honkaniemi J, Liimatainen S, Rainesalo S, Sulavuori S. Haloperidol in the Acute Treatment of Migraine: A Randomized, Double-Blind, Placebo-Controlled Study. Headache: The Journal of Head and Face Pain. 2006 May 25;46(5):781–7. Doi: 10.1111/j.1526-4610.2006.00438.x
18. Woldeamanuel Y, Rapoport A, Cowan R. The place of corticosteroids in migraine attack management: A 65-year systematic review with pooled analysis and critical appraisal. Cephalalgia. 2015 Oct 9;35(11):996–1024. Doi: 10.1177/0333102414566200
19. Godwin SA, Cherkas DS, Panagos PD, Shih RD, Byyny R, Wolf SJ, et al. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Headache. Ann Emerg Med. 2019 Oct;74(4):e41–74. Doi: 10.1016/j.annemergmed.2019.07.009
20. Nye BL, Ward TN. Clinic and Emergency Room Evaluation and Testing of Headache. Headache: The Journal of Head and Face Pain. 2015 Oct 30;55(9):1301–8. Doi: 10.1111/head.12648
21. Kowacs F, Roesler CA de P, Silva-Néto RP. "Migrânea" and "enxaqueca": not opposite, but complementary words. Arq Neuropsiquiatr. 2021 Mar;79(3):248–50. Doi: 10.1590/0004-282x-anp-2020-0292
22. Dodick D. Pearls: Headache. Semin Neurol. 2010 Feb 1;30(01):074–81. Doi: 10.1055/s-0029-1245000

Sara Luiza Ronzani da Cunha
https://orcid.org/0009-0000-7926-0283
Mauro Eduardo Jurno
https://orcid.org/0000-0002-8743-9395

Authors contribution: SLRC: data collection, analysis and writing of the text; MEJ: conception of the idea and review of the article.
Conflict of interest: The authors declare no conflicts of interest.
Funding: This research received no specific funding from public, commercial, or non-profit funding agencies.