ORIGINAL ARTICLE

Analgesic effects of adding lidocaine to morphine pumps after orthopedic surgeries

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Background: Opiate is used in patient-controlled intravenous analgesia pumps (PCIA) for controlling pain in post-surgical patients. Other drugs are remarkably added to opioid pumps to enhance quality, lengthen analgesia, and reduce side effects. Lidocaine, a local anesthetic which inhibits sodium channels, has anesthetic and analgesic effects when injected locally or intravenously. The objective of this study is to evaluate the analgesic effects of adding lidocaine 1% to different doses of morphine via IV pump to patient-controlled analgesia (PCA) after orthopedic surgeries. **Materials and Methods:** In a randomized clinical trial, 60 patients who had undergone orthopedic surgery of lower extremities were divided into three equal groups to control postoperative pain. Intravenous pump with 5 ml/h flow rate was used as the analgesic method. The solution consisted of lidocaine 1% plus 20 mg morphine for the first group, lidocaine 1% plus 10 mg morphine for the second group, and only 20 mg morphine for the third group (control group). Patients were checked every 12 h, and Visual Analog Scale (VAS), extra opioid doses, nausea/vomiting, and sedation scale were examined. **Results:** Pain score was lower in the first group compared to the other two groups. Mean VAS was 2.15 ± 0.2, 2.75 ± 0.2, and 2 ± 0.25 on the first day and 1.88 ± 0.1, 2.74 ± 0.3, and 2.40 ± 0.3 on the second day, respectively, in the three groups and the difference was statistically significant ($P < 0.01$ and <0.05, respectively). Also, 10% of patients in the first group needed extra opioid doses, while this figure was 30% in the second group and 25% in the third group ($P < 0.01$). Nausea/vomiting and sedation scores were not statistically different among the three groups. **Conclusion:** Compared to lidocaine 1% plus 10 mg morphine or 20 mg morphine alone in PCIA, adding lidocaine 1% to 20 mg morphine decreases the pain score and opioid dose after orthopedic surgeries without having side effects.

Key words: Lidocaine, morphine, patient-controlled analgesia

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INTRODUCTION

Patient-controlled analgesia (PCA) is one of the best postoperative analgesic methods.[1] Opioids are the most common drugs used in IV pumps for pain management, but they may cause nausea/vomiting and respiratory problems.[1,2] On the other hand, in some cases, it is difficult to reduce opioid doses because of the severe pain caused during the first few days. Therefore, it has been observed that adding local anesthetics, ketamine, adrenergic alpha-2 agonists, antihistamines, and nonsteroidal anti-inflammatory drugs to opioids in PCA to enhance the quality and length of analgesia and sedation reduces the opioid doses needed and its side effects, including nausea/vomiting and itching.[2]

Lidocaine, a local anesthetic which inhibits sodium channels, has anesthetic and analgesic effects when injected locally or intravenously. It has been shown that intravenous lidocaine injection can reduce postoperative pain and opiate consumption, and facilitates rehabilitation after surgery.[3,4] This drug is easy to administer and has the potential to be administered as a routine practice for different surgeries. Intravenous lidocaine has analgesic, antihyperalgesic, and anti-inflammatory properties. It can reduce the postoperative inflammatory response by blocking neural transmission at the site of tissue injury, thus attenuating neurogenic inflammation.[3-7] The objective of this study was to evaluate the analgesic effects of adding lidocaine 1% to 10 and 20 mg morphine (daily) in IV PCA after orthopedic surgeries. Due to the paucity of studies on the postoperative use of lidocaine in acute pain management, we tried to focus on its analgesic effects in acute postoperative period in this study.

MATERIALS AND METHODS

Considering $\alpha = 0.05$, $\beta = 20\%$, and the calculation power as 80%, the study population consisted of 50 patients. After obtaining approval from the institutional research committee with code IUMS-931,

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60 patients with American Anesthesiology Score (ASA) I and II, candidates for orthopedic tibia open reduction internal fixation (ORIF) surgery (between November 2008 and August 2009), were enrolled in this double-blinded clinical trial after they were informed of the study method and their written consent was obtained. The patients were divided into three equal groups through simple random sampling. The exclusion criteria were: patients with a history of epilepsy, diabetes, kidney diseases, hypertension, heart block, or addiction to drugs, severely obese patients, and patients with a medical history showing allergy to lidocaine and opioids. General anesthesia method was the same in all patients. After performing complete monitoring (ECG, pulse oximetry, blood pressure, and ETCO2) and preoxygenation and premedication with midazolam and fentanyl, induction was made by injection of propofol plus cisatracurium. After intubation, anesthesia was maintained with propofol infusion. After undergoing surgery and gaining complete consciousness, the patients were transferred to a ward and were included in this study for a maximum of 4 h after surgery. Postoperative analgesia was maintained with lidocaine (Lignodic 1%; Caspian, Rasht, Iran) using 100 ml intravenous infusion pumps at a dosage of 0.8 mg/kg/h with 4-6 ml/h flow rate [3-7] The pump solution in the first group contained lidocaine 1% plus 20 mg morphine (Darupakhsh, Tehran, Iran) (LM20), in the second group contained lidocaine 1% plus 10 mg morphine (LM10), and in the third group (the control group) contained only 20 mg morphine (M20). The patients were randomly assigned to receive one of these pumps. The lockout interval was fixed as 15 min. The researcher was not aware of the contents of the pumps, as another colleague prepared them. Patients were monitored every 12 h for 48 h to check for their Visual Analog Scale (VAS)/Verbal Rating Scale (VRS), extra opioid doses, nausea/vomiting, sedation score, satisfaction score (excellent, good, average, dissatisfied),[3,4,6,7] and demographic scores, which were recorded in their questionnaires by a colleague who was not aware of the study group. The definitions of the measured items are as follows:

Visual analog scale (VAS)

On a ruler scale from 0 to 10: 0 = no pain, 10 = most severe pain imaginable.

Verbal rating scale (VRS)

1 = No pain; 2 = mild pain; 3 = average pain; 4 = severe pain

Sedation score

0 = Restless; 1 = calm; 2 = sleepy; 3 = confused but responds to verbal instructions; 4 = no response to verbal instructions; 5 = no response to painful stimulations.

Nausea/vomiting score

1 = No vomiting/nausea; 2 = mild nausea/vomiting with no need for medicine; 3 = nausea and need for medicine; 4 = no response to a dose of anti-nausea medicine.

Satisfaction score

1 = Excellent; 2 = good; 3 = average; 4 = dissatisfied.

In the event that patients experienced side effects or did not achieve pain control (VAS ≥ 4 and average or high VRS), the content of the pump and dosage were changed as follows:

- VAS > 4: Increased lidocaine by 20% and administered 2 mg morphine IV injection
- Only nausea: Administered metoclopramide 10 mg IV injection
- Any symptoms of lidocaine poisoning: Stopped the pump

In case VAS was <1 or there was mild VRS at 48 h after PCA, lidocaine dose was cut by 50% every 12 h and then stopped. Additionally, the patients were checked for probable side effects like drowsiness, giddiness, and lip tingling.

In order to evaluate the gathered statistical data, SPSS 11.5 software was used. One-way analysis of variance (ANOVA) and Friedman and Duncan test were utilized to examine VAS/VRS, chi-square test was used for checking nausea/vomiting, and Hawke post-test was used to evaluate how much extra opioid was needed and the total opioid used.

RESULTS

Sixty patients who were candidates for lower extremity orthopedic surgery entered this study. The flow diagram is given in Figure 1. The difference among the three groups' demographic data (age, sex, weight, height, operation duration, ASA) was not statistically significant [Table 1].

Principal findings of the study in both groups included the scores of pain, sedation, average morphine dose, and satisfaction [Table 2].

Mean VAS/VRS scores using one-way ANOVA and Duncan tests were significantly lower in the first group (LM20) compared to the other two groups on the first day ($P < 0.01$ and <0.05, respectively).

On the second day, these test results displayed lower mean VAS/VRS scores in the first group (LM20) compared to the other two and the difference was statistically significant ($P < 0.01$ and <0.05, respectively).

The figure for the number of patients in need of extra opioid was 10% in the first group, 30% in the second group, and

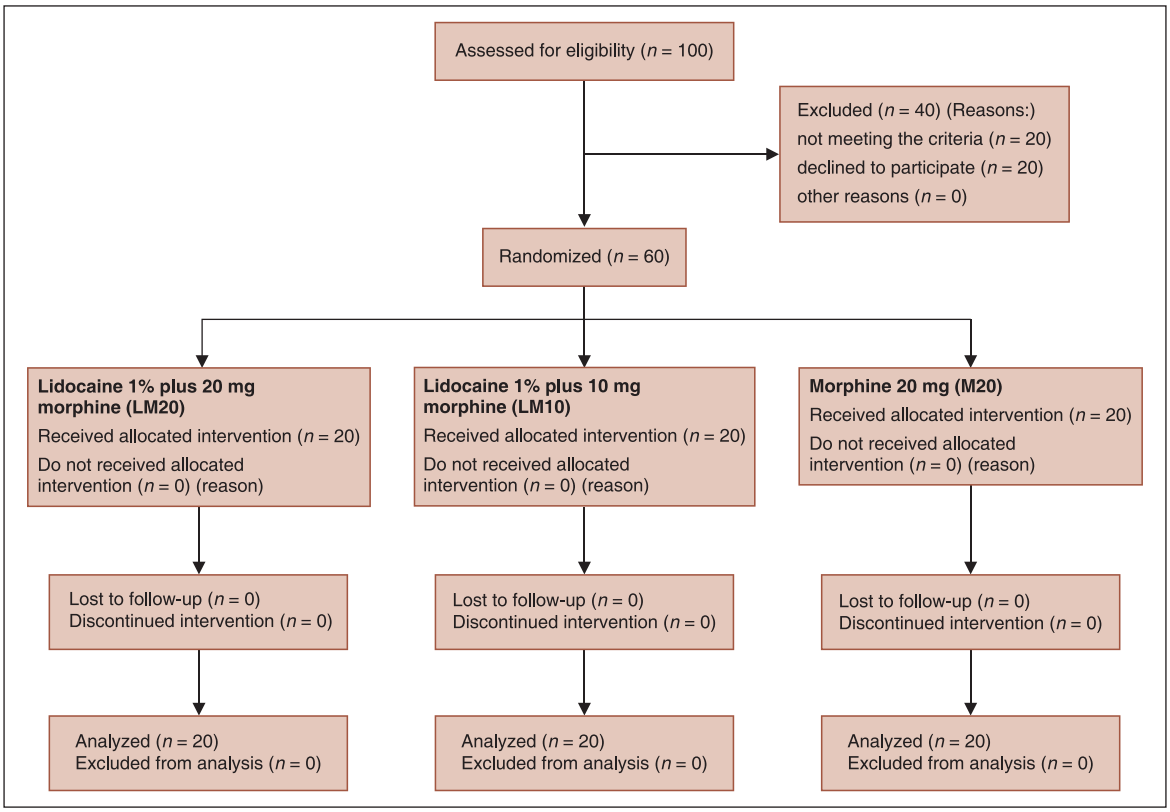

Figure 1: Flowchart

Table 1: Demographic data of the three groups

	Lidocaine 1% plus 20 mg morphine (LM20)	Lidocaine 1% plus 10 mg morphine (LM10)	Morphine 20 mg (M20)	*P*
Number of patients	20	20	20	
Sex (men/women)†	11/9	12/8	10/10	0.2
Age (years)	39.6±10.2	38.2±11.1	2.11±5.37	0.3
Height (cm)	167±9	170±10	172±6	0.15
Weight (kg)	72±12	68±11	71±10	0.23
ASA (I, II)	13/7	13/7	13/7	1.00
Operation duration (h)	3.8±0.5	3.5±0.6	3.4±0.9	0.12
Anesthesia duration (h)	4.2±0.45	4.1±0.5	3.9±0.7	0.20

†The difference among the three groups was not statistically significant ($P > 0.05$)

25% in the third group. Chi-square test results displayed a statistically significant difference ($P < 0.01$). Hawke post-test showed a statistically significant difference between the first group and the other two groups concerning the amount of morphine used ($P < 0.01$).

Although the extra morphine dose that was administered was larger in the second group (LM10) than in the other two groups, the total morphine dose used (average total morphine in the pump and extra morphine administered) was noticeably less in the second group than in the other two.

The side effects are listed in Table 3 and there was no statistically significant difference among the three groups ($P > 0.1$).

Sedation scores on 2 days were measured. On the first day, the number of patients with sedation score ≥2 (≥median) was 3, 9, and 7 in the three groups, respectively, and on the second day, the number was 2, 8, and 6, respectively. There were no differences in between the groups as measured by median test ($P = 0.116$, $P = 0.092$).

Satisfaction score was measured by chi-square test and was significantly better in the first group on the second day ($P = 0.004$).

Nausea/vomiting scores were measured and compared between groups by chi-square test, and no significant difference was between them ($P = 0.366$, $P = 0.402$).

DISCUSSION

Studies show that lidocaine can be effective in managing pain by blocking the sodium channels and possibly by having an inhibiting effect on *N*-methyl-D-aspartate (NMDA) receptors and protein G receptors because it can control the spontaneous impulses of pain in the posterior horn of the spinal cord and injured peripheral nerves. On the other hand,

Table 2: Findings of the study in the three groups (pain score, used morphine, and satisfaction)

	Lidocaine 1% plus 20 mg morphine (LM20)	Lidocaine 1% plus 10 mg morphine (LM10)	Morphine 20 mg (M20)	*P*
First day VAS	2.15±0.2	2.75±0.2	2±0.25	<0.01
Second day VAS	1.88±0.1	2.74±0.3	2.40±0.3	<0.01
Mean VAS	2.05±1.5	2.74±0.25	2.45±0.25	<0.05
Mean first day VRS	1.3±0.6	2.4±0.6	2.1±0.6	<0.05
Mean second day VRS	1.4±0.5	2.3±0.7	2.3±0.5	<0.05
Morphine dose used on the first day (mg)*	6±0.4	20±0.5	16±0.3	0.001
Morphine dose used on the second day (mg)*	5±0.8	16±0.7	14±0.5	0.001
Average total morphine used (mg)*	44±0.9	36±0.8	52±0.4	<0.01
Satisfaction*	70%	45%	55%	<0.05

†No statistically significant difference among the three groups; *The difference is statistically significant; VAS = Visual analog scale; VRS = Verbal rating scale

Table 3: Number of patients with the side effects noticed in the three groups

Side effects	Lidocaine 1% plus 20 mg morphine (LM20)	Lidocaine 1% plus 10 mg morphine (LM10)	Morphine 20 mg (M20)	*P*
Nausea/vomiting†	2	2	3	0.1
Urinary retention†	1	1	1	0.12
Giddiness†	–	–	1	0.18
Hallucination†	–	–	–	–
Higher than 2 sedation score†	2	2	1	0.1

†No statistically significant difference among the three groups

it controls afferent synapses in the transmission path, which also affects the posterior horn of the spinal cord.[7-10]

Lidocaine causes the selective attenuation of C fibers in the posterior column of the spiral cord, and thus can be effective in controlling the pain pathway.[10] The spura spinal analgesic mechanism of lidocaine is due to the changes brought about in the structure of the anterior brain, especially in cingulate cortex.[11-13]

In 1992, Marchettini *et al*. discussed the analgesic effect of lidocaine infusion in controlling and relieving neuropathic pain, mechanical hyperalgesia, and postherpetic neuralgia after herpes.[14] In Rathmell and Ballantyne's extensive meta-analysis in 2005, the effects of the systematic use of lidocaine in controlling neuropathic pain were examined and it was noted that lidocaine was more effective in controlling spontaneous responses than stimulated responses.[15]

Schwartzman *et al*. examined the effect of five daily infusions of lidocaine in patients suffering from severe complex regional pain syndrome and noted that the injection reduced mechanical and thermal sensitivity to pain in these patients.[16] Yardeni *et al*. studied the effect of lidocaine infusion before the operation on controlling the production of inflammatory mediators like interleukin-1 and -6 and the surgery-induced immune alterations. They found that the lidocaine infusion controlled the inflammatory responses considerably and reduced the postoperative inflammation.[17,18] In the study conducted by Thomas *et al*., it was found that intravenous lidocaine can have a remarkable effect on the phantom pain and opioid-resistant pain.[19]

Results from our study show that adding lidocaine 1% to 20 mg morphine in the IV PCA after orthopedic surgery reduced the pain score without causing side effects. This pain-reducing response to lidocaine in our study and other studies can be a guide for treatment with Oralsodium channel blocking agents, such as Mexiletine, Gabapentin, or Duloxetine (antidepressant).[7,13,15,20,21]

Opioids are the most common drugs used in patient-controlled intravenous analgesia pumps (PCIA), but there has always been a concern about their overdose and side effects. This is the reason why lidocaine was examined in this study as an auxiliary medicine to morphine in PCIA, and its probable capacity for decreasing the need for opioids was tested. According to the findings of our current study, adding lidocaine 1% (50 mg/h) to morphine infusion of 1 mg/h not only relieved pain and reduced the need for extra opioid doses, but also enhanced satisfaction without any side effects. However, adding lidocaine to morphine infusion of 0.5 mg/h was not noticeably successful. Taking into account the lack of any side effects resulting from lidocaine poisoning in these patients, it appears that lidocaine 1% at the mentioned infusion rate leads to no considerable side effects.

In a study by Gagnon *et al*. on patients suffering from spinal chord injuries with severe neuropathic pain, it was noted that lidocaine infusion at less than 50 mg/h (similar to the concentration in our study) did not have any notable effects on these patients' pain control and hyperalgesia.[22] This does not agree with the findings of our study. The discrepancy may originate from the fact that in our study, acute pain has been dealt with.

In another study on patients suffering from neuralgia after herpes, lidocaine infusion of 50 mg/h resulted in pain control and less sensitivity to mechanical stimulation. The effects can even be compared to higher than 100 mg/h infusions of lidocaine.[23] These findings agree with the results of the first group (LM20) in our study.

In Clarke *et al.*'s study, more than 200 mg/h infusion of lidocaine was used to control postoperative pain. It was noticed that this quantity can effectively control moderate and severe pain without causing side effects. Additionally, shorter hospitalization time of the group under study compared to the control group was one of the advantages of this method, which was economically considerable.[24]

In a study by Attal *et al*., lidocaine at a dose of 5 mg/kg/h controlled mechanical allodynia after brain strokes in central pain syndrome.[25]

In the patients suffering from neuropathic pain, lidocaine infusion at 1 mg/kg/h was used, while the serum lidocaine levels were checked every 8 h. Then lidocaine concentration was increased in a way that its plasma concentration was kept below 8 μg/ml.[26] The findings of the mentioned study show that this quantity was effective in controlling pain. Of course, it must be noted that lidocaine has an active metabolite named monoethylglycinexylidide, which plays a role in lidocaine poisoning and anesthesia, but cannot be measured when serum lidocaine levels are checked. This raises the question of using high quantities of lidocaine.

The work of other researchers shows that lidocaine (with plasma concentrations of 5-15 μg/ml) is safe and effective in controlling pain. Despite many meta-analyses carried out so far, there are many issues surrounding safe and effective intravenous lidocaine doses, all of which need more investigation. On the other hand, there are opposing views on the maximum allowed time for lidocaine infusion and a final agreement is still to be reached.[25,26] Recently, more investigations have been done on the perioperative use of lidocaine, which have shown positive effects in terms of better pain control and functional recovery and less opioid consumption.[27-31]

In Schwartzman *et al.*'s study, lidocaine at 5 μg/ml plasma concentration was examined for 5 days to control Complex Regional Pain Syndromepain and no side effects were observed.[16]

In conclusion, it seems that adding lidocaine to morphine in PCIA (when proper morphine concentration is chosen) can be a safe method with fewer complications in controlling postoperative pain and it can reduce the need for extra opioid doses.

Limitations of the study

Since there is no contentious agreement on the dose of lidocaine and its infusion standards, more research regarding higher concentrations and longer duration of lidocaine infusion should be carried out. Additionally, it is recommended that the anti-inflammatory effects of lidocaine be examined in future studies.

REFERENCES

1. Sinatra RS, Torres J, Bustos AM. Pain management after major orthopaedic surgery: Current strategies and new concepts. J Am Acad Orthop Surg 2002;10:117-29.
2. Kehlet H, Werner M, Perkins F. Balanced analgesia: What is it and what are its advantages in postoperative pain? Drugs 1999;58:793-7.
3. Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, *et al*. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. Br J Anaesth 2006;97:640-6.
4. Cui W, Li Y, Li S, Wang R, Li J. Systemic administration of lidocaine reduces morphine requirements and postoperative pain of patients undergoing thoracic surgery after propofol-remifentanil-based anaesthesia. Eur J Anaesthesiol 2010;27:41-6.
5. Woolf CJ, Wiesenfeld-Hallin Z. The systemic administration of local anaesthetics produces a selective depression of C-afferent fibre evoked activity in the spinal cord. Pain 1985;23:361-74.
6. Kang H, Kim BG. Intravenous lidocaine for effective pain relief after inguinal herniorrhaphy: A prospective, randomized, double-blind, placebo-controlled study. J Int Med Res 2011;39:435-45.
7. Attal N, Gaudé V, Brasseur L, Dupuy M, Guirimand F, Parker F, *et al*. Intravenous lidocaine in central pain: A double-blind, placebo-controlled, psychophysical study. Neurology 2000;54:564-74.
8. Leong MS, Solvason HB. Case report: Limbic system activation by intravenous lidocaine in a patient with a complex regional pain syndrome and major depression. Pain Med 2000;1:358-61.
9. Benson BE, Carson RE, Kiesewetter DO, Herscovitch P, Eckelman WC, Post RM, *et al*. A potential cholinergic mechanism of procaine's limbic activation. Neuropsychopharmacology 2004;29:1239-50.
10. Parekh PI, Spencer JW, George MS, Gill DS, Ketter TA, Andreason P, *et al*. Procaine-induced increases in limbic rCBF correlate positively with increases in occipital and temporal EEG fast activity. Brain Topogr 1995;7:209-16.
11. Servan-Schreiber D, Perlstein WM, Cohen JD, Mintun M. Selective pharmacological activation of limbic structures in human volunteers: A positron emission tomography study. J Neuropsychiatry Clin Neurosci 1998;10:148-59.
12. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. Pain 2000;87:7-17.
13. Tremont-Lukats IW, Challapalli V, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetics to relieve neuropathic pain: A systematic review and meta-analysis. Anesth Analg 2005;101:1738-49.
14. Marchettini P, Lacerenza M, Marangoni C, Pellegata G, Sotgiu ML, Smirne S. Lidocaine test in neuralgia. Pain 1992;48:377-82.
15. Rathmell JP, Ballantyne JC. Local anesthetics for the treatment of neuropathic pain: On the limits of meta-analysis. Anesth Analg 2005;101:1736-7.
16. Schwartzman RJ, Patel M, Grothusen JR, Alexander GM. Efficacy of 5-day continuous lidocaine infusion for the treatment of refractory complex regional pain syndrome. Pain Med 2009;10:401-12.
17. Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H. The effect of perioperative intravenous lidocaine on postoperative pain and immune function. Anesth Analg 2009;109:1464-9.
18. Harvey KP, Adair JD, Isho M, Robinson R. Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in

elective bowel surgery? A pilot study and literature review. Am J Surg 2009;198:231-6.
19. Thomas J, Kronenberg R, Cox MC, Naco GC, Wallace M, von Gunten CF. Intravenous lidocaine relieves severe pain: Results of an inpatient hospice chart review. J Palliat Med 2004;7:660-7.
20. Galer BS, Harle J, Rowbotham MC. Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: A prospective study. J Pain Symptom Manage 1996;12:161-7.
21. Schnider TW, Gaeta R, Brose W, Minto CF, Gregg KM, Shafer SL. Derivation and cross-validation of pharmacokinetic parameters for computer-controlled infusion of lidocaine in pain therapy. Anesthesiology 1996;84:1043-50.
22. Mailis-Gagnon A, Yegneswaran B, Bharatwal B, Krassioukov AV. Effects of intravenous sodium amobarbital vs lidocaine on pain and sensory abnormalities in patients with spinal cord injury. J Spinal Cord Med 2009;32:49-53.
23. Baranowski AP, De Courcey J, Bonello E. A trial of intravenous lidocaine on the pain and allodynia of postherpetic neuralgia. J Pain Symptom Manage 1999;17:429-33.
24. Clarke C, McConachie I, Banner R. Lidocaine infusion as a rescue analgesic in the perioperative setting. Pain Res Manag 2008;13:421-3.
25. Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology 2004;62:218-25.
26. Carroll I. Intravenous lidocaine for neuropathic pain: Diagnostic utility and therapeutic efficacy. Curr Pain Headache Rep 2007;11:20-4.
27. Tsai TY, Chang SK, Chou PY, Yeh LS. Comparison of postoperative effects between lidocaine infusion, meloxicam, and their combination in dogs undergoing ovariohysterectomy. Vet Anaesth Analg 2013 Jul 9.
28. Farag E, Ghobrial M, Sessler DI, Dalton JE, Liu J, Lee JH, *et al*. Effect of perioperative intravenous lidocaine administration on pain, opioid consumption, and quality of life after complex spine surgery. Anesthesiology 2013;119:932-40.
29. Grady MV, Mascha E, Sessler DI, Kurz A. The effect of perioperative intravenous lidocaine and ketamine on recovery after abdominal hysterectomy. Anesth Analg 2012;115:1078-84.
30. De Oliveira GS Jr, Fitzgerald P, Streicher LF, Marcus RJ, McCarthy RJ. Systemic lidocaine to improve postoperative quality of recovery after ambulatory laparoscopic surgery. Anesth Analg 2012;115:262-7.
31. Grady P, Clark N, Lenahan J, Oudekerk C, Hawkins R, Nezat G, *et al*. Effect of intraoperative intravenous lidocaine on postoperative pain and return of bowel function after laparoscopic abdominal gynecologic procedures. AANA J 2012;80:282-8.

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