▪ Headache Medicine 2026, v. 17, n. 3 ▪ p. 232-238 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2026.30

Original

Short-term naratriptan treatment does not worsen pain sensitivity in migraine: a prospective clinical trial

Luana Zanoni Schauffer[1], Mario Fernando Prieto Peres[2], Marina Luiza Veloso Ferreira[3], Pâmela Aparecida do Nascimento Rosa[3], Maria Eduarda Lessa Guerra[1], Mauro Eduardo Jurno[1,3]

[1]Minas Gerais State Hospital Foundation, Barbacena, Minas Gerais, Brazil
[2]Institute of Psychiatry of the University of São Paulo, São Paulo, São Paulo, Brazil
[3]José Bonifácio Lafayette de Andrada Foundation, Barbacena School of Medicine, Barbacena, Minas Gerais, Brazil

Luana Zanoni Schauffer
luanazanoni@hotmail.com

Edited by:
Marcelo Moraes Valença

Abstract

Background
Migraine represents one of the most disabling neurological disorders, frequently underdiagnosed and undertreated, with predominant reliance on acute medications that may precipitate medication overuse headache. Evidence indicates that triptans, including naratriptan, modulate central sensitization—a key pathophysiological mechanism in migraine—yet their short-term continuous use requires evaluation regarding impact on pain thresholds.

Objective
To investigate whether seven days of continuous naratriptan use alters cephalic pain thresholds in patients with migraine.

Methods
Prospective study involving 19 patients diagnosed with migraine per International Classification of Headache Disorders (ICHD-3) criteria, recruited from institutions in Barbacena, Minas Gerais, Brazil. Pain thresholds were assessed via pressure algometry (MED.DOR device) at bilateral cephalic sites before and after seven days of naratriptan 2.5 mg every 12 hours, with reassessment two weeks post-treatment. The primary analysis used paired equivalence testing with a prespecified margin of ±20% of the baseline mean.

Results
Mean overall pressure pain threshold (PPT) increased from 45.12 (SD 17.45) kgf at baseline to 50.56 (SD 16.86) kgf after seven days of treatment and was 51.64 (SD 14.30) kgf at follow-up. The mean paired change after treatment was +5.43 kgf (90% CI, 0.53 to 10.33 kgf). The prespecified equivalence bounds were −9.02 to +9.02 kgf; therefore, statistical equivalence was not demonstrated. The conventional paired comparison was not statistically significant (p=0.070).

Conclusion
Short-term continuous naratriptan use does not worsen pain sensitivity and may attenuate central sensitization processes in episodic migraine, supporting its safety for exacerbation management. Larger controlled trials are warranted.

Keywords
Migraine
Naratriptan
Central sensitization
Pain thresholds
Medication overuse headache
Triptans

Received: August 13, 2026
Revised: September 22, 2026
Accepted: September 28, 2026

© Copyright 2026

Introduction

Migraine is among the most disabling neurological conditions (1) and remains substantially underdiagnosed and undertreated (2). Most patients rely primarily on acute treatments rather than preventive strategies. However, frequent use of acute medications is common and may lead to medication overuse headache (MOH), a secondary disorder defined as the regular intake of acute medications on 10 to 15 days per month, depending on the drug class, for at least three consecutive months (3).

An ongoing debate persists in the literature regarding optimal treatment strategies for MOH. Recent studies suggest that limiting intake or employing washout strategies does not significantly improve headache outcomes. Nevertheless, concerns remain that daily use of acute medications may contribute to worsening of headache frequency. Among these, opioids are most likely to induce hyperalgesia, whereas much less is known about the potential role of triptans in this process.

In this context, central sensitization has been identified as a key mechanism in migraine pathophysiology and a potential therapeutic target for triptans. Evidence from Suzuki et al.(4) and Coppola et al.(5) demonstrates that triptans can modulate pain perception and reduce somatosensory cortex hyperexcitability, while Burstein's et al.(6) meta-analysis highlights the lower pain thresholds observed in migraine patients and suggests that naratriptan may help normalize this altered sensitivity.

Building on these findings, the present study investigates naratriptan's role as a modulator of pain thresholds, with implications for clinical practice, improved quality of life, and optimized therapeutic use of triptans. We test the hypothesis that the use of naratriptan over a defined period might negatively influence the process of sensitization and pain thresholds.

Methods

This is a prospective clinical study enrolled migraine patients, who were asessed cephalic pain thresholds following naratriptan daily use.

Participants were recruited at Faculdade de Medicina de Barbacena and Centro Universitário Presidente Antônio Carlos, and Hospital Regional de Barbacena Dr. José Américo. Eligible participants were over 18 years of age and provided informed consent after a detailed explanation of the study protocol.

Diagnosis was performed by the principal investigator using criteria from the International Classification of Headache Disorders, 3rd edition (ICHD-3).

Patients who met inclusion criteria - presence of a diagnosis of migraine according to the (ICHD-3), being over 18 years of age and agreeing to participate in the research after a detailed explanation of its design - were invited to participate and signed the informed consent form (ICF). The study was approved by the ethics and research committee of the José Bonifácio Lafayette de Andrada Foundation.

Pain thresholds were measured using a pressure algometer at the following bilateral anatomical points: frontal region, temporal region, vertex, occipital region, masseter muscle, and trapezius, as shown in Figure 1.



Figure 1. Anatomical sites for pressure pain threshold assessment with algometry.

Pressure pain threshold (PPT) was assessed using a digital pressure algometer (MED.DOR Pressure Algometer, MED. DOR, Brazil) equipped with a 1-cm² rubber tip. The device has a maximum measurement capacity of 50 kgf, with a resolution of 5 g in the 0–10 kg range and 10 g in the 10–50 kg range. Pressure was applied at a constant rate of 1 kgf/s until the participant reported the first sensation of pain. Measurements were recorded in kilogram-force (kgf). The sum of PPT measurements obtained across all anatomical sites assessed according to the study protocol ranged from 10.780 to 81.960 kgf across participants (7). The test was interrupted immediately after the onset of pain was indicated, and the final amount of force applied was recorded. The participants did not present with a headache or migraine attack at the time of the algometric assessment.

Following the initial measurement, participants received 14 doses of naratriptan 2.5 mg, administered every 12 hours over a 7-day period. On the eighth day, pain threshold measurements were repeated at the same anatomical sites.

Subsequently, participants remained off naratriptan for two weeks, after which the pain threshold was again assessed at the same sites. A timeline with the schedule of the study stages is shown in Figure 2.

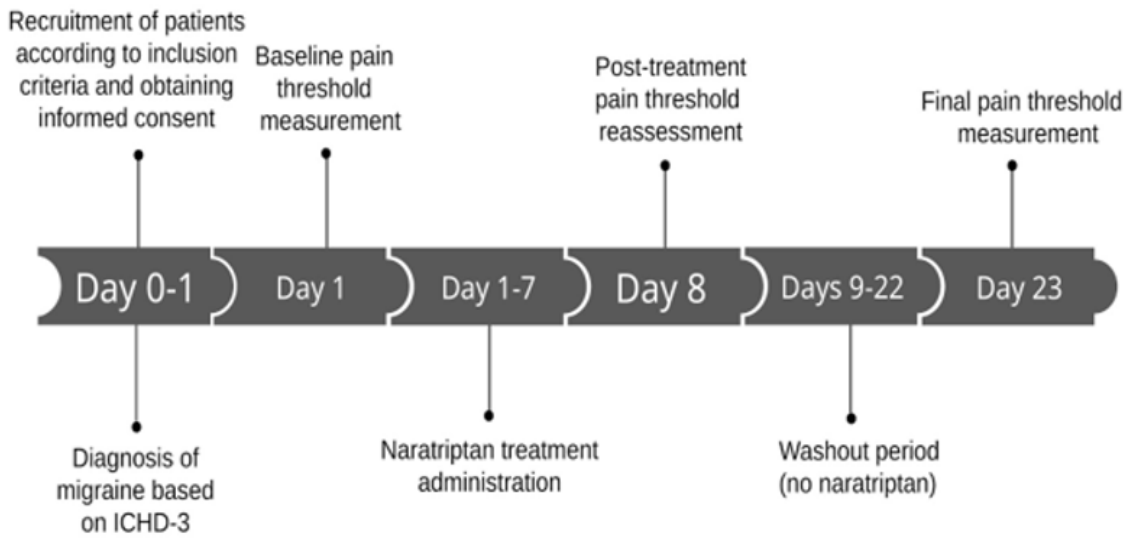


Figure 2. Timeline with the study stages.

The original study protocol targeted a sample of 20 participants, assuming a 20% change in pain threshold and 80% statistical power. Nineteen participants completed the study and were included in the final analysis.

For each participant, pressure pain threshold (PPT) values obtained at the predefined anatomical sites were summed to provide an overall PPT value at each of the three assessments: baseline (before naratriptan administration), after 7 days of naratriptan 2.5 mg twice daily, and after a subsequent 2-week period without naratriptan.

Statistical analysis

Continuous variables were summarized as mean and standard deviation (SD), and categorical variables as absolute and relative frequencies. The primary analysis compared overall PPT at baseline and after 7 days of naratriptan treatment using paired data. A paired equivalence analysis was performed using the Two One-Sided Tests (TOST) procedure, with the equivalence margin (Δ) prespecified as ±20% of the baseline mean. With a significance level of 0.05, equivalence was considered demonstrated if the 90% confidence interval (CI) for the mean paired difference was entirely contained within the prespecified equivalence bounds (–Δ to +Δ). A conventional two-sided paired t-test was additionally used to assess whether the mean change differed from zero. The third assessment, performed after a 2-week period without naratriptan, was considered a follow-up assessment and was analyzed descriptively in relation to baseline. Analyses were performed using STATA version 9.2.

Secondary exploratory analysis

As a secondary exploratory analysis, participants were classified according to the percentage change in overall PPT from baseline as increased (>10%), decreased (>10%), or stable (within ±10%). The numbers and proportions of participants in each category were reported. Among participants with changes exceeding 10%, the frequencies of increases and decreases were compared using an exact two-sided binomial test. A p value <0.05 was considered statistically significant.

Results

Nineteen participants completed all three study assessments. The mean overall PPT was 45.12 kgf (SD 17.45) at baseline,

50.56 kgf (SD 16.86) after 7 days of naratriptan treatment, and 51.64 kgf (SD 14.30) at the 2-week post-treatment follow-up. In the primary paired analysis, the mean change in PPT from baseline to the end of the 7-day treatment period was +5.43 kgf, corresponding to an increase of approximately 12.0% relative to the baseline mean. The 90% CI for the mean paired difference ranged from 0.53 to 10.33 kgf. The prespecified equivalence margin of ±20% of the baseline mean corresponded to –9.02 to +9.02 kgf. Because the upper limit of the 90% CI exceeded the upper equivalence bound, the prespecified criterion for statistical equivalence was not met. In the conventional two-sided paired analysis, the difference between baseline and post-treatment PPT did not reach statistical significance (p=0.070). Individual responses showed considerable variability. From baseline to the end of treatment, 9 of 19 participants (47.4%) showed an increase in PPT greater than 10%, 2 (10.5%) showed a decrease greater than 10%, and 8 (42.1%) remained within ±10% of their baseline value. Among participants with changes exceeding 10%, increases were more frequent than decreases (9 vs. 2); however, this difference did not reach statistical significance in the two-sided exact binomial test (p=0.065). At the 2-week post-treatment follow-up, 10 participants (52.6%) had PPT values more than 10% above baseline, 5 (26.3%) had values more than 10% below baseline, and 4 (21.1%) remained within ±10% of baseline. The sociodemographic characteristics, migraine attack frequency, and prophylaxis use are summarized in Table 1, and the individual PPT trajectories across the three assessments are presented in Figures 3-6 individual PPT trajectories across the three assessments are shown in the study figures.

Table 1. Sociodemographic and clinical characteristics of the study participants

Participant characteristics	
Mean age (years)	28.7
Sex	
Female	18 (94.8%)
Male	1 (5.2%)
Migraine frequency	
1 to 3 episodes/month	7 patients
4 to 6 episodes/month	8 patients
7 to 10 episodes/month	3 patients
> 10 episodes/month	1 patient
Prophylaxis use	
Yes	8 patients (42.1%)
No	11 patients (57.8%)

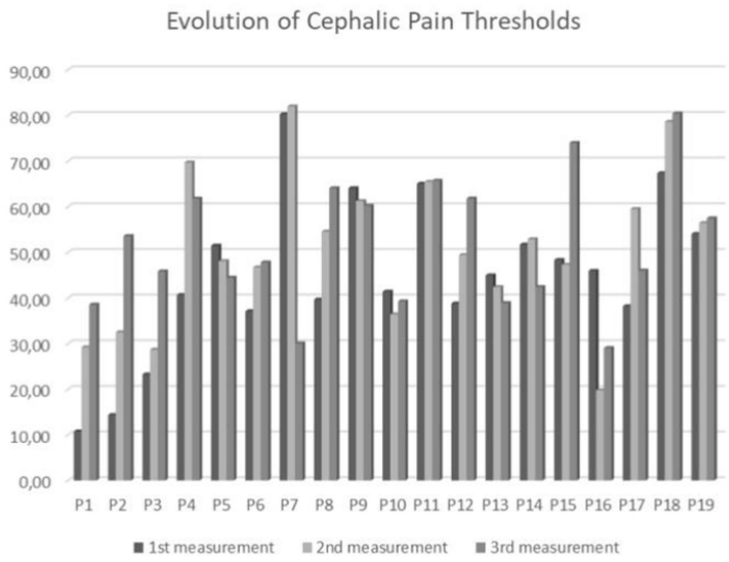


Figure 3. Mean cephalic pain thresholds before and after naratriptan use.

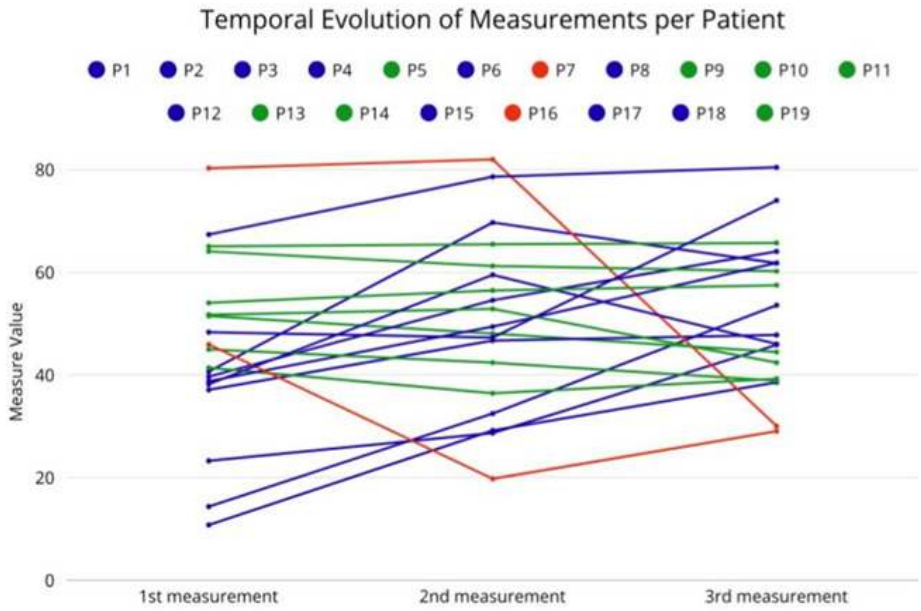


Figure 4. Temporal evolution of measurements per patient.The blue lines represent patients who showed a significant increase in pain thresholds during the measurements. The red lines represent patients who showed a reduction, and the green lines represent those who showed no changes.

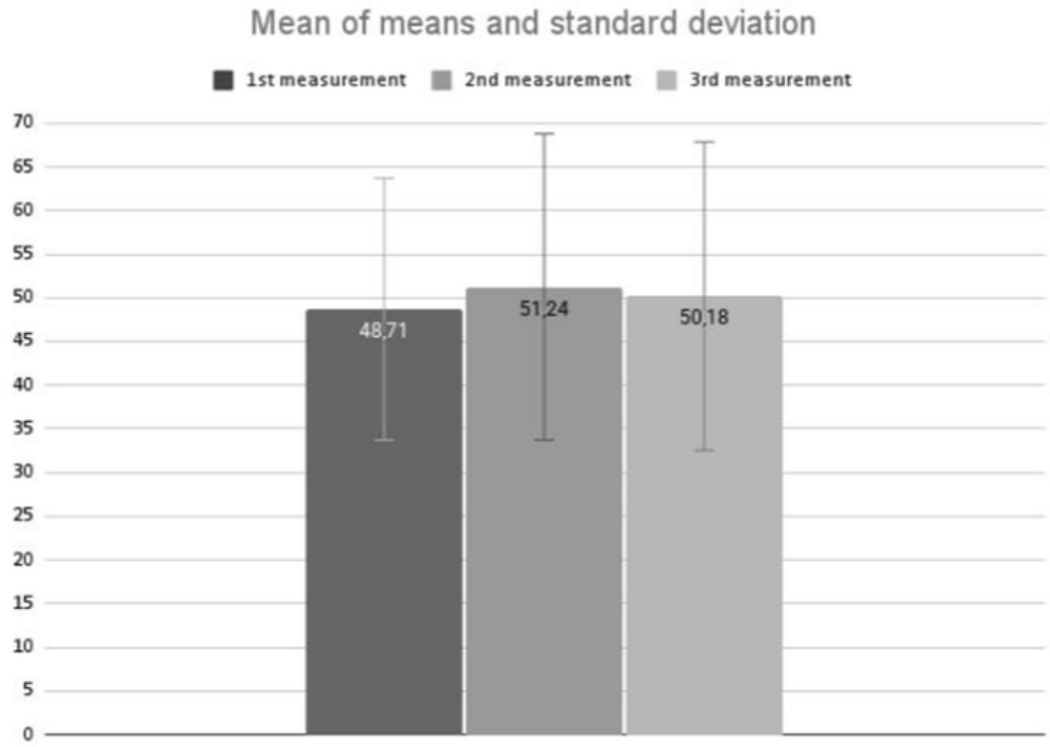


Figure 5. Mean of the means and standard deviation of the measurements.

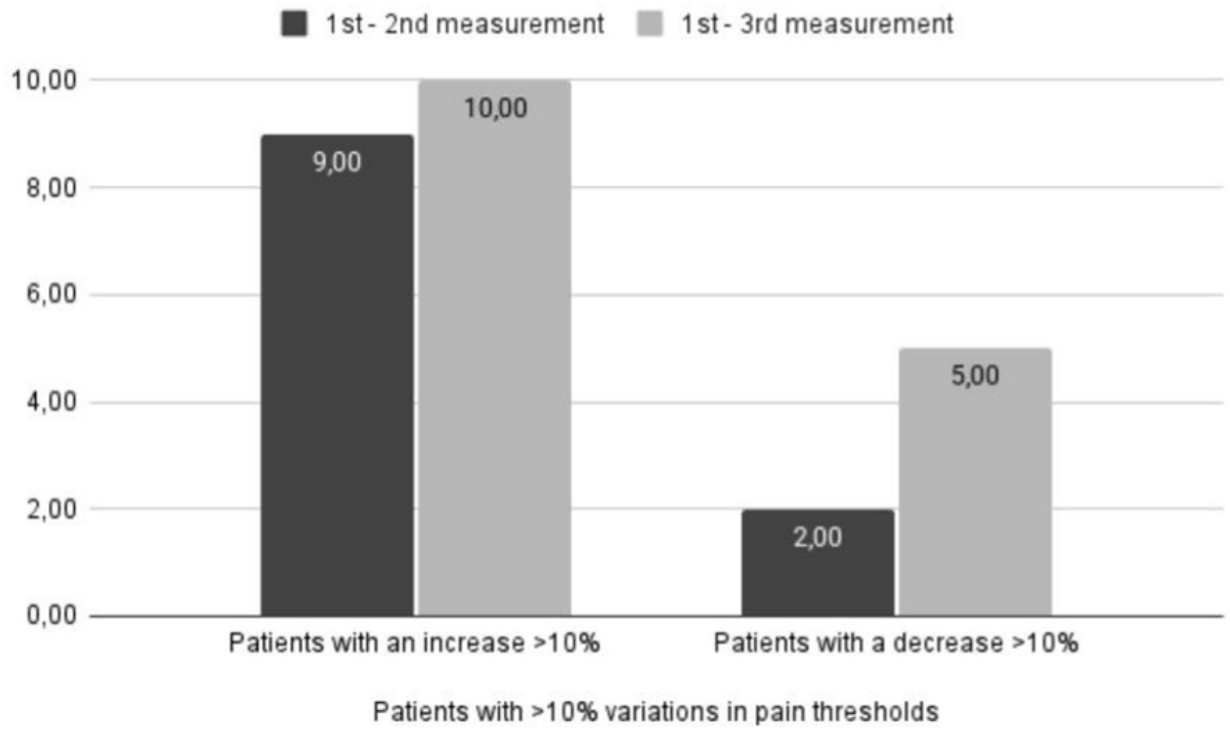


Figure 6. Patients who presented variations greater than 10% in pain thresholds throughout the study.

Discussion

The current data suggest that short-term, continuous administration of naratriptan does not increase pain sensitivity, in addition, our study suggests the opposite. That the reversal or attenuation of sensitization processes occur.

This is consistent with the findings of Coppola et al.(5), who demonstrated that pharmacological intervention can modulate cortical hyperresponsiveness in patients with chronic headache. Supporting the hypotheses that triptans may influence central processing of nociceptive stimuli beyond their vasoconstrictive effects.

The clinical significance of these findings extends to practice, in which naratriptan — a second-generation triptan known for its favorable side-effect profile and longer half-life — may serve as a useful tool in the broader management of migraine, particularly in patients susceptible to central sensitization and MOH. Importantly, no adverse events were observed during the short-term treatment protocol, reinforcing the safety of naratriptan in a controlled setting. It is likely that daily use of naratriptan for one week is a possible management strategy in migraine exacerbations when needed. However, it must be highlighted that prolonged or unsupervised triptan use may still result in MOH, emphasizing the need for careful patient selection and adequate follow-up. In 1 of the 19 cases, the possibility of worsening due to naratriptan could not be ruled out, even though neither the patient nor the examiner could establish a cause-effect relationship between the intake of naratriptan and the worsening of headaches.

This study is limited by its sample size and by the specific population assessed (students and hospital staff), a less severe population with lower frequency migraines, lack of previous preventive treatments, which may not be generalizable to a migraine population treated in tertiary centers. Despite these limitations, the statistically significant modifications in pain thresholds suggest a promising therapeutic avenue that should be further explored in larger and controlled clinical trials.

One may argue why we have not done the ideal study to prove that naratriptan is safe in frequent migraine, we thought that we should first test a short term use, as a first step of proving the concept, and then if we observe that no worsening happened we move to the next step.

Future research is necessary to confirm this results in a more severe migraine population, studying longer treatment durations, larger participant cohorts.

Conclusion

The findings support the hypothesis that continuous, short-term use of naratriptan does not cause worsening of pain thresholds in migraine patients. These results may guide the development of future clinical guidelines and therapeutic strategies designed to improve treatment outcomes and quality of life in this patient population.

References

1. Peres MFP, Sacco S, Pozo-Rosich P, Tassorelli C, Ahmed F, Burstein R, et al. Migraine is the most disabling neurological disease among children and adolescents, and second after stroke among adults: A call to action. Cephalalgia 2024;44. Doi:10.1177/03331024241267309.
2. Adams AM, Buse DC, Leroux E, Lanteri-Minet M, Sakai F, Matharu MS, et al. Chronic Migraine Epidemiology and Outcomes – International (CaMEO-I) Study: Methods and multi-country baseline findings for diagnosis rates and care. Cephalalgia 2023;43. Doi:10.1177/03331024231180611.
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211. Doi:10.1177/0333102417738202.
4. Suzuki K, Suzuki S, Shiina T, Kobayashi S, Hirata K. Central Sensitization in Migraine: A Narrative Review. J Pain Res 2022; Volume 15:2673–82. Doi:10.2147/JPR.S329280.
5. Coppola G, Currà A, Di Lorenzo C, Parisi V, Gorini M, Sava SL, et al. Abnormal cortical responses to somatosensory stimulation in medication-overuse headache. BMC Neurol 2010;10:126. Doi:10.1186/1471-2377-10-126.
6. Burstein R. Migraine pathophysiology: peripheral and central sensitization. European Journal of Pain 2006;10. Doi:10.1016/S1090-3801(06)60070-0.
7. de Oliveira NC, Silva KR, Santos AC, Alfieri FM. Reprodutibilidade e confiabilidade da algometria de pressão: os algômetros digital e analógico são comparáveis? Brazilian Journal Of Pain 2024;7:01–5. Doi:10.5935/2595-0118.20240055-pt.

Luana Zanoni Schauffer
https://orcid.org/0009-0005-2992-8480
Mario Fernando Prieto Peres
https://orcid.org/0000-0002-0068-1905
Marina Luiza Veloso Ferreira
https://orcid.org/0009-0001-6511-7379
Pâmela Aparecida do Nascimento Rosa
https://orcid.org/0009-0001-9433-2879
Maria Eduarda Lessa Guerra
https://orcid.org/0009-0002-4190-0374
Mauro Eduardo Jurno
https://orcid.org/0000-0002-8743-9395

Author contributions: MEJ: conceptualization, funding acquisition, methodology, resources, writing - review & editing; MLVF: data curation, visualization; MFPP: formal analysis, project administration; PANR: software; LZS: investigation supervision, writing - original draft; MELG: validation.

Conflict of interest: There is no conflict of interest to declare.

Funding: This study did not receive funding from other institutions. All financial costs were borne by the authors.

Acknowledgments: We thank our partner institutions in Barbacena for their logistical support, our colleagues for their collaboration, and the participants for their dedicated time.

Data availability statement: The datasets generated and/or analyzed during the current study are not publicly available due to [ethical/legal/privacy] restrictions but are available from the corresponding author upon reasonable request.