Lidocaine infusions for refractory chronic migraine: a retrospective analysis

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ABSTRACT

Introduction Patients with refractory chronic migraine have poor quality of life. Intravenous infusions are indicated to rapidly 'break the cycle' of pain. Lidocaine infusions may be effective but evidence is limited.

Methods The records of 832 hospital admissions involving continuous multiday lidocaine infusions for migraine were reviewed. All patients met criteria for refractory chronic migraine. During hospitalization, patients received additional migraine medications including ketorolac, magnesium, dihydroergotamine, methylprednisolone, and neuroleptics. The primary outcome was change in headache pain from baseline to hospital discharge. Secondary outcomes measured at the post-discharge office visit (25–65 days after treatment) included headache pain and the number of headache days, and percentage of sustained responders. Percentage of acute responders, plasma lidocaine levels, and adverse drug effects were also determined.

Results In total, 609 patient admissions met criteria. The mean age was 46±14 years; 81.1% were female. Median pain rating decreased from baseline of 7.0 (5.0–8.0) to 1.0 (0.0–3.0) at end of hospitalization ($p<0.001$); 87.8% of patients were acute responders. Average pain (N=261) remained below baseline at office visit 1 (5.5 (4.0–7.0); $p<0.001$). Forty-three percent of patients were sustained responders at 1 month. Headache days (N=266) decreased from 26.8±3.9 at baseline to 22.5±8.3 at the post-discharge office visit ($p<0.001$). Nausea and vomiting were the most common adverse drug effects and all were mild.

Conclusion Lidocaine infusions may be associated with short-term and medium-term pain relief in refractory chronic migraine. Prospective studies should confirm these results.

Key messages

What is already known on this topic

⇒ Refractory chronic migraine is very difficult to treat and intravenous infusions are recommended when other treatments have failed. Lidocaine infusions have been suggested as a possible treatment but existing studies are limited.

What this study adds

⇒ In this retrospective cohort study, the authors demonstrated acute and subacute improvement in refractory chronic migraine pain in patients who were hospitalized and received lidocaine infusions continuously for several days.

How this study might affect research, practice, or policy

⇒ This study provides a rational basis for performing a randomized controlled trial to evaluate lidocaine infusions as an effective treatment for refractory chronic migraine.

INTRODUCTION

Chronic migraine is less common than episodic migraine but is associated with a higher disease burden and cost, and has a global prevalence between 0.9% and 2.2%.[1] To be diagnosed with chronic migraine according to the International Classification of Headache Disorders, third edition (ICHD-3), patients must have ≥15 headache days per month for ≥3 months, in which ≥8 days of the month meet criteria for migraine with or without aura or respond to treatment specifically for migraine.[2] Though definitions vary, refractory chronic migraine (rCM) has been defined as the failure of all available preventives and presence of at least 8 debilitating headache days per month for at least 6 consecutive months.[3] For these patients, inpatient hospitalization for treatment with multiday intravenous infusions is indicated.

One treatment that has been suggested in the population with rCM is a continuous multiday lidocaine infusion. The exact mechanism of action of intravenous lidocaine in treating rCM is unknown, but some experts have suggested that its central anti-nociceptive, anti-hyperalgesic, and anti-inflammatory effects play a key role.[4] Few studies have evaluated lidocaine infusions for rCM beyond the immediate post-treatment period. The primary objective of this study was to assess the change in pain from baseline to hospital discharge after receiving a continuous lidocaine infusion and aggressive inpatient treatment. Secondary objectives included pain at 1 month, change in number of headache days from baseline to 1 month, incidence of treatment-limiting adverse drug effects (ADEs), acute and sustained responder rates, and lidocaine plasma levels.

METHODS

The electronic medical record (EMR; Epic) was queried for all patients with rCM hospitalized from

April 1, 2017 through April 1, 2020 to the Jefferson Inpatient Headache Unit in Philadelphia, Pennsylvania, USA for inpatient continuous infusion with lidocaine. While patients with rCM are admitted for aggressive inpatient treatment and lidocaine is not mandatory, few patients (<1%) are admitted who do not receive lidocaine during their first admission. Only those who received lidocaine were included in this study. This study was an analysis of consecutive patients treated during this time period. All patients met the ICHD-3 criteria for chronic migraine and the European Headache Federation criteria for rCM, which includes failure or contraindication to at least one agent from each of the seven available preventative medication classes and suffering from at least 8 debilitating headache days per month for at least 6 consecutive months.[3] All hospital admissions occurred at the same location and their duration was planned for approximately 5–7 days based on clinical experience but in some cases was shorter or longer based on clinical factors. Data were collected from the baseline pretreatment interview at time of admission, inpatient treatment, and first post-discharge office visit. Data that were collected included: demographics; current, average, and worst pain in the past month; preventive migraine medications taken on outpatient basis; inpatient medications; plasma lidocaine levels and associated pain ratings; lidocaine infusion rates; ADEs associated with lidocaine infusion rate decreases or early discontinuation; and number of headache days in the previous month. It was determined a priori that any patient admission without both a baseline current pain rating and a discharge pain rating would be excluded from analyses.

Treatment protocol

Preventive medications (except mexiletine) taken at home were generally continued during admission. Lidocaine infusion was started at 1 mg/min and titrated to a maximum of 4 mg/min based on daily plasma levels, pain response, and tolerability. Plasma levels greater than 5 µg/mL or intolerable ADEs led to a decrease or cessation of lidocaine infusion. Lidocaine infusions were titrated based on clinical response as well as presence of ADEs and the protocol was flexible to allow for clinical judgment. Patients were placed on continuous ECG monitoring (telemetry) and treatment was continued until patients achieved a significant decrease in pain level, freedom from pain for 12–24 hours, or experienced intolerable ADEs. Patients were also given scheduled intravenous ketorolac, dihydroergotamine, methylprednisolone, magnesium, and neuroleptics (promethazine, prochlorperazine, chlorpromazine, haloperidol, or metoclopramide) throughout the admission unless a known contraindication or intolerance existed.

Hospital discharge criteria included being pain free (pain rating of 0/10) for 12–24 hours, achieving a pain level that the patient stated as allowing him or her to have improved function, or having minimal response to therapy by hospital day 5. These criteria were not strictly applied, however, and some patients were permitted to have hospitalization for additional days if pain was slowly but steadily improving.

Pain, lidocaine, and ADE assessments

Pain ratings were assessed by the medical providers at least once daily during treatment. Pain ratings were assessed by nurses, nurse practitioners, or physicians during office visits. All headache pain ratings were measured on a 0–10 Numerical Rating Scale (NRS) in which 0=no pain and 10=worst pain imaginable. Consistent with established definitions, a 'headache day' was defined as a day for which the patient reported moderate or severe pain for at least 4 hours[5] and the number of headache days that occurred during the previous 30 days before office visit 1 was recorded. At baseline and both post-discharge office visits, patients were asked to state the number of headache days they had experienced during the previous 28 days as well as their current, worst daily, and average daily pain ratings on a 0–10 NRS. However, not all providers consistently documented all of these outcomes, resulting in some missing data.

Venous plasma lidocaine levels were monitored each morning starting on the second day of hospitalization. All changes in lidocaine infusion rate were recorded. The lidocaine infusion rate and pain rating closest to the time the plasma level was drawn were also recorded and these were used for correlation analyses.

The primary outcome was the change in current pain rating from baseline to end of hospitalization. Secondary outcomes included the change in the number of headache days from baseline to the post-discharge office visit, changes in pain rating (average and current) from baseline to the post-discharge office visit, and the relationships between pain ratings and plasma lidocaine levels, pain ratings and lidocaine infusion rates, and the change in current pain ratings and total lidocaine dose over the admission. Acute and sustained responder rates were also determined. An acute responder was defined as a patient with a decrease in current pain rating of 2 or more points (0–10 NRS) from baseline prior to treatment to end of treatment according to a previously published definition.[6] A sustained responder was defined as an acute responder who maintained a decrease of 2 or more points as measured by average pain versus baseline at the post-discharge office visit. Differences in pain outcomes based on receipt of other inpatient medications besides lidocaine (ketorolac, dihydroergotamine, neuroleptics, magnesium, and methylprednisolone) were also determined. Based on the recommendation of the neurologist headache experts (CGL and SDS), only post-discharge office visits that occurred between 25 and 65 days were included in analyses to eliminate inclusion of visits that occurred too early or too late (ie, a few days after discharge or many months after discharge) to allow for meaningful analysis.

Patients were assessed daily for ADEs. Only ADEs that were significant enough to result in a lidocaine rate change or discontinuation were recorded for the study.

Statistical analysis

Demographic variables (age, sex, race) are reported as means±SD or percentages. For those variables, the Mann-Whitney U and Pearson X^2 tests were used to compare patients with single admission with those with repeat admissions for lidocaine treatment. Changes in headache days and pain ratings from baseline to the various time points were analyzed using the Wilcoxon signed-rank test. Subgroup analyses were performed for repeat admissions with statistical significance determined using the Mann-Whitney U test. Single point means were determined for lidocaine plasma levels, pain ratings, and lidocaine infusion rates. Correlations between pain ratings and plasma levels, pain ratings and lidocaine infusion rates, and change in pain and total lidocaine dose were determined using Spearman's r correlation coefficient according to the technique described by Bland and Altman.[7] Co-administered medications during hospitalization were coded as binary variables (received or not received) and the effect on change in pain (baseline to end of admission) from each administered medication was compared between groups using the Mann-Whitney U test. Normally distributed continuous data are expressed as means±SD and not

Table 1 Preventive outpatient migraine medications taken at time of hospitalization

Medication class	Number of patients
Anti-convulsants, n (%)*	222/609 (36.5)
Anti-depressants, n (%)†	254/609 (41.7)
Beta-blockers, n (%)‡	99/609 (16.3)
Botulinum toxin, n (%)	212/609 (34.8)
CGRP antagonists, n (%)§	349/609 (57.3)

*Anti-convulsants included valproic acid, topiramate, oxcarbazepine, carbamazepine, and lamotrigine.
†Anti-depressants included duloxetine, amitriptyline, venlafaxine, and nortriptyline.
‡Beta-blockers included metoprolol, nadolol, propranolol, and timolol.
§CGRP antagonists included erenumab, fremanezumab, galcanezumab, and eptinezumab.
CGRP, calcitonin gene-related peptide.

Table 2 Pain outcomes at baseline and the post-discharge office visit (25–65 days after discharge)

	Baseline pretreatment	Post-discharge office visit	P value*
Median current pain (IQR)†	7.0 (5.0–8.0) N=609	5.0 (3.0–7.0) N=79	<0.001
Median average pain (IQR)	7.0 (6.0–8.0) N=498	5.5 (4.0–7.0) N=261	<0.001
Mean headache days in prior month (SD)	26.8 (3.9) N=550	22.5 (8.3) N=266	<0.001

*Pain data analyzed using the Wilcoxon signed-rank test.
†Pain ratings were assessed using a 0–10 Numerical Rating Scale where 0=no pain and 10=worst pain imaginable.
N, sample size.

normally distributed data are expressed as median (IQR). Data were analyzed using SPSS V.28 and GraphPad Prism V.9.0. A p value of <0.05 was considered statistically significant.

RESULTS

Demographics and inpatient medications

The initial EMR query returned 832 patient admissions. After exclusions based on missing baseline current pain or discharge pain, 609 patient admissions in 537 unique patients remained for analysis (online supplemental file 1); 72 admissions were repeat admissions. The mean age of the 537 patients was 46±14 years old, 81.1% were female, and the mean body mass index was 29.8±8.0 kg/m^2. The breakdown of race was 89.8% white, 6.4% African American, and 2.0% Hispanic; the remainder were either listed as 'other' or not reported. The mean number of days in between admissions for repeat admissions was 215.2±108.7. The range was 33–506 days. The mean duration of treatment for all admissions was 5.2±1.6 days.

Preventive migraine medications taken at the time of hospital admission are shown in table 1. In addition to lidocaine, patients received the following intravenous medications during hospitalization: ketorolac (513 of 609, 84.2%), dihydroergotamine (556 of 609, 91.3%), methylprednisolone (328 of 609, 53.9%), magnesium (596 of 609, 97.9%), and neuroleptics (promethazine, prochlorperazine, chlorpromazine, haloperidol, or metoclopramide) (585 of 609, 96.1%).

Pain outcomes

For the primary outcome of the change from baseline current pain to discharge current pain, pain ratings for all 609 admissions decreased from 7.0 (5.0–8.0) on admission to 1.0 (0.0–3.0) at discharge (p<0.001). For secondary outcomes, average pain at the post-discharge office visit was lower than baseline pain (5.5 (4.0–7.0) vs 7.0 (5.0–8.0), p<0.001). The number of headache days (N=266) decreased from 26.8±3.9 at baseline to 22.5±8.3 at the post-discharge office visit (p<0.001). On subgroup analysis of patients who had received lidocaine previously (N=244), pain ratings decreased from 7.0 (6.0–8.5) at time of admission to 1.0 (0.0–3.0) at discharge (p<0.001). There was a statistically significant but clinically unimportant difference between the number of headache days at baseline between this subgroup who had received lidocaine and patients who had not previously received lidocaine (27.2±3.5 vs 26.5±4.2 days, p<0.01). At the post-discharge office visit, there was no difference in headache days between patients who had and had not previously received lidocaine, respectively (23.6±8.2 vs 22.0±8.4 days, p=0.07).

Current and average pain ratings were both lower at the post-discharge office visit compared with baseline (table 2). The correlation coefficient between patients' pain ratings and plasma lidocaine concentrations (R=−0.08, p=0.02) indicated poor correlation.[8] The correlation between pain ratings and lidocaine infusion rates was similarly poor (R=−0.03, p=0.05).

Using the responder definition previously described in which an acute responder was a patient with a decrease of at least 2 points in the 0–10 NRS in current pain, 87.8% of patient admissions (535 of 609) were acute responders. Within the cohort of acute responders (N=535) with available data on average pain (N=229), 43.2% (99 of 229) demonstrated sustained response at the post-discharge office visit. Responders are shown in figure 1. The mean duration of treatment for acute responders (N=535) was 5.2±1.6 days vs 5.8±1.5 days for non-responders (N=74; p<0.01). For sustained responders (N=99), duration of treatment was 5.3±1.5 days vs 5.1±1.5 days for non-responders (N=130; p=0.27). The mean age for acute responders was 46±14 years vs 45±18 years for non-responders (p=0.62);

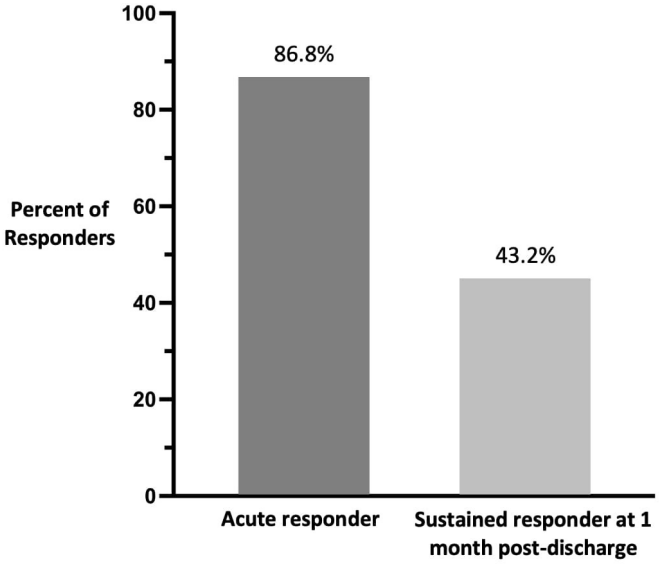

Figure 1 Acute and sustained responders after treatment with lidocaine infusion. Acute responders were patients reporting a decrease of at least 2 points in 0–10 Numerical Rating Scale for current pain from beginning to end of treatment. Sustained responders were those acute responders whose average pain remained at a level 2 points below baseline at 1 month.

Table 3 Changes in pain from baseline to discharge based on receipt of various intravenous migraine medications

Medication	Received drug, median pain (IQR)*	Did not receive drug, median pain (IQR)*	P value
Ketorolac	−4.5 (−3 to −6.5) N=513	−6.0 (−3.1 to −7.0) N=96	0.03
Dihydroergotamine	−4.8 (−3.0 to −6.9) N=556	−5.0 (−3.0 to −7.0) N=53	0.48
Methylprednisolone	−4.0 (−2.0 to −6.5) N=328	−5.0 (−3.5 to −7.0) N=281	<0.001
Magnesium	−5.0 (−3.0 to −7.0) N=596	−5.0 (−2.3 to −8.0) N=13	0.57
Neuroleptics†	−5.0 (−3.0 to −7.0) N=585	−4.0 (−2.3 to −6.4) N=24	0.37

*Pain was assessed on a 0–10 Numerical Rating Scale where 0=no pain and 10=worst pain imaginable.
†Neuroleptics included promethazine, prochlorperazine, chlorpromazine, haloperidol, and metoclopramide.

for sustained responders, the mean age was 46±14 years vs 46±14 years for non-responders (p=0.91).

Patients who received ketorolac during admission (N=513) had a smaller change in pain from baseline to discharge compared with those who did not receive ketorolac (N=96); (−4.5 (−3 to −6.5) vs −6.0 (−3.1 to −7.0), p=0.03). Similarly, patients who received methylprednisolone (N=328) had a smaller change in pain compared with those who did not (N=281); (−4.0 (−2.0 to −6.5) vs −5.0 (−3.5 to −7.0), p<0.001). There were no significant differences in change in pain based on administration of any other headache medications administered during hospitalization. Those results are shown in table 3.

The mean total lidocaine dose for the cohort was 13 609.1±3977.0 mg. There was no statistically significant correlation between total lidocaine dose and change in pain from baseline to discharge (R=0.033, p=0.46). The mean total lidocaine dose for sustained responders was 13 838.8±4183.8 mg vs 13 491.7±4129.6 mg for non-responders (p=0.59).

Safety and tolerability

The most common ADE was nausea/vomiting, followed by cardiovascular changes, unspecified other, hallucinations/nightmares/visual changes, sedation/sleepiness, anxiety, dizziness/lightheadedness, cerebrovascular accident-like symptoms, urinary retention, and then paresthesias. A summary of ADEs is shown in table 4.

Table 4 Rate-limiting adverse drug effects (ADEs) associated with lidocaine infusions

ADE	Percentage of patients
Nausea/vomiting	16.6
Cardiovascular changes	12.0
Unspecified other	12.0
Hallucinations/nightmares/visual changes	10.3
Sedation/sleepiness	6.4
Anxiety	6.2
Dizziness/lightheadedness	4.8
CVA-like symptoms	2.0
Urinary retention	1.3
Paresthesias	0.5

CVA, cerebrovascular accident.

DISCUSSION

We found that patients with rCM who received multiday continuous lidocaine infusion as part of aggressive inpatient treatment had a significant improvement in pain immediately following the infusion and 43.2% of those acute responders had sustained response at 1 month. Treatment was well tolerated overall but some patients did experience rate-limiting ADEs as shown above. The high acute responder rate indicates that the combination of lidocaine with other aggressive intravenous therapies was associated with rapid relief. The effect did wane over time reflecting the clinical severity of rCM and the challenge of treating patients who have often failed dozens of medications prior to being hospitalized for treatment. Silberstein *et al*[9] created four categories of rCM, with the most severe being class IV, defined as 'failure of adequate treatment trials of 3 drugs…' as well as 'failed aggressive infusion or inpatient treatment…' Patients included in this study were all class IV, indicating the most severe disease. Similar results have been described for other intravenous infusions used for rCM, including ketamine.[10] Our results support the use of lidocaine infusions in a challenging population with rCM and can help those treating challenging patients with headache have informed discussions about likelihood for relief and expected duration of relief. It is important to note that because of the severity of the disease process in these patients, using typical outcome measures such as improvement in pain of at least 50% at a time point of 3 months might not be practical and could result in underutilization of effective treatments. Patients in class IV as described above have virtually constant migraine pain and for many even temporary relief can allow resumption of normal activities.

Rosen *et al*[11] retrospectively studied a similar patient population and reported a mean decrease of 4 points on a 10-point pain scale after multiday lidocaine infusion. They did not report on any outcomes beyond hospital discharge so it is not known if those patients who acutely responded had sustained response. Our study expands on their findings because we included pain data at 1 month as well as the number of headache days, an important outcome in migraine trials.[5] Williams *et al*[12] reported retrospective data on a cohort of patients with primarily migraine diagnoses and medication overuse headache and found that 90% of patients experienced absence or improvement by end of the 8.7-day treatment and 70% had absence or improvement at 6 months. It should be noted, however, that their study included chronic daily headache and the patients had substantially less severe disease than those in our study.

The percentage of responders decreased from 87.8% at the end of admission to 43.2% at 1 month, mostly reflecting the extremely challenging nature of rCM, especially those in class IV as defined by Silberstein *et al*.[9] Identifying and studying therapies that are effective in this highly refractory patient population is extremely difficult and the challenges of using placebo for such desperate patients have been noted by some authors.[13] We were unable to identify demographic or other characteristics of sustained responders and did not find a difference in the total lidocaine dose administered to sustained responders versus those who were not sustained responders. Some of this may be related to the retrospective study design or there may be subtle patient factors, such as genetic differences or comorbidities that have not yet been identified.

Widespread adoption of lidocaine infusions for headache disorders has not occurred and this treatment is only available in a few experienced centers in the USA. Part of the challenge is due to inadequate insurance coverage for lidocaine as a result of the lack of randomized controlled trials supporting its use. In most randomized controlled trials of migraine medications, patients with rCM are excluded.[5 9 14] As a result, patients not meeting typical criteria have few or no options for treatment and often must turn to experimental or more aggressive therapies, which are often not covered by insurance. Conducting clinical trials in rCM is a challenge because of the ethical issues introduced by the use of placebo for patients with refractory disease. Additionally, patients who have failed multiple prior preventive migraine treatments have a lower response to placebo than those who have not.[15] Despite these hurdles, prospective studies in patients with rCM should be performed and supported by funding agencies so that evidence is generated to support aggressive therapies.

The observation that patients who did not receive ketorolac or methylprednisolone actually reported slightly lower pain ratings than those who did receive these medications is difficult to explain. Because such patients likely had more comorbidities that caused reluctance to use these medications, such as diabetes mellitus or chronic kidney disease, they may have been previously undertreated by outpatient physicians and thus were effectively managed with fewer treatments while hospitalized.

There are several possible explanations for the lack of correlation between lidocaine plasma levels and pain ratings and between total lidocaine dose and change in pain. First, the minimum effective plasma level for lidocaine has not been established and some patients respond despite low plasma levels. Plasma levels in our practice are primarily used to ensure toxic levels are not exceeded. In patients demonstrating good analgesic response early in the treatment course, lidocaine is titrated less aggressively than for those in whom response is poor. This is the likely explanation of why lidocaine infusion rates are not predictive of analgesia. In patients not demonstrating an initial response, lidocaine is typically increased until response is achieved, toxic levels are approached (≥5 µg/mL), or intolerable ADEs are reported. Optimal titration of this infusion is a balance between pain relief and ADEs, which are typically dose dependent. In our experience, response to treatment with lidocaine typically becomes apparent during the first few days but because a minority of patients may get relief with longer infusions, we often will permit additional treatment days despite minimal initial response. Because hospitalization is expensive and demands a significant time commitment from the patient, lidocaine infusions are typically increased to the point of intolerability for those not initially responding at lower rates in order to be certain that the patient is in fact a non-responder. This has also been noted for ketamine infusions, which have been suggested as a treatment for rCM as well.[6] Given the potential high cost of hospitalization, it is logical to question if similar results could be obtained with outpatient infusions. Outpatient lidocaine has not been well studied and a single study of intravenous lidocaine boluses for patients with migraine in the emergency department found that only 29% of patients reported relief at 12 hours.[16] The benefits of repeated outpatient lidocaine infusions are unknown but are a topic for future studies.

This study has limitations. First, not all patients completed follow-up visits after lidocaine infusions and some pain ratings and headache days were unavailable. In our extensive experience with rCM, patients who respond well are less likely to schedule follow-up visits and as a result the post-treatment pain ratings in this study may be higher than those observed across all patients with rCM in the practice. Additionally, many patients travel significant distances for treatment and such patients may have been less likely to follow up. Second, some patients had multiple admissions that were included in the analysis during the study period. We decided to include multiple admissions and treat each as a separate set of data points because the degree of pain and disability was different for each admission for the same patient and was spaced apart generally by 6 months or more, allowing for adequate washout time since the last lidocaine treatment. Third, we did not compare outcomes between patients who did and did not take various preventive medications prior to admission. Because of the wide variety of preventive medications taken, we did not believe that analysis would be meaningful. Last, while unlikely because of the refractory and severe nature of the disease, it is possible that hospitalization itself could have contributed to pain relief.

In conclusion, continuous lidocaine infusions were associated with improvement in acute pain in most patients and a decrease in both average pain and the number of headache days per month that extended out to 1 month. Most patients were acute responders, 43% of whom maintained improvement at 1 month and were sustained responders. ADEs occurred in a minority of patients and were mild. Lidocaine may be a viable treatment option for patients with rCM who have failed other treatments. A prospective, randomized, double-blind trial is needed to confirm these results but may be challenging given the refractory nature of the disease and the associated ethical dilemmas.

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Patient consent for publication Not required.

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REFERENCES

1 Diener H-C, Solbach K, Holle D, *et al*. Integrated care for chronic migraine patients: epidemiology, burden, diagnosis and treatment options. *Clin Med* 2015;15:344–50.
2 Headache classification Committee of the International headache Society (IHS) the International classification of headache disorders, 3rd edition. *Cephalalgia* 2018;38:1–211.
3 Sacco S, Braschinsky M, Ducros A, *et al*. European headache federation consensus on the definition of resistant and refractory migraine : Developed with the endorsement of the European Migraine & Headache Alliance (EMHA). *J Headache Pain* 2020;21:76.
4 Berk T, Silberstein SD. The use and method of action of intravenous lidocaine and its metabolite in headache disorders. *Headache* 2018;58:783–9.
5 Silberstein SD, Dodick DW, Bigal ME, *et al*. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med* 2017;377:2113–22.
6 Schwenk ES, Dayan AC, Rangavajjula A, *et al*. Ketamine for refractory headache: a retrospective analysis. *Reg Anesth Pain Med* 2018;43:875–9.
7 Bland JM, Altman DG, Correlation ADG. Correlation, regression, and repeated data. *BMJ* 1994;308:896.
8 Akoglu H. User's guide to correlation coefficients. *Turk J Emerg Med* 2018;18:91–3.
9 Silberstein SD, Dodick DW, Pearlman S. Defining the pharmacologically intractable headache for clinical trials and clinical practice. *Headache* 2010;50:1499–506.
10 Schwenk ES, Torjman MC, Moaddel R, *et al*. Ketamine for refractory chronic migraine: an observational pilot study and metabolite analysis. *J Clin Pharmacol* 2021;61:1421–9.
11 Rosen N, Marmura M, Abbas M, *et al*. Intravenous lidocaine in the treatment of refractory headache: a retrospective case series. *Headache* 2009;49:286–91.
12 Williams DR, Stark RJ, lignocaine I. Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. *Cephalalgia* 2003;23:963–71.
13 Mojica JJ, Schwenk ES, Lauritsen C, *et al*. Beyond the Raskin Protocol: Ketamine, Lidocaine, and Other Therapies for Refractory Chronic Migraine. *Curr Pain Headache Rep* 2021;25:77.
14 Lipton RB, Goadsby PJ, Smith J, *et al*. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology* 2020;94:e1365–77.
15 Ashina M, Tepper S, Brandes JL, *et al*. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: a subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2018;38:1611–21.
16 Bell R, Montoya D, Shuaib A, *et al*. A comparative trial of three agents in the treatment of acute migraine headache. *Ann Emerg Med* 1990;19:1079–82.