Intranasal Lidocaine in Acute Treatment of Migraine: A Randomized Controlled Trial

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Study objective: The study aims to evaluate the efficacy and safety of intranasal lidocaine administration for migraine treatment.

Methods: This single-center, double-blind, randomized, controlled trial was conducted in a tertiary care emergency department. Included patients met the migraine criteria of the International Headache Society. Patients were randomized to intranasal lidocaine or saline solution; all participants received 10 mg of intravenous metoclopramide. Patient pain intensity was assessed with an 11-point numeric rating scale score. The primary outcome measure was the change in pain scores at 15 minutes; secondary outcomes were changes in pain intensity after pain onset and need for rescue medication.

Results: Patients (n=162) were randomized into 2 groups with similar baseline migraine characteristics and numeric rating scale scores. The median reduction in numeric rating scale score at 15 minutes was 3 (interquartile range [IQR] 2 to 5) for the lidocaine group and 2 (IQR 1 to 4) for the saline solution group (median difference = 1.0; 95% confidence interval 0.1 to 2.1). The reduction in pain score at 30 minutes was 4 (IQR 3 to 7) for the lidocaine group and 5 (IQR 2 to 7) for the saline solution group (median difference = 1.0; 95% confidence interval 0.1 to 2.1). Need for rescue medication did not differ between the groups, and local irritation was the most common adverse event in the lidocaine group.

Conclusion: Although intranasal lidocaine was found no more efficacious than normal saline solution in our study, future studies should focus on patients who present earlier after headache onset. [Ann Emerg Med. 2016; -:1-9.]

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

INTRODUCTION

Background

Headache is a frequent presentation to the emergency department (ED). The statistics on the prevalence and burden of headache disorders in the United States indicate that headache is the fourth leading cause of visits to the ED, accounting for 3.1% of all visits. In all ambulatory care settings, migraine accounts for 0.5% of all presentations.

Current meta-analyses and systematic reviews reveal that abortive treatment of migraine consists of numerous medications, including triptans, nonsteroidal anti-inflammatory drugs, acetaminophen, aspirin, and antiemetics. These medications are widely used in the acute treatment of migraine, but uncertainty remains in regard to the comparative efficacy of presently available drugs. Intranasal administration is now viewed as effective in the treatment of acute migraine because of its rapid effectiveness, lack of need for an injection site, and rare adverse reactions.

Importance

The entire pathophysiologic mechanism of migraine and its therapeutic pathways is not clearly understood. Activation of the trigeminovascular system and central brain sites is one of the suggested mechanisms involved in migraine pathogenesis. The sphenopalatine ganglion may have a pivotal role in the cranial parasympathetic outflow through the release of neuropeptides and may contribute to migraine pain by activating or sensitizing intracranial nociceptors. Reducing this parasympathetic outflow to brain sites by blocking the sphenopalatine ganglion was previously studied as a migraine treatment using different application methods. The sphenopalatine ganglion is located in an accessible region through both nostrils; thus, local
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MATERIALS AND METHODS

Study Design and Setting

This single-center, prospective, double-blind, placebo-controlled, randomized trial was carried out with patients with acute migraine attack. Results are reported according to the Consolidated Standards of Reporting Trials guideline. The study was conducted from January to October 2014 in an academic ED with an annual census of approximately 45,000 patients per year. The efficacy and safety of intranasal lidocaine were compared with those of intranasal normal saline solution in the acute treatment of migraine. This study was performed in accordance with the tenets of the Declaration of Helsinki, and institutional review board approval was obtained. Although this trial was not registered in a clinical trial database, the study protocol was previously declared to the institutional review board. The patients were asked to sign an informed consent form before their enrollment in the study.

Selection of Participants

Patients older than 18 years who presented to the ED with acute headache and who met International Headache Society criteria for migraine were included in the study. Patients were excluded if they refused to give informed consent; had received any analgesic drug within 6 hours before the ED visit; had any hemodynamic abnormality, documented allergy to the study drugs, or meningismus symptoms; or were pregnant. Because most patients with pain do not receive any medication before an ED visit in Turkey, we specified any analgesic use within 6 hours as an exclusion criterion.

Interventions

The randomization schedule was generated with a computer-based program (http://www.randomization.com). Eligible patients were randomly assigned in a 1:1 ratio to receive either a single intranasal dose of 10% lidocaine (Xylocaine 10% Pump Spray; Astra Zeneca Ilaç San., İstanbul, Turkey) (1 puff = 10 mg) or normal saline solution (1 puff of intranasal 0.9% saline solution spray). The placebo vial was prepared beforehand by a study nurse, and it was identical in appearance and color to the drug vial. If the patient had a unilateral headache, the study drug was administered as 1 puff in the ipsilateral nostril, in accordance with the Barre method. Briefly, the patient was asked to lie supine, with the head dangling from the edge of the bed. The patient’s head was turned 30 degrees toward the side with the headache, the application was performed with the patient in this position, and the patient was asked to hold the position for 30 seconds (Figure 1). If

Editor’s Capsule Summary

What is already known on this topic

Intranasal lidocaine may reduce pain from migraine headache.

What question this study addressed

In migraine patients receiving protocol-based analgesic care, did intranasal lidocaine reduce pain?

What this study adds to our knowledge

In this randomized clinical trial of patients arriving between 5 and 7 hours after onset, intranasal lidocaine performed similarly to placebo in reducing pain while causing additional local irritation.

How this is relevant to clinical practice

Better treatments are needed for the emergency department management of headache. Clinical trials of intranasal lidocaine are conflicting, but the treatment has biologic promise.

Research we would like to see

A larger randomized clinical trial focused on patients arriving earlier after headache onset.

anesthetics may affect the ganglion and prevent its signal transmission.

The parasympathetic outflow theory suggests that early interventions affecting the sphenopalatine ganglion might be more beneficial when delivered through an intranasal route in early-presenting migraineurs. In contrast, late presenters might not derive the same benefits if vasodilation and the effects on deep brain tissues involved in migraine attack have already occurred because peripheral nerve blocks might have no effect on pain control.

The efficacy of intranasal lidocaine versus placebo was evaluated in 3 randomized trials of migraine headache. However, drug administration methods and outcome measures were different in each study and the results were conflicting.

Goals of This Investigation

The aim of the present trial was to investigate the efficacy and safety of an intranasal 10% lidocaine treatment compared with placebo for patients presenting to the ED with migraine headache and receiving intravenous metoclopramide as part of standard care. Also, we aimed to evaluate the relationship between pain onset and the efficacy of lidocaine.
the headache was bilateral, the application was performed in both nostrils (1 puff in each), with the provider turning the head 30 degrees to the left and right. All randomized patients received intravenous metoclopramide (10 mg in 100 mL normal saline solution) (Primsel; Osel İlaç San., İstanbul, Turkey) with the nasal application of the study drug.

Methods of Measurement

All ED patients were assessed for migraine headache at presentation according to International Headache Society criteria. After selection of an eligible patient by a senior emergency medicine resident, he or she was asked to sign an informed consent form to participate in the study and was assigned to the intranasal lidocaine or intranasal saline solution group. The enrollment period continued all day, and senior residents received training about the study protocol and International Headache Society criteria before the study. The randomization sequence was performed by having the study nurse hand the 10% lidocaine or saline solution spray to the physician, who was blinded to the randomization schedule. The other nurses and the patient were also blinded to the administered treatment.

Each patient allocated to the treatment groups was asked by the physician to describe the intensity of the headache, using an 11-point numeric rating scale score (10 = worst possible headache, 0 = no headache). The study drug was then administered by the physician intranasally, and 2 additional scores were recorded at 15 and 30 minutes. Patients who verbally expressed continuing headache at 30 minutes received intravenous fentanyl at 1 µg/kg as a rescue medication. The implementing physicians had been previously taught the Barre method.

Outcome Measures

The primary outcome measure was defined as absolute change in pain scores between the groups at 0 to 15 minutes. The secondary outcome measures were the relationship between pain onset time and treatment response, any adverse event, and the need for rescue analgesics in the ED. Other secondary outcomes, including patient satisfaction, recurrent ED visits, and relief of pain, were assessed by telephone follow-up 24 to 72 hours after discharge.

Primary Data Analysis

All statistical analyses were performed with SPSS (version 15.0; SPSS Inc., Chicago, IL) and Stata/SE (version 12.0; StataCorp, College Station, TX). Intention-to-treat analysis was performed for all randomized patients; missing patient responses were accepted as the last observation carried forward. Thus, last numeric rating scale scores (first or second measurements) were regarded as following scores for individuals who left the study at any time.

The primary outcome, which was the median between-group change in numeric rating scale score at the 15th minute, was assessed with the Mann-Whitney U test, and median differences were expressed with 95% confidence intervals (CIs). The difference of medians was calculated with the method proposed by Bonett and Price. All statistical analyses were 2 sided. We also performed a literature review and a short meta-analysis to quantify how this investigation updated our knowledge (Medcalc Statistiscal Software; version 16.8; Medcalc, Ostend, Belgium). Studies were included in the meta-analysis if they reported the exact proportions of patients with treatment benefit. Random and fixed effects were calculated by means of using previous trials and expressed with odds ratios. In the meta-analysis, an improved outcome was defined as a 50% reduction in symptom severity.

The sample size was estimated with G-Power for Mac OS X (version 3.1.9.2; Universität Düsseldorf, Germany).
Our goal was power to detect a 13-mm difference on the visual analog scale according to the study by Todd and Funk. We assumed that the SD of our data would be 2.8, according to the migraine trial by Friedman et al. Thus, assuming a 2-sided \( \alpha = .05 \), we anticipated a sample size of 148 patients to achieve 80% power. An additional 10% (\( n = 14 \) individuals) was included to account for potential protocol violations. We accounted for missing data at the 15- and 30-minute measurements (because of withdrawal) by counting these outcomes as the last observation carried forward.

**RESULTS**

During the study period, 1,383 patients were screened for migraine headache. A total of 193 patients were assessed for eligibility according to the International Headache Society criteria for migraine, and 31 patients were excluded from the study (Figure 2). Ultimately, 162 patients were included in the randomization (81 for each treatment arm). Of these, 3 subjects in the lidocaine group and 4 in the normal saline solution group discontinued after baseline measurement. Also, 6 subjects in the lidocaine group and 1 in the normal saline solution group discontinued after the 15-minute measurement.

**Characteristics of Study Subjects**

The lidocaine and saline solution groups were similar in age and migraine characteristics (Table 1). There were more male patients in the lidocaine group than the saline solution group (30.9% versus 14.8%). The median time to ED presentation was 5 hours from the beginning of pain onset for the lidocaine group (interquartile range [IQR] 2 to 12) and 7 hours for the saline solution group (IQR 3 to 14).

**Main Results**

The baseline numeric rating scale scores were similar for both treatment groups. The primary outcome measure (ie, the median reduction in numeric rating scale score at 15 minutes) was 3 (IQR 2 to 5) for the lidocaine group and 2 (IQR 1 to 4) for the saline solution group (median difference \( = 1.0 \) [95% CI \( -0.1 \) to 2.1]). The reduction in pain score at 30 minutes was 4 (IQR 3 to 7) for the lidocaine group and 5 (IQR 2 to 7) for the saline solution group (median difference \( = -1.0 \) [95% CI \( -2.1 \) to 0.1]) (Table 2). The numeric rating scale changes at 15 and 30 minutes in the lidocaine and saline solution groups are shown in Figure 3A and B, respectively. A subgroup analysis was performed for baseline sex differences. Median pain reduction for male patients was \( -1.0 \) points.
A short meta-analysis was conducted according to the studies by Maizels and Geiger\textsuperscript{10} and Blanda et al.\textsuperscript{11} together with our results (Figure 5). The study by Mohammadkarimi et al.\textsuperscript{15} was excluded from the analysis because they did not reveal the exact number of patients who benefited from the treatment. At least 50% reduction in symptom severity was accepted as treatment benefit in the studies. The results of the meta-analysis revealed that intranasal lidocaine was effective in acute migraine headaches when the results of the 3 trials were pooled (odds ratio 1.73; 95% CI 1.07 to 2.80; $I^2$=67\%) (Table 4), although there was substantial heterogeneity across the trials. In addition, the effect was no longer significant when a random-effects meta-analytic model was applied.

**LIMITATIONS**

The present study has several limitations: First, intranasal lidocaine is more irritating than intranasal saline solution; thus, the lidocaine group experienced this discomfort, which may have interfered with blinding of the participants in the lidocaine arm. However, this is an inevitable problem in studies involving local anesthetics because they produced a burning sensation in mucosal tissues.

Second, the comparisons for median numeric rating scale changes between the lidocaine and saline solution groups across different intervals were secondary outcomes for the present study, and the results probably did not reach an actual power sufficient to claim an accurate interval for implementation of intranasal lidocaine. Future studies involving only early-presenting migraineurs may add valuable information about those who might particularly benefit from intranasal treatment.

Third, both treatment groups received intravenous metoclopramide, and this trial cannot make any recommendation in regard to use of intranasal lidocaine without metoclopramide. In addition, our meta-analysis demonstrated a high degree of statistical heterogeneity across studies, and confidence in the conclusion that intranasal lidocaine was effective was different according to whether a fixed- or random-effects approach was used.

### Table 2. Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lidocaine 10%, n=81</th>
<th>Normal Saline Solution, n=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (SD), y</td>
<td>36 (12)</td>
<td>35 (11)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>25 (30.9)</td>
<td>12 (14.8)</td>
</tr>
<tr>
<td>History of migraine, No. (%)</td>
<td>76 (93.8)</td>
<td>67 (82.7)</td>
</tr>
<tr>
<td>Pain onset, median (IQR), h</td>
<td>5 (2–12)</td>
<td>7 (3–14)</td>
</tr>
<tr>
<td>Unilateral headache, No. (%)</td>
<td>45 (55.6)</td>
<td>33 (40.7)</td>
</tr>
<tr>
<td>Throbbing pain, No. (%)</td>
<td>56 (69.1)</td>
<td>64 (79.0)</td>
</tr>
<tr>
<td>Nausea and vomiting, No. (%)</td>
<td>62 (76.5)</td>
<td>70 (86.4)</td>
</tr>
<tr>
<td>Photophobia, No. (%)</td>
<td>73 (90.1)</td>
<td>73 (90.1)</td>
</tr>
<tr>
<td>Phonophobia, No. (%)</td>
<td>67 (82.7)</td>
<td>70 (86.4)</td>
</tr>
<tr>
<td>Aura, No. (%)</td>
<td>23 (28.4)</td>
<td>20 (24.7)</td>
</tr>
</tbody>
</table>

(95% CI –4.1 points to 2.1 points); female patients had a median pain reduction of 0.0 points (95% CI –1.1 points to 1.1 points) at 15 minutes.

The secondary outcome measure (ie, the efficacy of the lidocaine treatment) was compared with that of normal saline solution according to pain onset time. No significant difference was found between the groups (Figure 4).

A total of 10 patients in the lidocaine group (12.3%) and 14 in the saline solution group (17.3%) required the rescue drug at 30 minutes. No serious adverse events, including anaphylaxis, akathisia, dystonia, and seizure, were reported in either group. Only 1 patient in the lidocaine group experienced palpitations after the drug was implemented intranasally, which resolved after an observation period (sinus tachycardia). The most prominent adverse event was local irritation in the application area; 40 patients in lidocaine group (49.4%) reported a transient irritation in their noses, whereas 9 in the saline solution group (11.1%) experienced it, a statistically significant difference (difference 38.3%; 95% CI 23.9% to 51.1%).

A telephone survey was conducted among randomized patients between 24 and 72 hours after discharge. This survey was configured with dichotomous answers assessing continuing pain and the need for analgesic use after discharge, ED revisits for any reason, and the patients’ overall satisfaction with the treatment implemented in the ED (Table 3). At this interval, 81% of the patients in both groups (n=66 per group) could be reached by telephone.
Fourth, our study was conducted in a single center with a relatively small sample size, which limits the generalizability of our findings. Pain perception and pain limits could vary among different communities; thus, the results should be evaluated from this viewpoint.

DISCUSSION

Acute migraine is common in the ED, and treatment by means of the intranasal route has gained popularity because of its rapid application and relatively few adverse effects. Our study suggests that intranasal 10% lidocaine is no more effective than normal saline solution at the intervals studied; this lack of effect holds true when the time between pain onset and presentation is taken into account. In our study, no statistically significant difference was observed between the groups in regard to the need for rescue medication or the occurrence of any adverse events; however, patients in the lidocaine group experienced more nasal local irritation.

The current literature reveals conflicting results for intranasal lidocaine administration in migraine patients; different application methods and doses may be responsible for the contradictory findings for this local treatment. Intranasal lidocaine was first investigated by Maizels and Geiger as a treatment for migraine attacks in a randomized controlled trial in 1999. The application was performed by administration of 0.5 mL of 4% lidocaine to the side affected by headache, using the Barre method. The absolute pain reduction in the lidocaine group was 35.8% at 15 minutes compared with 6.5% in the placebo group.

A later randomized, double-blinded, controlled trial conducted by Blanda et al in 2001 treated 49 migraine patients with lidocaine or a placebo. In their trial, all patients received 10 mg prochlorperazine intravenously. The lidocaine group (n=27) received 1 mL of 4% lidocaine and the placebo group (n=22) received 1 mL of saline solution; both treatments were administered intranasally with the Barre method. The primary outcome was established as a 50% visual analog scale score reduction at 5 minutes, and a 6.2% difference (95% CI –11.2 to 23.6) in absolute pain reduction was found between the 2 groups at 5 minutes. The results at 15 and 30 minutes remained similar between the groups. In 2014, Mohammadkarimi

**Table 3.** Results of the telephone survey conducted 24 to 72 hours after discharge.

<table>
<thead>
<tr>
<th>Secondary Outcome Measures, No. (%)</th>
<th>Lidocaine 10%, n = 66</th>
<th>Normal Saline Solution, n = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain after discharge</td>
<td>32 (48.5)</td>
<td>22 (33.3)</td>
</tr>
<tr>
<td>Need for analgesics after presentation</td>
<td>38 (57.6)</td>
<td>40 (60.6)</td>
</tr>
<tr>
<td>ED revisit</td>
<td>9 (13.6)</td>
<td>4 (6.1)</td>
</tr>
<tr>
<td>Overall satisfaction from implemented treatment</td>
<td>40 (60.6)</td>
<td>54 (81.8)</td>
</tr>
</tbody>
</table>

**Figure 3.** The NRS changes on the waterfall plots at the 15th minute (A) and 30th minute (B). A colored circle on the gray line means the value was unchanged between pre and post. A black circle means the post value was not recorded.

**Figure 4.** The boxplot for the efficacy of the lidocaine treatment and normal saline based on pain onset time (0 to 30th minute). The N is the number of subjects represented in each time period.
et al\textsuperscript{15} carried out a randomized, double-blinded, controlled trial with ED patients with undifferentiated headaches. A statistically significant visual analog scale score reduction was observed in patients treated intranasally with 10\% lidocaine compared with a placebo 15 minutes after administration.

Previously, 2 trials had conflicting results about using intranasal lidocaine in migraine headaches.\textsuperscript{10,11} In the meta-analysis, adding our results still favors using this drug in the acute treatment of migraine headaches. However, these studies were heterogenous by means of application methods, the amount of administered drug, and outcome measures.

Sphenopalatine ganglion blockage using local anesthetics has also increased in popularity in recent years for the acute treatment of headaches. In 2003, Yarnitsky et al\textsuperscript{12} investigated parasympathetic blockage using 2\% viscous lidocaine in patients with headache and found that cranial parasympathetic outflow contributed to migraine pain by activating or sensitizing intracranial nociceptors. A local anesthetic applied to the sphenopalatine ganglion before the central sensitization occurred was suggested as potentially useful for the acute treatment of migraine. However, according to this theory, sphenopalatine ganglion blockage would be ineffective after central sensitization had occurred and deep brain tissues were involved. More recently, Schaffer et al\textsuperscript{13} carried out a similar study using bupivacaine for sphenopalatine ganglion blockage in patients with acute anterior- and global-based headaches and found no difference in headache relief between the bupivacaine and normal saline solution groups 15 minutes after administration (absolute risk reduction 7.5\% [95\% CI –13\% to 27.1\%]). However, as a secondary outcome they found that more patients in the bupivacaine group were headache free (24.7\% difference; 95\% CI 2.6\% to 43.6\%) at 24 hours. We also found that more patients were pain free at 24 to 72 hours after intranasal lidocaine administration (48.5\% versus 33.3\%), although no statistically significant difference was observed between the 2 groups during the ED phase of the study. A recent retrospective study by Mandato et al\textsuperscript{21} of patients with chronic headache found through image-guided sphenopalatine ganglion block that a visual analog scale score reduction was observed among patients with migraine and cluster headache at the first and following days (36\% at day 30).

An argument can be made that the success of an intranasal sphenopalatine ganglion blockage may vary, depending on the application time. In our study, the patients treated soon after pain onset seemed to benefit from the implemented treatment; however, this effect disappeared after several hours. The results of the study by Schaffer et al\textsuperscript{13} and of our study revealed that a treatment for sphenopalatine ganglion blockage administered in the ED decreased the pain after 24 hours despite the lack of an observed effect between the 2 groups while the patients were in the ED. Therefore, a reasonable conclusion is that administration of intranasal lidocaine in the ED could help prevent potential parasympathetic outflow in these patients after 24 hours.

\textbf{Figure 5.} Meta-analysis of the studies of intranasal lidocaine in acute migraine treatment.

\textbf{Table 4.} Meta-analysis with and without the current investigation for adjusted odds ratios.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Lidocaine 10%, Treatment Benefit/Total, n</th>
<th>Normal Saline Solution, Treatment Benefit/Total, n</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maizels and Geiger,\textsuperscript{10} 1999</td>
<td>34/95</td>
<td>8/62</td>
<td>3.76 (1.60–8.83)</td>
</tr>
<tr>
<td>Blanda et al,\textsuperscript{11} 2001</td>
<td>2/27</td>
<td>3/22</td>
<td>0.51 (0.08–3.34)</td>
</tr>
<tr>
<td>Overall (without the current study)</td>
<td>36/122</td>
<td>11/84</td>
<td>2.25 (1.22–4.17)</td>
</tr>
<tr>
<td>Current study</td>
<td>56/81</td>
<td>53/81</td>
<td>1.18 (0.61–2.28)</td>
</tr>
<tr>
<td>Overall (with the current study), fixed effects</td>
<td>92/203</td>
<td>64/165</td>
<td>1.73 (1.07–2.80)</td>
</tr>
<tr>
<td>Overall (with the current study), random effects</td>
<td>92/203</td>
<td>64/165</td>
<td>1.58 (0.57–4.32)</td>
</tr>
</tbody>
</table>

\textit{OR}, Odds ratio.
Lidocaine appeared to have a good safety profile in our study because the most common adverse reaction was local irritation (49.4%). Similarly, Maizels and Geiger\(^{10}\) reported local irritation (82%), numbness in the throat (13%), nausea (11%), and dizziness (5%) as adverse effects experienced by their lidocaine group. Blanda et al\(^{11}\) reported no adverse events after intranasal lidocaine use in their population. No extrapyramidal adverse effects were observed during the study period, which could be related to the slow infusion rate of the intravenous metoclopamide.

In our study, any analgesic drug use within 6 hours was specified as an exclusion criterion. Although this interval seems long for any patient presenting with pain, the number of annual ED visits exceeds total inhabitants in Turkey, and many patients do not receive any analgesics before coming to the ED.

In conclusion, intranasal lidocaine showed no enhanced efficacy compared with normal saline solution in patients with acute migraine attack in our study; however, in the context of previous knowledge, our results may favor using lidocaine in this setting. Also, the effect of lidocaine may be different in early-presenting migraineurs, which can be evaluated in future studies. The most common adverse reaction after lidocaine use was local irritation, and no serious adverse events were encountered in our population. In the present study, local irritation could be a confounding factor in comparisons of the overall satisfaction of the study drugs. Consequently, intranasal lidocaine treatment of migraine patients in the ED may decrease headache intensity, and this effect may be related to decreased neuropeptide release.

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**Author contributions:** NA and NOD conceived the study and designed the trial. NA, CA, and LEA supervised the conduct of the trial and data collection. NOD and MP provided statistical advice on study design and analyzed the data. NOD, EY, and SY drafted the article, and all authors contributed substantially to its revision. NOD 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**


