European Journal of Clinical Pharmacology (2022) 78:27–33
https://doi.org/10.1007/s00228-021-03219-5

CLINICAL TRIAL

Intravenous lidocaine vs. NSAIDs for migraine attack in the ED: a prospective, randomized, double-blind study

Sultan Tuna Akgol Gur[1] · Elif Oral Ahiskalioglu[2,3] · Muhammed Enes Aydin[2,3] · Abdullah Osman Kocak[1] · Pelin Aydin[4] · Ali Ahiskalioglu[2,3]

Received: 13 April 2021 / Accepted: 9 September 2021 / Published online: 16 September 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract

Purpose Although different forms of lidocaine are used for migraine attack headaches, the effect of intravenous lidocaine is still limited. This study aimed to investigate the effects of intravenous lidocaine infusion for the treatment of migraine attack headaches.

Methods A hundred patients with migraine attacks, aged between 18 and 65, were randomly divided into two groups. The lidocaine group ($n=50$) received a 1.5 mg/kg lidocaine bolus and a 1 mg/kg infusion (first 30 min), followed by a 0.5 mg/kg infusion for a further 30 min intravenously. The non-steroidal anti-inflammatory drug (NSAID) group ($n=50$) received 50 mg dexketoprofen trometamol and saline at the same volume as the lidocaine at the same time intervals intravenously. The Visual Analog Scale (VAS) pain scores, additional analgesia requirement, side effects, and revisits to the emergency department were recorded.

Results The VAS score was significantly lower in the lidocaine group than in the NSAID group for the first 20th and 30th minutes ($p=0.014$ and $p=0.024$, respectively). There was no difference between the VAS scores for the remaining evaluation times ($p>0.05$). In terms of secondary outcomes, rescue medication requirement was not different between the two groups at both the 60th and 90th minutes ($p>0.05$). However, the number of patients revisiting ED within 48–72 h was statistically less in the lidocaine group than in the NSAID group (1/50 vs. 8/50; $p=0.031$).

Conclusion Intravenous lidocaine may be an alternative treatment method for patients with migraine attack headaches in the emergency department.

Keywords Migraine · Headache · Attack treatment · Intravenous lidocaine · Pain

Introduction

Migraine is a common disease that primarily progresses with severe headaches, causes neurological problems, and appears in the form of attacks [1]. This condition, which considerably affects human life and causes a decrease in personal activities, is also one of the most common reasons for visiting emergency departments [2]. Knowledge of the pathophysiology of migraine is important in determining the appropriate acute therapeutic approaches. The most common known theories in migraine is the activation of the trigeminovascular structures found in the diencephalic and brain stem nuclei causes meningeal vasodilation, neurogenic inflammation, and central sensitization, leading to headaches [3].

The current approach in the acute treatment of migraine should address the needs of the patient. Symptoms accompanying pain are individual. Pain intensity, nausea, and pain repetition should be questioned, and well known, and early intervention and combined approaches should be applied. Antiemetics, diphenhydramine, paracetamol, and non-steroid anti-inflammatory drugs (NSAIDs) are frequently

✉ Elif Oral Ahiskalioglu
drelforl@hotmail.com; eoral.ahiskalioglu@atauni.edu.tr

[1] Department of Emergency Medicine, Ataturk University School of Medicine, Erzurum, Turkey

[2] Department of Anesthesiology and Reanimation, Ataturk University School of Medicine, 25070 Erzurum, Turkey

[3] Clinical Research, Development and Design Application and Research Center, Ataturk University School of Medicine, 25240 Erzurum, Turkey

[4] Department of Anesthesiology and Reanimation, Erzurum State Hospital, Erzurum, Turkey

used. In some specific cases, steroids, triptans, ergotamines, and dopamine antagonists can be preferred. Furthermore, intranasal ketamine, an anesthetic agent, can be used in emergency departments in the treatment of migraine [4, 5].

Lidocaine is an amide local anesthetic with a wide mechanism of action. A low-dose intravenous infusion of this drug can reduce pain in chronic conditions. A lidocaine infusion is inexpensive and easy to apply and has few side effects. In recent years, the use of intravenous lidocaine has been widely adopted in anesthesia practice in the postoperative period of many surgical procedures [6, 7]. It has also been used to reduce propofol consumption in short-term interventional procedures, such as colonoscopy and endoscopic retrograde cholangiopancreatography [8, 9], as well as in emergency departments to relieve pain caused by biliary colic [10], acute abdominal problems [11], rib fracture [12], and renal colic [13].

In this study, our primary goal was to investigate the analgesic effect of intravenous lidocaine administration in the treatment of migraine attacks. Our secondary goal was to assess the effect of lidocaine use on reducing the need for rescue analgesia and readmission to the emergency department.

Material and method

After obtaining approval from the Local Ethics Committee of Atatürk University Medical Faculty, a total of 100 patients aged 18 to 65 years presented to the emergency department with migraine attack headaches (ICHD-3 criteria) with at least a 1-year history of migraine, no medication overuse, and 48 h of headache-free time between migraine attacks were included in the study. The study was planned as randomized, prospective, and double-blind. Written informed consent was obtained from all patients after giving them detailed information about the medications to be applied and pain evaluation.

The exclusion criteria were age under 18 or over 65, systolic blood pressure below 80 mmHg or over 200 mmHg, heart rate below 50 beats/min or above 150 beats/min, oxygen saturation value below 92%, respiratory rate below 8 or over 30, known lidocaine allergy, drug or alcohol addiction, ischemic heart disease, severe kidney and liver disease, long-term opioid and non-opioid analgesic use, pregnancy, inability to communicate, weight under 40 kg, presence of active bleeding, and symptomatic headaches.

The patients were randomly divided into two groups at a 1:1 ratio using a computer program: the lidocaine group ($n = 50$) and the NSAID group ($n = 50$). The practitioners, those who prepared the medication, those who evaluated the patients, and patients themselves were unaware of which groups received which drug mixtures. The volumes of the infusion solutions prepared for the groups contained the same volume of saline to ensure that the study was conducted in a double-blinded manner (Table 1). Patients were undergoing cardiac monitoring during infusion.

Study protocol

In the lidocaine group, 1.5 mg/kg lidocaine was given first as an intravenous (IV) bolus, followed by a 1 mg/kg/h IV lidocaine infusion over the first 30 min + 100 mL saline and a 0.5 mg/kg/h IV lidocaine infusion over the second 30 min. In the NSAID group, the patients received normal saline at the same bolus volume as the other group, and then were administered 50 mg dexketoprofen in 100 mL saline and a saline infusion at the same volume as lidocaine over the first 30 min. For the second 30 min, the patients received normal saline at the same bolus volume as in the lidocaine group.

Outcomes

Pain was evaluated using the Visual Analog Scale (VAS) based on a 0 to 10 scale (0 = no pain, VAS 10 = the most severe pain ever experienced). The VAS scores were obtained at the time of presentation and at the 20th, 30th, 60th, and 90th minutes. During the follow-up of the patients, signs of toxicity, such as numbness in the tongue, arrhythmia, metallic taste, tinnitus, anaphylaxis, nausea, and vomiting, were noted. For the patients with a VAS score of 4 and above the 60th and 90th minutes, 1 mcg/kg fentanyl was administered as a rescue analgesic. Lastly, the patients that revisited the emergency department within 48–72 h were noted.

Sample size and statistical analyses

The sample size calculation was based on our primary aim VAS score. The preliminary study indicated that the

Table 1 Study groups and blindization

Intravenous solution	Lidocaine group	NSAID group
Bolus injection	1.5 mg/kg lidocaine	Same volume saline as lidocaine
Infusion (first 30 min)	1 mg/kg/h lidocaine in 100 mL saline	50 mg dexketoprofen trometamol in 100 mL saline
Infusion (second 30 min)	0.5 mg/kg/h lidocaine	Same volume saline as lidocaine

VAS score at the 20th minute should be 6.10 ± 1.10 for the NSAID group ($n = 10$) and 5.50 ± 1.08 for the lidocaine group ($n = 10$). A total sample size of 42 patients for each group was calculated using G*Power (Heinrich-Heine-University, Düsseldorf, Germany) version 3.1.9.2 with a two-tailed test at an alpha probability of 0.05, power of 0.80, and an effect size of 0.550. Considering possible dropouts, we decided to include at least 50 patients in each group.

Statistical analyses were performed using SPSS Statistics, version 22.0 (IBM, Armonk, NY, USA). The normality distribution of data was assessed with the Kolmogorov–Smirnov test. Descriptive statistics included mean values with standard deviation or percentages depending on the characteristics of the data. Continuous variables were expressed as mean ± standard deviation (*SD*) or median (*IQR*) values. The groups were compared using the *t*-test for normally distributed data while the Mann–Whitney *U* test was used for skewed data. Nominal variables were compared using the chi-square or Fisher's exact test. A *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 142 patients were evaluated for eligibility during the study period. After 42 patients were excluded, the data of a total of 100 patients were analyzed (Fig. 1). There was no significant difference between the two groups in terms of demographic data and the baseline characteristics of the patients ($p > 0.05$) (Table 2).

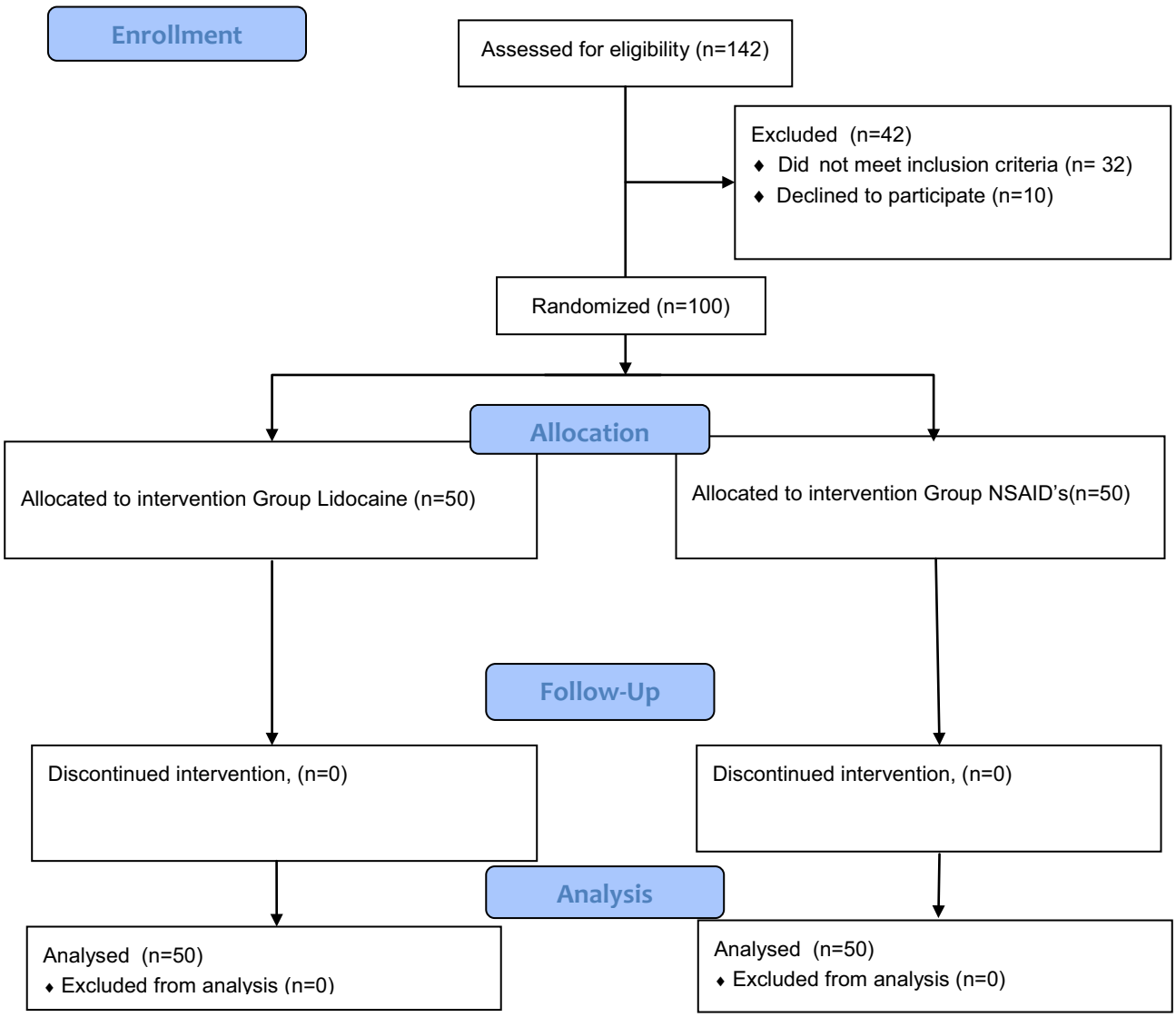

Fig. 1 CONSORT flow diagram

Table 2 Demographic and baseline characteristics of the study groups

	Lidocaine ($n=50$)	NSAID ($n=50$)	*p*
Age (years)	43 [33–55]	37 [33–54]	0.512[a]
Sex (F/M)	31/19	27/23	0.806[b]
Onset time of migraine attack (min)	235 [180–300]	280 [210–300]	0.685[a]
Systolic blood pressure at admission	120 [113–129]	121 [117–129]	0.576[a]
Diastolic blood pressure at admission	80 [72–87]	80 [72–85]	0.945[a]
Pulse at admission	77 [66–87]	77 [69–87]	0.989[a]
Respiratory rate at admission	16 [14–17]	16 [14–18]	0.696[a]
SpO_2 at admission	96 [94–97]	96 [95–97]	0.739[a]
Temperature (°C)	36.7 [36.0–37.0]	36.7 [36.0–36.9]	0.869[a]

Values are presented as number or median and 25th–75th percentile [*IQR*]

[a]Mann–Whitney *U* test

[b]Fisher's exact test

When the pain scores of the patients were examined, the VAS scores at the first 20th and 30th minutes were significantly lower in the lidocaine group compared to those in the NSAID group ($p=0.014$ and $p=0.024$, respectively). However, there was no significant difference between the two groups in terms of the VAS scores recorded at the remaining evaluation times ($p>0.05$) (Table 3).

Concerning secondary outcomes, at the 60th minute, the rescue medication requirement of the lidocaine group did not significantly differ compared to that of the NSAID group (14/50 vs. 15/50, $p=0.826$). Similarly, there was no difference between the groups in terms of rescue medication requirement at the 90th minute (2/50 vs. 4/50, $p=0.678$). However, the rate of patients revisiting the emergency department within 48–72 h was statistically significantly lower in the lidocaine group compared to that in the NSAID group (1/50 vs. 8/50, $p=0.031$) (Table 3).

Discussion

This study showed that intravenous lidocaine administered to patients presenting with migraine attacks decreased their pain scores in the early period. In addition, although intravenous lidocaine does not reduce the need for rescue medication, it can be an alternative treatment option by reducing revisits to the emergency department.

Migraine attacks are generally characterized by unilateral, severe throbbing headaches. Decreased concentration, nasal congestion, lacrimation, and rhinorrhea may also be seen. After pain, the patient feels tired and lethargic. In order to increase the quality of life and work force of migraine patients, it is very important that appropriate treatment be given, especially in the acute period. Pharmacological approaches are divided into two groups as acute phase and preventive. While the aim is to relieve symptoms during the attack in the acute approach, it is to decrease the frequency,

Table 3 VAS scores and recurrent pain of the patients

	Lidocaine ($n=50$)	NSAID ($n=50$)	*p* value
VAS scores on admission	8 [7–9]	8 [7–9]	0.593[a]
At the 20th min of the intervention	6 [5–6]	6 [6–7]	0.014[a]
At the 30th min of the intervention	4 [4–5]	5 [4–6]	0.024[a]
At the 60th min of the intervention	4 [3–5]	4 [3–5]	0.211[a]
At the 90th min of the intervention	4 [3–4]	3 [2–4]	0.180[a]
Rescue medication requirement at the 60th min (yes/no)	14/36	15/35	0.826[a]
Rescue medication requirement at the 90th min (yes/no)	2/48	4/46	0.678[a]
Revisit to the emergency department within 48–72 h (yes/no)	1/49	8/42	0.031[c]

Values are presented as median and 25th–75th percentile (*IQR*)

VAS Visual Analog Scale, *min* minute

[a]Mann–Whitney *U* test

[b]Chi-square test

[c]Fisher's exact test

duration, and intensity of attacks in the preventive approach [3].

Lidocaine reduces peripheral nociceptor sensitization and central hyperextension through its Na channel blocker effect. There are many activity models that explain the clinical role of lidocaine in peripheral and central pain management. It is known to have anti-inflammatory properties since it has been shown to reduce inflammatory cytokines. It also blocks NMDA receptors. Studies have shown that lidocaine reduces spontaneous pain and mechanical hyperalgesia, and also prevents central sensitization [14]. Due to these properties, we considered that lidocaine might be effective in the treatment of migraine attacks.

Lidocaine has been used in different ways for headache relief for many years. It has been used safely in nerve blocks, trigger point injections, or intranasal forms [15, 16]. Intravenous lidocaine has been reported to be effective in the treatment of acute/chronic headache and trigeminal neuralgia [17–21]. Previous authors reported that intravenous lidocaine may be safe and effective treatment for children with status migrainosus [22]. In our literature review, intravenous lidocaine (1 mg/kg) is reported to have no effect on acute migraine by Reutens et al. [23]. But another study showed intravenous lignocaine (2 mg/min) is effective on chronic headaches [24].

Although lidocaine, which has a wide area of use, is a safe agent, its side effects are frequently reported in cases of overdose. When the plasma concentration of local anesthetics exceeds certain values, they may show toxic effects. The dose of lidocaine we used in the study (1.5 mg/kg) is much lower than the toxic dose (4–7 mg/kg). Although continuous lidocaine infusions can theoretically cause toxicity over time, blood concentrations are reported to remain well below the toxic level in clinical studies. Similarly, in our patients, we did not encounter any side effects that could develop due to lidocaine. The lidocaine dose should be reduced by 50% in the presence of severe hepatic insufficiency since the half-life of lidocaine is considerably prolonged in patients with hepatic failure accompanied by congestive heart failure [25]. Another possible situation to consider is the prolongation of the half-life of lidocaine due to changes in the volume distribution in geriatric patients [26]. On the other hand, there are still some considerations that need clarification although the NSAIDs are the first-choice analgesics in ED for acute migraine attacks due to their efficacy and adverse effects. Renal dysfunction, gastrointestinal bleeding, and thrombosis dysfunction are the well-known adverse effects of NSAIDs. Risk–benefit analysis plays an important role in determining appropriate treatment protocols.

In our study, we applied lidocaine as an IV bolus and infusion. The post-IV bolus activity of lidocaine starts immediately and has a duration of 10–20 min. The other drug used in the study, i.e., dexketoprofen trometamol, reaches its maximum plasma concentration within 15–40 min [27, 28]. In our study, the better pain scores of the lidocaine group at the first 30th minute compared to those of the NSAID group can be attributed to this rapid effect of lidocaine. Similar analgesic efficacy was observed after 30 min in both groups. Pain attacks in migraine can last 4 to 72 h. We aimed to decrease the rate of recurrence or persistence of pain with lidocaine infusions. As a result, fewer patients that received lidocaine revisited the emergency department within 48–72 h.

The use of opioids in migraine acute treatment is very controversial [29]. Opioids can cause hypersensitivity in migraine. However, studies have shown that this effect can occur after only a high dose of opioids [3]. Our study used fentanyl as rescue analgesia with a dose of 1 mcg/kg single dose.

There are some limitations to this study. First, we investigated the bolus effect of a single dose of lidocaine, and we continued with a lidocaine infusion after the bolus dose. The single-dose effect on migraine pain can be evaluated by future studies. Second, we did not measure the plasma lidocaine levels. Dose-finding studies can also help determine optimal lidocaine dosage to provide clinical efficacy. Third, the study was conducted with a relatively small sample in a single center, limiting the generalizability of the findings. Pain perception can vary among patients with genetic differences; thus, the results should be evaluated considering this variation. In this study, only lidocaine and NSAIDs were compared, and further comparative studies are needed to evaluate other medications and/or combinations in migraine treatment. Finally, advanced clinical and experimental studies are needed in which biochemical markers are also assessed for lidocaine effects.

In conclusion, in the treatment of migraine attacks compared to NSAIDs, IV lidocaine may be an alternative option in the multimodal analgesic concept since it has a rapid effect and reduces revisits to the emergency department.

Clinical implications

- The analgesic effect of intravenous lidocaine on migraine attack treatment is still limited.
- This study aims to investigate the effect of intravenous lidocaine infusion for migraine attack treatment on emergency department.
- Intravenous lidocaine may be an alternative drug for migraine attacks.
- Intravenous lidocaine reduces revisits to the emergency department.

Author contribution ST Akgol Gur, EO Ahiskalioglu: Planning, data collection, sample analysis, writing the first draft, evaluating and modifying the final manuscript. ME Aydin, AO Kocak: Data collection and evaluating subsequent drafts and the final manuscript. P. Aydin: Sample analysis, writing and the final manuscript. A. Ahiskalioglu: Writing and the final manuscript, supervisor.

Declarations

Ethic approval and patient consent This study was conducted at the Ataturk University Faculty of Medicine, Erzurum, Turkey. It was approved by the local ethics board approval (B30.2ATA.0.01.00/462) and followed the Helsinki statement, and signed consent was obtained from all participants before the experiment.

Conflict of interest The authors declare no competing interests.

References

1. Becker WJ (2015) Acute migraine treatment in adults. Headache 55(6):778–793. https://doi.org/10.1111/head.12550
2. Robblee J, Grimsrud KW (2020) Emergency department and inpatient management of headache in adults. Curr Neurol Neurosci Rep 20(4):7. https://doi.org/10.1007/s11910-020-01030-w
3. Ong JJY, De Felice M (2018) Migraine treatment: current acute medications and their potential mechanisms of action. Neurotherapeutics 15(2):274–290. https://doi.org/10.1007/s13311-017-0592-1
4. Bilhimer MH, Groth ME, Holmes AK (2020) Ketamine for migraine in the emergency department. Adv Emerg Nurs J 42(2):96–102. https://doi.org/10.1097/tme.0000000000000296
5. Benish T, Villalobos D, Love S, Casmaer M, Hunter CJ, Summers SM, April MD (2019) The THINK (Treatment of Headache with Intranasal Ketamine) trial: a randomized controlled trial comparing intranasal ketamine with intravenous metoclopramide. J Emerg Med 56(3):248-257.e241. https://doi.org/10.1016/j.jemermed.2018.12.007
6. Beaussier M, Delbos A, Maurice-Szamburski A, Ecoffey C, Mercadal L (2018) Perioperative use of intravenous lidocaine. Drugs 78(12):1229–1246. https://doi.org/10.1007/s40265-018-0955-x
7. Ates İ, Aydin ME, Ahiskalioglu A, Ahiskalioglu EO, Kaya Z, Gozeler MS (2020) Postoperative analgesic efficacy of perioperative intravenous lidocaine infusion in patients undergoing septorhinoplasty: a prospective, randomized, double-blind study. Eur Arch Otorhinolaryngol 277(4):1095–1100. https://doi.org/10.1007/s00405-020-05801-6
8. Forster C, Vanhaudenhuyse A, Gast P, Louis E, Hick G, Brichant JF, Joris J (2018) Intravenous infusion of lidocaine significantly reduces propofol dose for colonoscopy: a randomised placebo-controlled study. Br J Anaesth 121(5):1059–1064. https://doi.org/10.1016/j.bja.2018.06.019
9. Ates I, Aydin ME, Albayrak B, Disci E, Ahiskalioglu EO, Celik EC, Baran O, Ahiskalioglu A (2020) Pre-procedure intravenous lidocaine administration on propofol consumption for ERCP: a prospective, randomized, double-blind study. J Gastroenterol Hepatol. https://doi.org/10.1111/jgh.15356
10. Akhgar A, Pouryousefi T, Nejati A, Rafiemanesh H, Hossein-Nejad H (2020) The efficacy of intravenous lidocaine and its side effects in comparison with intravenous morphine sulfate in patients admitted to the ED with right upper abdominal pain suspected of biliary colic. Am J Emerg Med. https://doi.org/10.1016/j.ajem.2020.04.010
11. Chinn E, Friedman BW, Naeem F, Irizarry E, Afrifa F, Zias E, Jones MP, Pearlman S, Chertoff A, Wollowitz A, Gallagher EJ (2019) Randomized trial of intravenous lidocaine versus hydromorphone for acute abdominal pain in the emergency department. Ann Emerg Med 74(2):233–240. https://doi.org/10.1016/j.annemergmed.2019.01.021
12. Johnson M, Strait L, Ata A, Bartscherer A, Miller C, Chang A, Stain SC, Tafen M (2020) Do lidocaine patches reduce opioid use in acute rib fractures? Am Surg 86(9):1153–1158. https://doi.org/10.1177/0003134820945224
13. Miller ACC, Faza C, Bigalli AAC, Khan AM, Sewell KA, King A, Vahedian-Azimi A, Zehtabchi S (2020) Intravenous amide anesthetics to treat pain associated with renal colic in the emergency department: a systematic review. Arch Acad Emerg Med 8(1):e27
14. Kandil E, Melikman E, Adinoff B (2017) Lidocaine infusion: a promising therapeutic approach for chronic pain. J Anesth Clin Res 8(1) https://doi.org/10.4172/2155-6148.1000697
15. Karadaş Ö, Gül HL, Inan LE (2013) Lidocaine injection of pericranial myofascial trigger points in the treatment of frequent episodic tension-type headache. J Headache Pain 14(1):44. https://doi.org/10.1186/1129-2377-14-44
16. Avcu N, Doğan N, Pekdemir M, Yaka E, Yılmaz S, Alyeşil C, Akalın LE (2017) Intranasal lidocaine in acute treatment of migraine: a randomized controlled trial. Ann Emerg Med 69(6):743–751. https://doi.org/10.1016/j.annemergmed.2016.09.031
17. Williams DR, Stark RJ (2003) Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. Cephalalgia 23(10):963–971. https://doi.org/10.1046/j.1468-2982.2003.00623.x
18. Matharu MS, Cohen AS, Goadsby PJ (2004) SUNCT syndrome responsive to intravenous lidocaine. Cephalalgia 24(11):985–992. https://doi.org/10.1111/j.1468-2982.2004.00886.x
19. Berk T, Silberstein SD (2018) The use and method of action of intravenous lidocaine and its metabolite in headache disorders. Headache 58(5):783–789. https://doi.org/10.1111/head.13298
20. Bell R, Montoya D, Shuaib A, Lee MA (1990) A comparative trial of three agents in the treatment of acute migraine headache. Ann Emerg Med 19(10):1079–1082. https://doi.org/10.1016/s0196-0644(05)81507-0
21. Masic D, Liang E, Long C, Sterk EJ, Barbas B, Rech MA (2018) Intravenous lidocaine for acute pain: a systematic review. Pharmacotherapy 38(12):1250–1259. https://doi.org/10.1002/phar.2189
22. Ayulo MA Jr, Phillips KE, Tripathi S (2018) Safety and efficacy of IV lidocaine in the treatment of children and adolescents with status migraine. Pediatr Crit Care Med 19(8):755–759. https://doi.org/10.1097/pcc.0000000000001629
23. Reutens DC, Fatovich DM, Stewart-Wynne EG, Prentice DA (1991) Is intravenous lidocaine clinically effective in acute migraine? Cephalalgia 11(6):245–247. https://doi.org/10.1046/j.1468-2982.1991.1106245.x
24. Kaube H, Hoskin KL, Goadsby PJ (1994) Lignocaine and headache: an electrophysiological study in the cat with supporting clinical observations in man. J Neurol 241(7):415–420. https://doi.org/10.1007/bf00900958
25. Orlando R, Piccoli P, De Martin S, Padrini R, Palatini P (2003) Effect of the CYP3A4 inhibitor erythromycin on the pharmacokinetics of lignocaine and its pharmacologically active metabolites in subjects with normal and impaired liver function. Br J Clin Pharmacol 55(1):86–93. https://doi.org/10.1046/j.1365-2125.2003.01718.x
26. Daykin H (2017) The efficacy and safety of intravenous lidocaine for analgesia in the older adult: a literature review. Br J Pain 11(1):23–31. https://doi.org/10.1177/2049463716676205

27. Gungor F, Akyol KC, Kesapli M, Celik A, Karaca A, Bozdemir MN, Eken C (2016) Intravenous dexketoprofen vs placebo for migraine attack in the emergency department: a randomized, placebo-controlled trial. Cephalalgia 36(2):179–184. https://doi.org/10.1177/0333102415584604
28. Rodríguez MJ, Arbós RM, Amaro SR (2008) Dexketoprofen trometamol: clinical evidence supporting its role as a painkiller. Expert Rev Neurother 8(11):1625–1640. https://doi.org/10.1586/14737175.8.11.1625
29. Kelley NE, Tepper DE (2012) Rescue therapy for acute migraine, part 3: opioids, NSAIDs, steroids, and post-discharge medications. Headache 52(3):467–482. https://doi.org/10.1111/j.1526-4610.2012.02097.x

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.