A Comparison of Headache Treatment in the Emergency Department: Prochlorperazine Versus Ketamine

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Study objective: Intravenous subdissociative-dose ketamine has been shown to be effective for pain management, but has not been specifically studied for headaches in the emergency department (ED). For this reason, we designed a study to compare standard treatment (prochlorperazine) with ketamine in patients with benign headaches in the ED.

Methods: This study was a multicenter, double-blind, randomized, controlled trial with a convenience sample of patients presenting to the ED with benign headaches. Patients were randomized to receive either prochlorperazine and diphenhydramine or ketamine and ondansetron. Patients’ headache severity was measured on a 100-mm visual analog scale (VAS) at 0, 15, 30, 45, and 60 minutes. Nausea, vomiting, anxiety, and the need for rescue medications were also tracked. Patients were contacted at 24 to 48 hours posttreatment to rate their satisfaction and to determine whether they were still experiencing a headache.

Results: There were a total of 54 subjects enrolled. Two patients in the ketamine group and one in the prochlorperazine group withdrew because of adverse effects of the medications. In regard to the primary outcome, at 60 minutes, the prochlorperazine group had a mean improvement in VAS pain scores of 63.5 mm compared with 43.5 mm in the ketamine group, corresponding to a between-groups difference of 20.0 mm (95% confidence interval [CI] 2.8 to 37.2 mm) and a P value of .026. At 45 minutes, the prochlorperazine group had a mean improvement in pain scores of 56.1 mm compared with 38.0 mm in the ketamine group, a difference of 18.1 mm (95% CI 1.0 to 35.2 mm). At 24- to 48-hour follow-up, the mean satisfaction score was 8.3 of 10 for prochlorperazine and 4.9 of 10 for ketamine, a difference of 3.4 (95% CI 1.2 to 5.6). There was not a statistically significant difference in the percentage of patients who had a headache at follow-up or in other secondary outcomes.

Conclusion: Prochlorperazine appears to be superior to ketamine for the treatment of benign headaches in the ED.

Please see page XX for the Editor’s Capsule Summary of this article.

INTRODUCTION

Background

In the emergency department (ED), one of the most common chief complaints is headache. A number of previous studies have demonstrated the efficacy of a variety of medications for migraines and other benign headaches. Some of the options for treating these types of headaches include dopamine antagonists, opioids, nonsteroidal anti-inflammatory drugs, triptans, antiepileptics, and ergot derivatives. Among the available options, dopamine antagonists appear to be the most effective, with multiple studies demonstrating their superiority over opioids, nonsteroidal anti-inflammatory drugs, triptans, and antiepileptics. A commonly used dopamine antagonist, and one that has a great deal of evidence to support its use for benign headaches, is prochlorperazine. Although some data suggest that droperidol may be even more effective than prochlorperazine, the current national shortage limits its use.

Importance

Despite the general effectiveness of dopamine antagonists and the variety of options for benign headache treatment, many patients who present to the ED still have headaches 24 hours after treatment. In one study, 31% of patients still had moderate to severe headaches 24 hours after discharge. Often, emergency physicians resort to opioids for refractory headaches despite evidence to suggest that the drugs increase both length of stay and rate of return ED visits.
Editor’s Capsule Summary

What is already known on this topic
Ketamine has analgesic properties and is gaining popularity as a treatment for acute pain.

What question this study addressed
Does ketamine with ondansetron relieve acute, benign headache pain better than standard treatment with prochlorperazine and diphenhydramine?

What this study adds to our knowledge
In this 54-patient randomized trial, the ketamine and ondansetron regimen was less effective and associated with more adverse effects than standard first-line therapy.

How this is relevant to clinical practice
Ketamine and ondansetron is unlikely to be better than standard treatments for acute benign headache.

Research we would like to see
Because headache is among the most common adverse effects of ondansetron, further headache research should omit this component. Ketamine alone or with alternative adjuvant agents may be helpful, but future prospective randomized trials are needed.

Ketamine is an N-methyl-D-aspartate receptor antagonist that has both analgesic and dissociative properties.14 Previous studies have demonstrated the effectiveness of ketamine for postoperative pain,15,16 pain in burn patients,17 and chronic pain.18 New studies have also shown ketamine to be useful for acute pain in the ED by both the intranasal19 and intravenous routes.20 To our knowledge, there are no published prospective studies that evaluate the effectiveness of intravenous ketamine for the treatment of benign headaches in the ED.

Goals of This Investigation
We performed a double-blind, randomized, controlled study comparing ketamine with prochlorperazine to assess the efficacy of ketamine for benign headaches in the ED.

MATERIALS AND METHODS
Study Design and Setting
This was a multicenter, prospective, double-blind, randomized, controlled trial performed in Las Vegas, NV, with a convenience sample of patients presenting to the ED with a chief complaint of headache. The primary site for the study was a county, academic, tertiary care facility and the secondary site was a military hospital. Subjects were enrolled only when a pharmacist who was familiar with the study protocol was available to prepare medications. (This was generally 2 PM to 2 AM.) Each of the 2 hospitals involved in the study received approval for it from their respective institutional review boards. This was an investigator-initiated study without any pharmaceutical company involvement.

Selection of Participants
Previous data have shown that patients presenting to the ED with an undifferentiated headache improve with all the above-described headache medications regardless of whether they meet the definition of migraine, tension headache, or another primary headache disorder.3,7,9,21 Therefore, this study enrolled patients who presented to the ED with a “benign headache,” which was defined as a headache that was thought to likely be a primary headache without signs or symptoms of serious intracranial pathology. In particular, patients who presented to the ED with complaint of a headache could be included if they met the following criteria: aged 18 to 65 years, temperature less than 100.4°F (38°C), diastolic blood pressure less than 104 mm Hg, and normal neurologic examination result. Patients were excluded if they were pregnant or breastfeeding, were a prisoner, had meningeal signs, had signs of acute angle closure glaucoma, had head trauma within the previous 2 weeks, had a lumbar puncture within the previous 2 weeks, had a thunderclap onset of their headache, weighed more than 150 kg or less than 40 kg, had a known allergy to one of the study drugs, had a history of schizophrenia or bipolar disorder, had a history of intracranial hypertension, did not speak English, or had received pain medication in the ED before enrollment. Written, informed consent was obtained from each patient.

Interventions
After enrollment, each patient was randomized either to the standard treatment arm to receive prochlorperazine 10 mg intravenously along with diphenhydramine 25 mg intravenously, or to the study arm to receive intravenous ketamine at 0.3 mg/kg along with intravenous ondansetron at 4 mg. The diphenhydramine or ondansetron was administered first, and immediately afterward the prochlorperazine or ketamine was administered. The prochlorperazine or ketamine was diluted in saline solution so that the total volume was 5 mL and was administered during 2 minutes. The diphenhydramine was diluted in
saline solution so that the total volume was 2 mL (the same volume as the ondansetron). Both groups also received a 500-mL normal saline solution bolus after the study medications were administered. The ED pharmacist was responsible for preparing the medications, using a double-blind protocol. He or she recorded the arm to which the patient was randomized. Randomization was performed with a random-number generator. Only the pharmacist had access to the randomization records and did not reveal the randomization until the interim analysis that led to the discontinuation of the study, as described below.

Emergency providers were instructed not to administer any rescue medications for at least 30 minutes. The electronic medical record order read “randomized study medication” (for the ketamine or prochlorperazine) and “randomized add-on medication” (for the ondansetron or diphenhydramine).

Methods of Measurement
Enrolled patients filled out a brief data collection form including age, sex, race, telephone number, and baseline headache severity, using a 100-mm visual analog scale (VAS). Repeated headache severity scores were measured at 15, 30, 45, and 60 minutes. Time zero began immediately before the administration of the study drugs. VAS scores for nausea and anxiety have previously been validated and were assessed at those intervals as well. The presence or absence of vomiting and the development of subjective restlessness during the 60-minute data collection period were also assessed. The need for rescue medications was extracted from the patient’s chart at a later time by a trained research assistant.

Trained research assistants contacted patients 24 to 48 hours postdischarge by telephone or e-mail to ask them to rate their satisfaction with the drug they received on a scale of 0 to 10, and to ask whether they were currently having a headache (yes or no). Up to 5 telephone calls were made to the patient if he or she did not answer. If the patient was admitted, he or she was approached in the hospital by an investigator or research assistant for follow-up.

Outcome Measures
The primary outcome measure was the difference in pain scores between the prochlorperazine and ketamine groups, measured as the absolute difference between the means at 60 minutes. Secondarily, we measured the difference between the pain scores at the other intervals, rate of admission, nausea scores, rate of vomiting, rate of use of rescue medications for headache, rate of the development of subjective restlessness, headache resolution with telephone follow-up, and patient satisfaction.

Primary Data Analysis
We define significant pain relief as an absolute decrease of 25 mm in the mean VAS score to show clinical benefit, similar to previous studies. Because intravenous ketamine has not been previously studied for headache, to our knowledge, it was of interest to see how much the pain scores decreased within the ketamine group, but we powered our study to detect a difference of 25 mm between groups. Thirty-two patients would be needed in each group to find a 25-mm difference between the group means on the VAS at 60 minutes, with a power of 0.80, an alpha of .05, and an SD of 35 (similar to previous studies, but slightly overestimated). We aimed for 35 patients per group to account for an approximately 10% dropout rate. The individual VAS measurements were compared by using repeated-measures ANOVA. A dropout sensitivity analysis was performed by reanalyzing the data after assuming dropouts had excellent results (complete resolution of pain), neutral results (no change in pain score), and terrible results (worsening to a pain score of 100).

RESULTS
Between March 2016 and March 2017, a total of 54 patients were enrolled at the 2 centers. Twenty-nine patients were randomized to receive prochlorperazine and 25 were randomized to receive ketamine (Figure 1). The subjects in our study were diverse, including an age range of 18 to 58 years and patients who identified as white, black, Hispanic, Asian, Native American, and multiracial. Baseline data for each study group, including age, sex, baseline VAS scores, and the percentage of patients with vomiting, along with their headaches, are listed in Table 1.

Three patients (2 in the ketamine group and 1 in the prochlorperazine group) were withdrawn from the study after receiving the randomized medications. Two patients withdrew from the ketamine arm because of dysphoria, one withdrawing 15 minutes after treatment and one after having received only half of the ketamine dose. The patient in the prochlorperazine group who withdrew developed akathisia and left the ED approximately 15 minutes after receiving the medications. Although there were only 3 adverse events serious enough to require patients to withdraw from the study and there were no “serious adverse events” (those requiring advanced life support measures), several providers in each of the 2 EDs enrolling patients expressed concern that patients receiving ketamine were experiencing severe dysphoria. Because the study was double-blinded, it was uncertain whether these concerns had any merit. We decided that they warranted an unplanned interim analysis, and the study was discontinued.
before enrollment of the goal of 70 patients because the interim analysis highly suggested the superiority of prochlorperazine over ketamine.

In regard to the primary outcome, at 60 minutes, the average VAS pain score decreased an average of 63.5 mm (95% confidence interval [CI] 52.7 to 74.3 mm) in the prochlorperazine group, whereas it decreased 43.5 mm (95% CI 30.2 to 56.8 mm) in the ketamine group. The difference between groups was thus 20.0 mm (95% CI 2.8 to 37.2 mm). A repeated-measures ANOVA demonstrated the difference in pain score improvement between groups to be statistically significant (P = .03). The pretreatment and posttreatment VAS pain scores for each patient at 45 and 60 minutes are depicted in Figure 2.

The dropout sensitivity analysis demonstrated consistency of the superiority of prochlorperazine over ketamine in regard to the primary outcome. When it was assumed that dropouts had excellent outcomes (100% pain relief), the prochlorperazine group still had a higher mean decrease in VAS scores, by 20.2 mm (95% CI 4.0 to 36.5 mm). When it was assumed that the dropouts had terrible outcomes (worsening of pain to a VAS score of 100), the prochlorperazine group still had a higher mean decrease in VAS scores, by 24.8 mm (95% CI 5.0 to 44.6 mm). When it was assumed that the dropouts had neutral outcomes (no change in pain scores), the prochlorperazine group still had a higher mean decrease in VAS scores, by 21.3 mm (95% CI 3.9 to 38.7 mm).

At 45 minutes, the prochlorperazine group had a mean improvement in VAS pain scores of 56.1 mm compared with 38.0 mm in the ketamine group, corresponding to a between-groups difference of 18.1 mm (95% CI 1.0 to 35.2 mm). A comparison of all mean VAS pain scores can be found in Table 2.

Two of the 28 patients in the prochlorperazine group (7.1%) vomited during the data collection period compared with 3 of the 23 patients in the ketamine group (13.0%), corresponding to a difference of 5.9% (95% CI –10.9% to 22.7%) between groups.

Table 1. Basic demographic and clinical characteristics of patients at enrollment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prochlorperazine-Diphenhydramine</th>
<th>Ketamine-Ondansetron</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>37.4 (10.4)</td>
<td>32.3 (10.3)</td>
<td>5.1 (-1.0 to 11.1)</td>
</tr>
<tr>
<td>Women, %</td>
<td>71.40</td>
<td>82.60</td>
<td>-11.2 (-34.0 to 11.6)</td>
</tr>
<tr>
<td>Pain, mm</td>
<td>78.3 (17.7)</td>
<td>77.8 (14.6)</td>
<td>0.5 (-8.9 to 9.9)</td>
</tr>
<tr>
<td>Anxiety, mm</td>
<td>46.1 (38.4)</td>
<td>37.8 (35.7)</td>
<td>8.3 (-12.7 to 29.3)</td>
</tr>
<tr>
<td>Nausea, mm</td>
<td>47.6 (35.2)</td>
<td>47.1 (33.0)</td>
<td>0.5 (-19.3 to 20.4)</td>
</tr>
<tr>
<td>Vomiting, %</td>
<td>57.10</td>
<td>56.50</td>
<td>0.6 (-26.7 to 27.9)</td>
</tr>
</tbody>
</table>

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In total, 8 of 28 patients (28.6%) in the prochlorperazine group and 11 of 23 patients (47.8%) in the ketamine group received rescue medications. Therefore, the difference between groups was 19.2% (95% CI –7.1% to 45.6%).

Three of the 28 patients in the prochlorperazine group (10.7%) developed subjective restlessness compared with 3 of 23 in the ketamine group (13.0%), corresponding to a difference of 2.3% (95% CI –15.6% to 20.2%) between the groups.

One patient in the prochlorperazine group (3.6%) and 2 in the ketamine group (8.7%) were admitted to the hospital, corresponding to a difference of 5.1% (95% CI –8.3% to 18.5%) between groups.

Twenty-four- to 48-hour follow-up was successfully performed for 20 of 28 patients in the prochlorperazine group (71%) and 18 of 23 in the ketamine group (78%). Among patients for whom follow-up was successful, the average satisfaction score was 8.3 (of 10) for prochlorperazine and 4.9 for ketamine. Thus, the mean satisfaction score was 3.4 points higher (95% CI 1.2 to 5.6) for prochlorperazine, a statistically significant result. See Figure 3 and Figure E1 (available online at http://www.annemergmed.com) for details.

On follow-up call, 6 of 20 patients (30%) in the prochlorperazine group were having a headache compared with 9 of 18 in the ketamine group (50%), corresponding to a difference of 20% (95% CI –10.6% to 50.6%) between groups.

Figure 2. Vertical lines depict the pre- and posttreatment pain scores for each patient, sorted by baseline pain scores for 45 (A) and 60 (B) minutes. Box plots (with whiskers representing the upper and lower adjacent values) are depicted for pretreatment, posttreatment, and change scores by group.
Previous data suggest that the minimum clinically significant change in VAS anxiety scores is approximately 10 to 15 mm. During 60 minutes, the average VAS nausea score decreased from 47.6 to 8.7 mm in the prochlorperazine group, and it decreased from 37.8 to 16.6 mm in the ketamine group. Therefore, the average VAS anxiety score decreased 12.5 mm more (95% CI –9.1 to 34.1 mm) in the prochlorperazine group than in the ketamine group.

One previous study found that the minimum clinically significant difference in VAS nausea scores was 22 mm. During 60 minutes, the average VAS nausea score decreased from 47.6 to 8.7 mm in the prochlorperazine group, and it decreased from 47.1 to 24.2 mm in the ketamine group. Therefore, the average VAS nausea score decreased 16.0 mm more (95% CI –5.2 to 37.2 mm) in the prochlorperazine group than in the ketamine group.

LIMITATIONS
This study was limited by convenience sampling because patients could be enrolled only when an ED pharmacist was available. Although the study was performed at 2 different EDs, the sample size was small. We did not reach our goal of 70 patients, and the decision to stop enrollment early weakens our study. We had not planned on performing an interim analysis of the data, but a number of providers at both sites expressed concern that some of the patients receiving ketamine were experiencing extreme dysphoria. As a result, some providers refused to enroll additional patients. These concerns prompted an interim analysis to determine whether there was any validity to these concerns. Given the results of the interim analysis and the concerns expressed by providers, we believed it was best to discontinue the study.

Although our study took great measures to maintain double-blinding, there was a potential for unblinding because many patients exhibited ketamine-specific reactions such as nystagmus and confusion. These reactions likely allowed some providers to guess which medications their patients received, and thus may have allowed providers to develop their concerns that ketamine was causing dysphoria.

We did not formally maintain a screening log of all headache patients in the ED and reasons patients were not

**Table 2. Mean VAS pain scores.**

<table>
<thead>
<tr>
<th>Time, Minutes</th>
<th>Prochlorperazine-Diphenhydramine</th>
<th>Ketamine-Ondansetron</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>78.3</td>
<td>77.8</td>
<td>0.5 (–8.9 to 9.9)</td>
</tr>
<tr>
<td>15</td>
<td>50.9</td>
<td>38.7</td>
<td>12.2 (–6.2 to 30.7)</td>
</tr>
<tr>
<td>Change from 0–15 min</td>
<td>–27.4</td>
<td>–39.1</td>
<td>11.7 (–4.8 to 28.3)</td>
</tr>
<tr>
<td>30</td>
<td>31.8</td>
<td>45.8</td>
<td>–14.1 (–31.1 to 3.0)</td>
</tr>
<tr>
<td>Change from 0–30 min</td>
<td>–46.5</td>
<td>–32.0</td>
<td>–14.6 (–31.2 to 2.0)</td>
</tr>
<tr>
<td>45</td>
<td>22.2</td>
<td>39.8</td>
<td>–17.6 (–35.7 to 0.59)</td>
</tr>
<tr>
<td>Change from 0–45 min</td>
<td>–56.1</td>
<td>–38.0</td>
<td>–18.1 (–35.2 to –1.0)</td>
</tr>
<tr>
<td>60</td>
<td>14.8</td>
<td>34.3</td>
<td>–19.5 (–37.8 to –1.3)</td>
</tr>
<tr>
<td>Change from 0–60 min</td>
<td>–63.5</td>
<td>–43.5</td>
<td>–20.0 (–37.2 to –2.8)</td>
</tr>
</tbody>
</table>

**Figure 3.** Mirrored histogram showing satisfaction scores (from 0 to 10) at 24- to 48-hour follow-up for prochlorperazine-diphenhydramine and ketamine-ondansetron.
sedative for intubation and procedural sedation, some of the aura in patients with migraines with aura. Some evidence supports the use of diphenhydramine with prochlorperazine to reduce akathisia, and most of the physicians in our EDs routinely administer the 2 medicines in combination. Therefore, we decided to make the combination of prochlorperazine and diphenhydramine the standard therapy for our study. The use of ondansetron with ketamine and diphenhydramine with prochlorperazine may have resulted in confounding. In particular, the package insert for ondansetron indicates that the administration of ondansetron may result in a headache. This may have negated some of the potential benefits of ketamine in reducing headache scores.

Finally, approximately a quarter of our patients were lost to follow-up at 24 to 48 hours. This could have resulted in dropout bias and it makes the secondary outcomes from 24 to 48 hours less reliable.

DISCUSSION

To our knowledge, this was the first study to evaluate intravenous ketamine for use in the treatment of benign headaches in the ED. One previous study suggested that subcutaneous ketamine might be beneficial in preventing and treating migraines, and another study found that intranasal ketamine might be useful in reducing the severity of the aura in patients with migraines with aura. Our study is more broadly applicable to the patients treated in the ED.

In addition to ketamine’s well-established use as a sedative for intubation and procedural sedation, some recent literature suggests that ketamine is nearly a panacea, with reported benefits for the treatment of pain, depression, and seizures. Indeed, one recent study found that intravenous ketamine at 0.3 mg/kg was as efficacious as morphine at 0.1 mg/kg. Our study indicates that ketamine is not a first-line medication for headaches, and it suggests that patients often do not like receiving subdissociative-dose intravenous ketamine.

Although the difference in VAS pain scores between groups at 60 minutes did not quite reach our target of 25 mm, there was still a statistically significant greater reduction in pain scores at 45 and 60 minutes for prochlorperazine compared with ketamine. We were able to find statistically significant results despite not reaching our goal sample size because the SD of pain scores was smaller than anticipated. Although the argument could be made that we did not show a clinically significant difference between groups because we did not meet our prespecified target of a 25-mm difference, previous data have defined a clinically important difference in VAS pain scores to be 18 mm, which was reached at 60 minutes. Moreover, nearly every other data point (percentage of patients developing vomiting, percentage of patients requiring rescue medicines, percentage of patients admitted to the hospital, VAS anxiety scores, VAS nausea scores, and percentage of patients having a headache at follow-up) trended toward the superiority of the prochlorperazine group. Even the development of subjective restlessness (which was designed to be an approximate surrogate for akathisia) was slightly more frequent in the ketamine group. Although ketamine is not believed to cause akathisia, it may produce another uncomfortable sensation that a few patients identified as “restlessness.” However, the one patient who withdrew from the prochlorperazine group was documented as having akathisia, so it is likely that she would have said she was restless if she had stayed in the study.

Of particular concern was that the satisfaction scores of the patients in the ketamine group were much lower than those in the prochlorperazine group, with 4 of the patients (of the 18 for whom follow-up was successful) scoring ketamine a zero of 10. This does not include the 2 patients who withdrew from the ketamine group because of dysphoria. The lowest satisfaction score in the prochlorperazine group was a 3.

We did not specifically determine why some of our patients disliked ketamine so strongly, but we hypothesize that some patients do not like the ketamine “high” or “unreality” that seems to occur fairly consistently at 0.3 mg/kg when given by intravenous push. It is possible that satisfaction scores would have been higher if we had used a lower dose (0.1 to 0.2 mg/kg) of intravenous ketamine, but we chose 0.3 mg/kg according to the reported success of a previous study.

One other recent study found that a short infusion of intravenous ketamine during 15 minutes resulted in a lower rate of a sensation of unreality compared with intravenous push. This study had not been published when our study was designed, and the use of ketamine by slow infusion might have resulted in more favorable results for the ketamine group in our study. However, the necessity of an infusion pump provides a practical barrier to the use of ketamine in this manner, and even when a slow infusion was used in this recently published study, 54% of patients still developed a sensation of unreality.

In our study, the only area in which the ketamine group was superior to the prochlorperazine group was pain score at 15 minutes (and this was not statistically significant). This is likely because ketamine has a short half-life, and its maximum effects were observed at 15 minutes. Indeed, at 30...
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minutes, the average VAS pain scores for the ketamine group actually increased compared with the 15-minute scores.

Our study does not suggest that ketamine has no role for patients who present to the ED with benign headaches. The patients in the ketamine group still achieved sizable reductions in pain scores, but our data strongly suggest the superiority of prochlorperazine over ketamine for headaches.

In summary, the combination of prochlorperazine and diphenhydramine appears to be superior to the combination of ketamine and ondansetron for the treatment of benign headaches in the ED. More studies are needed to further assess the efficacy of ketamine as an adjunct to the standard headache therapy.

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**Author contributions:** TZ and MG conceived the study and drafted the article. TZ, MG, CP, JP, and AR designed the trial. TZ, CP, AB, JP, AR, WF, and JMC supervised the conduct of the trial and data collection. TZ, CP, AB, WF, JSS, and JMC undertook recruitment of participating centers and patients and managed the data, including quality control. TZ provided statistical advice on study design and analyzed the data. All authors contributed substantially to article revision. TZ takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**REFERENCES**


Figure E1. Scatter plot demonstrating the relationship between the reduction in VAS pain score (0 to 100 mm) and satisfaction score (0 to 10) at 24- to 48-hour follow-up.