



REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br



SCIENTIFIC ARTICLE

Intravenous lidocaine for post-mastectomy pain treatment: randomized, blind, placebo controlled clinical trial



Tania Cursino de Menezes Couceiro^{a,*}, Luciana Cavalcanti Lima^{a,b},
Léa Menezes Couceiro Burle^a, Marcelo Moraes Valença^c

^a Instituto de Medicina Integral Professor Fernando Figueira (IMIP), Recife, PE, Brazil

^b Faculdade Pernambucana de Saúde (FBS), Recife, PE, Brazil

^c Department of Neurology and Neurosurgery, Universidade Federal de Pernambuco, Recife, PE, Brazil

Received 28 April 2014; accepted 19 May 2014

Available online 30 March 2015

KEYWORDS

Postoperative pain;
Treatment;
Local anesthetic;
Pain;
Intravenous lidocaine

Abstract

Background and objective: Postoperative pain treatment in mastectomy remains a major challenge despite the multimodal approach. The aim of this study was to investigate the analgesic effect of intravenous lidocaine in patients undergoing mastectomy, as well as the postoperative consumption of opioids.

Methods: After approval by the Human Research Ethics Committee of the Instituto de Medicina Integral Prof. Fernando Figueira in Recife, Pernambuco, a randomized, blind, controlled trial was conducted with intravenous lidocaine at a dose of 3 mg/kg infused over 1 h in 45 women undergoing mastectomy under general anesthesia. One patient from placebo group was.

Results: Groups were similar in age, body mass index, type of surgery, and postoperative need for opioids. Two of 22 patients in lidocaine group and three of 22 patients in placebo group requested opioid ($p = 0.50$). Pain on awakening was identified in 4/22 of lidocaine group and 5/22 of placebo group ($p = 0.50$); in the post-anesthetic recovery room in 14/22 and 12/22 ($p = 0.37$) of lidocaine and placebo groups, respectively. Pain evaluation 24 h after surgery showed that 2/22 and 3/22 patients ($p = 0.50$) of lidocaine and placebo groups, respectively, complained of pain.

Conclusion: Intravenous lidocaine at a dose of 3 mg/kg administered over a period of an hour during mastectomy did not promote additional analgesia compared to placebo in the first 24 h, and has not decreased opioid consumption. However, a beneficial effect of intravenous lidocaine in selected and/or other therapeutic regimens patients cannot be ruled out.

© 2014 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. All rights reserved.

* Corresponding author.

E-mails: taniacouceiro@yahoo.com.br, taniacursinomcouceiro@gmail.com (T.C.d.M. Couceiro).

PALAVRAS-CHAVE

Dor pós-operatória;
Tratamento;
Anestésico local;
Dor;
Lidocaína intravenosa

Lidocaína intravenosa no tratamento da dor pós-mastectomia: ensaio clínico aleatório encoberto placebo controlado**Resumo**

Justificativa e objetivo: O tratamento da dor pós-operatória em mastectomia continua sendo um grande desafio apesar da abordagem multimodal. O objetivo deste estudo foi investigar o efeito analgésico da lidocaína intravenosa em pacientes submetidas a mastectomia, como também, o consumo de opioide pós-operatório.

Métodos: Após aprovação pelo comitê de ética e pesquisa em seres humanos do Instituto de Medicina Integral Prof. Fernando Figueira em Recife - Pernambuco foi realizado ensaio clínico aleatório encoberto placebo controlado com lidocaína intravenosa na dose de 3 mg/kg infundida em uma hora, em 45 mulheres submetidas a mastectomia sob anestesia geral. Excluída uma paciente do grupo placebo.

Resultados: Os grupos foram semelhantes quanto à idade, índice de massa corpórea, tipo de intervenção cirúrgica e necessidade de opioide no pós-operatório. Solicitaram opioide 2/22 pacientes nos grupos da lidocaína e 3/22 placebo ($p=0,50$). Identificada a dor ao despertar em 4/22 no grupo lidocaína e 5/22 ($p=0,50$) no grupo placebo; na sala de recuperação pós-anestésica em 14/22 e 12/22 ($p=0,37$) nos grupos lidocaína e placebo respectivamente. Ao avaliar a dor 24 horas após o procedimento cirúrgico 3/22 e 2/22 ($p=0,50$) das pacientes relataram dor em ambos os grupos respectivamente.

Conclusão: A lidocaína intravenosa na dose de 3mg/kg administrada em um período de uma hora no transoperatório de mastectomia não promoveu analgesia adicional em relação ao grupo placebo nas primeiras 24 horas e não diminuiu o consumo de opioide. Contudo, um efeito benéfico da lidocaína intravenosa em pacientes selecionadas e/ou em outros regimes terapêuticos não pode ser descartado.

© 2014 Sociedade Brasileira de Anestesiologia. Publicado por Elsevier Editora Ltda. Todos os direitos reservados.

Introduction

Postoperative pain remains inadequately treated despite its predictability and progress of various analgesic techniques and drugs available for its control.¹ Some authors report that, regardless of the type of surgical procedure, postoperative pain is present and with varying intensity.²⁻⁴ The incidence of postoperative pain in breast cancer is low when treated properly,⁵ however, it can result in cardiovascular and respiratory complications, as well as persistent postoperative pain.⁶ Therefore, adequate pain control is of paramount importance in clinical practice.

In this context, the multimodal approach to postoperative pain should be considered, given the analgesic results obtained with each particular drug and the lower incidence of adverse effects.^{6,7}

In order to provide postoperative analgesia, intravenous lidocaine has been used intra- and post-operatively as part of multimodal approach,⁸ with proven analgesic effect in postoperative abdominal⁹ and pelvic surgery, such as colectomy¹⁰ and prostatectomy,¹¹ respectively.

In addition to the analgesic action, local anesthetics have anti-inflammatory action,¹¹ justifying the use of intravenous lidocaine to modulate the inflammatory response resulting from postoperative pain.¹² Other benefits are the reduced need for postoperative opioids,^{8,10} reduced complications such as nausea and vomiting, and reduced pain intensity in the first 24 h.¹⁰

Meta-analyses^{9,13} show conflicting results regarding the analgesic effect of lidocaine on postoperative pain, highlighting the need to specify the real value of intravenous lidocaine for postoperative pain relief in patients undergoing mastectomy. The objective of this study was to investigate the analgesic effect of intravenous lidocaine in the first 24 h in women undergoing mastectomy, as well as to assess the consumption of opioids postoperatively.

Methods

After approval by the Human Research Ethics Committee of the Integrative Medicine Institute Prof. Fernando Figueira (IMIP), under number 2026 CAAE 0202009917210, and obtaining written informed consent from participants, a randomized, placebo controlled, blind clinical trial was performed from July 2011 to August 2012, at the IMIP, Recife, Pernambuco, Brazil.

The study included women aged between 18 and 75 years who underwent mastectomy for breast cancer treatment. Exclusion criteria were patients with relative or absolute contraindication to the use of lidocaine (allergy to local anesthetics, changes in atrioventricular conduction, uncontrolled epilepsy, porphyria, and malignant hyperthermia), those receiving antidepressants and/or anticonvulsants, with cardiac arrhythmia and any type of rheumatic disease, distant metastasis or in contralateral breast, patients who

do not understand the numerical scale (NS) of pain assessment and/or have used opioids in the past 24 h.

Data were collected using a standardized questionnaire to characterize the sample. Data included age, body mass index (BMI), type of surgery, adjuvant treatment, and pain history, such as headache and surgery breast pain. The variables studied were presence and intensity of pain 24 h after surgery at three different time points (M1 upon awakening from anesthesia, M2 = 1 h after admission to the post-anesthesia care unit (PACU), and M3 = 24 h after the surgical procedure) and the need for postoperative opioids. Pain was assessed at rest, using a NS pain from 0 to 10 (0 = no pain and 10 = worst possible pain). For analysis, pain severity was categorized as absent (0), mild (1–3), moderate (4–7), severe (7–9), and very severe (10).

Patients were randomly allocated into two groups (lidocaine or placebo) on a 1:1 ratio by drawing blocks of four patients, as in the event of suspension or discontinuation of study, the number of patients would remain similar in both groups. To ensure that the study was blind, the lidocaine and placebo ampoules were prepared in similar vials and numbered sequentially. All patients underwent general anesthesia with fentanyl ($5 \mu\text{g kg}^{-1}$), propofol (1.0 mg kg^{-1}), and rocuronium (0.3 mg kg^{-1}) and maintained with 1.5% sevoflurane in 50% fraction of inspired oxygen. Bolus dose of lidocaine was not administered and, after incision, the 1 h infusion of saline solution (100 mL) containing the total dose of lidocaine (3 mg kg^{-1}) or placebo was started.

All patients received intravenous dipyrone (2 g) and ketoprofen (100 mg) during surgery as prophylaxis of postoperative pain. The chest wall was infiltrated with a solution containing 0.025% bupivacaine and epinephrine 1:400,000, according to the Mastology Service conduct. For postoperative analgesia 1 g dipyrone was prescribed every 6 h. In case of pain, codeine (30 mg) associated with paracetamol (200 mg) was prescribed to be administered according to patients' request.

The sample size calculation was based on the assumption of a 5% alpha-error, 10% beta-error, and 90% power and considering that lidocaine group had a 70% reduction in opioid consumption, while the placebo group would have a 30% reduction.¹³ A loss of 10% was presumed, resulting in 44 subjects divided into two groups of 22 patients each.

For data analysis, EPI-INFO™ software version 3.5.1 for Windows™ was used. Data were presented as absolute and relative frequency distribution and presented in tables. Numerical variables were represented as measures of central tendency (mean) and dispersion (standard deviation and range). Chi-square test with Yates' correction application and Fisher's exact test were used to verify the existence of an association between categorical variables. A p -value < 0.05 was considered significant.

Results

Forty-four patients who underwent mastectomy were evaluated, 22 from lidocaine group and 22 from placebo group (Fig. 1, flowchart). One patient from placebo group was excluded because, although she has shown to understand how to use the proposed rating scale of pain (NS) and therefore have been included in the study, she could not evaluate

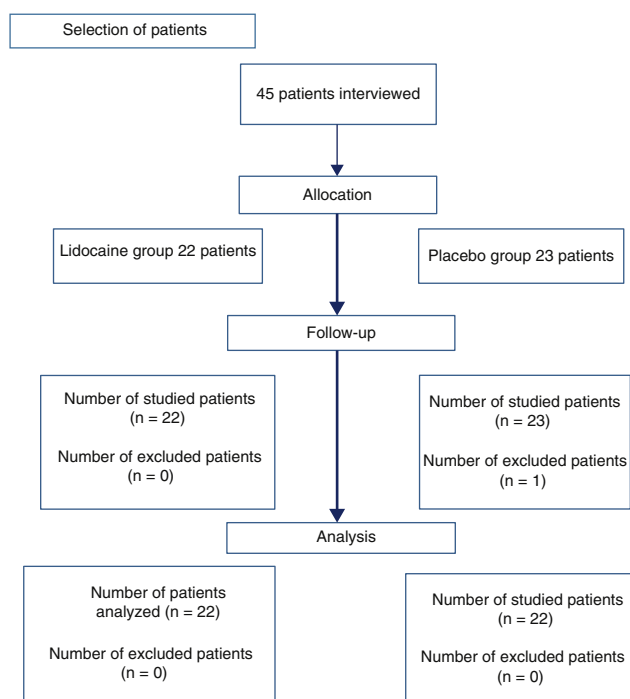


Figure 1 CONSORT flowchart. n , number of patients.

the pain using the NS postoperatively. The groups were similar in age, body mass index, adjuvant chemotherapy treatment before mastectomy, and history of pain (Table 1). Regarding the type of surgery, two-thirds of patients in both groups underwent Madden's mastectomy and the other one-third underwent mastectomy with sentinel lymph node removal (Table 1).

There was no difference between groups regarding postoperative pain at rest in any of the time points assessed: upon awakening from anesthesia (M1), 1 h after PACU admission (M2), and 24 h after the surgical procedure (M3) (Table 2).

Opioid consumption in the first 24 h after surgery was similar in the lidocaine and placebo groups (Table 2).

Discussion

This study demonstrated that intravenous administration of lidocaine during surgery at a dose of 3 mg kg^{-1} in 1 h was not superior to placebo for postoperative analgesia in patients undergoing mastectomy.

Other authors¹⁰ reported benefit with the use of intravenous lidocaine for postoperative pain relief. The authors found improved analgesia in patients undergoing laparoscopic colectomy when using an initial dose of 1.5 mg kg^{-1} followed by continuous infusion of $2.0 \text{ mg kg}^{-1} \text{ g}$, which lasted for 24 h postoperatively.

De Oliveira et al.¹⁴ evaluating pain in women undergoing, ambulatory laparoscopic surgery who received lidocaine (1.5 mg kg^{-1}) 20 min prior to surgical incision, followed by an infusion of $2 \text{ mg kg}^{-1} \text{ h}^{-1}$ up to the end of surgical procedure, observe pain relief in the lidocaine group.

The lidocaine benefit evidenced by these authors may be related to the different infusion regimens used. The infusion

Table 1 Sample characterization according to groups.

| Characteristic | Lidocaine | Placebo | <i>p</i> |
|--------------------------|---------------|---------------|-------------------|
| Age (years) ^a | 52.4 ± 12.4 | 47.0 ± 11.0 | 0.10 ^b |
| BMI ^a | 28.1 ± 8.1 | 28.2 ± 3.9 | 0.89 ^b |
| Prior QT | 11/22 (50%) | 10/22 (45.4%) | 0.38 ^c |
| Headache | 6/22 (30%) | 9/22 (40.9%) | 0.34 ^c |
| Breast pain | 10/22 (45.5%) | 8/22 (36.3%) | 0.37 ^c |
| Madden's mastectomy | 17/22 (77.2%) | 17/22 (77.2%) | – |

QT, chemotherapy; BMI, body mass index.
^a Mean ± standard deviation.
^b Chi-square test.
^c Yates' correction and Fisher's exact test.

Table 2 Occurrence and intensity of pain at three different times and postoperative opioid requirement in 24 h.

| | Lidocaine | | Placebo | | <i>p</i> |
|---------------------------------|-----------|------|----------|------|----------|
| | <i>n</i> | % | <i>n</i> | % | |
| <i>Postoperative pain</i> | | | | | |
| Upon awakening | 4/22 | 18.1 | 5/22 | 22.7 | 0.50 |
| 1st hour of PO (PACU) | 14/22 | 63.6 | 12/22 | 63.4 | 0.37 |
| 24th hour of PO | 11/22 | 50.0 | 12/22 | 54.5 | 0.50 |
| <i>Pain in a 24-h period</i> | | | | | |
| Mild to moderate | 20/22 | 90.9 | 19/22 | 86.3 | 0.50 |
| Severe to very severe 24 h | 2/22 | 9.09 | 3/22 | 13.6 | |
| <i>Postoperative opioid use</i> | | | | | |
| Opioid 24 h | 3/22 | 13.6 | 2/22 | 9.0 | 0.50 |

n, sample; Opioid 24 h, opioid requirement in the first 24 h after surgery; PACU, post-anesthesia care unit; PO, postoperative.

of lidocaine for 24 h postoperatively may have resulted in suppression of central sensitization¹⁵ and thus contributed to obtain good analgesic effect in comparison with our study. The use of bolus before surgery may lead us to think that the administration of lidocaine before surgical incision can promote better postoperative pain results by reducing the release of inflammatory substances.

Regarding the dose, in a recent study¹⁶ using intravenous lidocaine in patients who underwent mastectomy, the authors evaluated 36 patients divided into two groups, with 19 women in the placebo group and 17 in the lidocaine group. Lidocaine was administered at a dose of 1.5 mg kg⁻¹ before surgical incision, followed by the same dose every hour, which lasted up to 60 min after closing the surgical incision. The perioperative conduct for postoperative pain management was the use of ketorolac at a single dose of 30 mg. The authors found that lidocaine was able to provide superior analgesia to placebo only in the fourth hour after surgery. These authors¹⁶ found a decrease in the central hyperalgesia and a decreased incidence and severity of persistent postoperative pain in the lidocaine group.

In our study, the absence of additional analgesic effect in the early postoperative period (first 4 h after surgery) in the lidocaine group may have been masked by the efficiency of the preconized postoperative pain prophylaxis, as we the administration of ketoprofen (100 mg) and dipyrone (2 g) followed by dipyrone (1 g) every 6 h for 24 h was systematized. Associated with these drugs, infiltration of the chest

wall ipsilateral to the mastectomy with local anesthetic and vasoconstrictor was performed in all patients.

Currently, there is no consensus about the best lidocaine administration method. Several infusion regimens have been used: exclusively during surgery,⁸ intraoperatively and continued for 1 h¹⁶ or 24 h¹⁰, and even as patient-controlled analgesia.¹⁷ However, in our study the choice of lidocaine administration for a period of 1 h without using an initial dose (bolus) was based on a report of another study by this investigator,¹⁸ which showed benefit when using intravenous lidocaine for a short period of time, and because the surgical procedure in the institution usually has an average duration of 1 h.

The choice of the 3 mg kg⁻¹ dose was based on the analgesic results of therapeutic doses used in clinical practice (2–5 mg mL⁻¹), which achieved serum levels of 2 µg mL⁻¹. Because the mild adverse effects begin with serum levels above 3 µg mL⁻¹, this dose results in a safety pharmacology window for the use of intravenous lidocaine.^{19,20}

Therefore, studies that stipulate the beginning of IL infusion in relation to the surgical incision time, duration of infusion in the postoperative period, and the total dose of intravenous lidocaine to be administered are required to define its actual role in postoperative analgesia in women undergoing mastectomy.

However, the non-observation of analgesic advantages in patients undergoing mastectomy may be more related to the type of pain resulting from surgical procedure than

properly to the infusion regimen used, as the pain resulting from cholecystectomies has visceral origin, while the post-mastectomy pain has somatic origin. On the other hand, it should be considered that the severity of pain in the postoperative period of this surgery varies from mild to moderate and the use of simple analgesics such as dipyrone associated with anti-inflammatory drugs results in adequate analgesia.

In this study, opioid requirement was equal in both groups. These data are similar to those reported by other authors who evaluated opioid consumption in women undergoing mastectomy.¹⁶ This result differs from studies with outpatients undergoing laparoscopic surgery,¹⁴ laparoscopic colectomy,¹⁰ and cholecystectomies,²¹ in which the authors observed a decrease of about 50% in opioid consumption during the first 24 h.

A human study²² shows that there is an excitatory action of the local anesthetic in the intestine smooth muscle and thus a decreased colonic distension and postoperative discomfort. This action justifies the lidocaine ability to alleviate visceral pain, as demonstrated in animal models^{23,24} and proven from the reported results in abdominal surgery.

This positive analgesic response in abdominal surgery can probably be explained by the inhibitory action of intravenous lidocaine in visceromotor reflexes secondary to colon and rectum distention, which contributes to the relief of visceral pain.^{9,10,13} It is noteworthy that in the pain caused by hip arthroplasty²⁵ and mastectomy,¹⁶ intravenous lidocaine did not promote analgesia, probably because these surgical procedures result in somatic pain that is less inhibited by lidocaine.²⁶

This finding helps to emphasize the hypothesis that intravenous lidocaine has a preferred analgesic effect on visceral^{9,10,13} and neuropathic^{26,27} pain. However, recent studies have demonstrated that intravenous lidocaine has analgesic¹³ and antihyperalgesic^{28,29} actions resulting from peripheral blockade of ectopic impulses involved in nociception and also from its action on potassium channels, calcium channels, and G-protein coupled receptors. It also has anti-inflammatory action^{30,31}, an effect resulting from the lower neutrophil accumulation at the site of injury and reduced release of inflammatory mediators.^{29,30} These actions justify its use in multimodal approach to postoperative analgesia.

Some limitations of this study should be considered. Pain was assessed only at rest. It is known that pain can arise or worsen with limb movement on the operated side, and pain assessment at this point could bring additional information. Pain on movement was not assessed because not moving the operated side member in the first 24 h after the surgical procedure is the Mastology Service protocol. The pain symptom evaluation was performed for a short period after surgery (24 h). However, Grigora et al.¹⁶ found no difference between pain scores when evaluated patients undergoing mastectomy up to the seventh postoperative day.

Regarding persistent postoperative pain after mastectomy, the benefit of lidocaine has been observed.¹⁶ However, this type of pain was not assessed in our study.

Therefore, additional studies are needed to identify the lowest dose able to promote analgesia, "What is the most appropriate regime for infusion?", and finally, identify the value of lidocaine in the multimodal treatment of acute and chronic postoperative pain. Thus, in this study, intravenous lidocaine at a dose of 3 mg kg⁻¹ administered over a

1 h period perioperatively during mastectomy did not promote additional analgesia compared to placebo within the first 24 h and did not decrease opioid consumption. However, a beneficial effect of intravenous lidocaine in selected patients and/or other therapeutic regimens cannot be ruled out.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

We thank the Cristália Produtos Químicos e Farmacêuticos LTDA for the ethical and careful preparation of drugs for the study (lidocaine and placebo).

References

1. White PF. Pain management after ambulatory surgery: where is disconnect? *Can J Anaesth.* 2008;55:201–7.
2. Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. *Yale J Biol Med.* 2010;83:11–25.
3. Maier C, Nestler N, Richter H. The quality of pain management in German hospitals. *Dtsch Arztebl Int.* 2010;107:607–14.
4. Couceiro TCM, Valença MM, Lima LC, et al. Prevalência e influência do sexo, idade e tipo de operação na dor pós-operatória. *Rev Bras Anesthesiol.* 2009;59:314–20.
5. Couceiro TCM, Valença MM, Raposo MCF, et al. Prevalence of postmastectomy pain syndrom and associated risk factors: a cross-sectional cohort study. *Pain Manag Nurs.* 2014;15:731–7.
6. Elvir-Lorenzo OL, White PF. Postoperative pain management after ambulatory surgery: role of multimodal analgesia. *Anesthesiol Clin.* 2010;28:217–24.
7. White P, Kehlet H. Improving postoperative pain management what are the unresolved issues? *Anesthesiology.* 2010;112:220–5.
8. Lauwick S, Kim DJ, Michelagnoli G, et al. Functional walking capacity as an outcome measure of laparoscopic prostatectomy: the effect of lidocaine infusion. *Br J Anaesth.* 2009;103:213–9.
9. Sun Y, Li T, Wang N, et al. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Dis Colon Rectum.* 2012;55:1183–94.
10. Kaba A, Laurent SR, Detroz BJ, et al. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology.* 2007;106:11–8.
11. Beloeil H, Mazoit JX. Effect of local anesthetics on the postoperative inflammatory response. *Ann Fr Anesth Reanim.* 2009;28:231–7.
12. Clarke C, McConachie I, Banner R. Lidocaine infusion as a rescue analgesic in the perioperative setting. *Pain Res Manag.* 2008;13:421–3.
13. Marret E, Rolin M, Beaussier M, et al. Meta-análise of intravenous lidocaine and postoperative recovery after abdominal surgery. *Br J Surg.* 2008;95:1331–8.
14. De Oliveira GS, Fitzgerald P, Streicher LF. Systemic lidocaine to improve postoperative quality of recovery after ambulatory laparoscopic surgery. *Anesth Analg.* 2012;115:262–7.
15. Olschewsk A, Schnobel-Eehalt R, Li Y, et al. Mexiletine and lidocaine suppress the excitability of dorsal horn neurons. *Anesth Analg.* 2009;109:258–64.

16. Grigoras A, Lee P, Sattar F, et al. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. *Pain*. 2012;28:567–72.
17. Cepeda MS, Delgado M, Ponce M, et al. Equivalent outcomes during postoperative patients-controlled intravenous analgesia with lidocaine plus morphine versus morphine alone. *Anesth Analg*. 1996;83:102–6.
18. Couceiro TCM, Valença MM. Lidocaína endovenosa no tratamento da síndrome SUNCT secundária a tumor de hipófise, Seguimento de uma paciente por um período de quatro anos. Relato de caso. *Rev Dor*. 2013;14:320–2.
19. Lauretti GR. Mecanismos envolvidos na analgesia da lidocaína venosa. *Rev Bras Anesthesiol*. 2008;58:280–6.
20. Oliveira CMB, Issy AM, Sakata RK. Lidocaína por via venosa intra-operatória. *Rev Bras Anesthesiol*. 2010;60:325–33.
21. Saadawy IM, Kaki AM, Ab El Latif AA, et al. Lidocaine vs. magnesium: effect on analgesia after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand*. 2010;54:549–56.
22. McKay A, Gottschalk A, Ploppa A, et al. Systemic lidocaine decreased the perioperative opioid analgesic requirements but failed to reduce discharge time after ambulatory surgery. *Anesth Analg*. 2009;109:1805–8.
23. Maggi CA, Manzini S, Meli A. contribution of neurogenic and myogenic factors in the response of rat proximal colon to distention. *Am J Physiol*. 1987;252:G447–57.
24. Ness TJ. Intravenous lidocaine inhibits visceral nociceptive reflexes and spinal neurons in the rat. *Anesthesiology*. 2000;92:1685–91.
25. Martin F, Cherif K, Gentili ME, et al. Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *Anesthesiology*. 2008;109:118–23.
26. Kastrup J, Bach FW, Petersen P, et al. Lidocaine treatment of painful diabetic neuropathy and endogenous opioid peptides in plasma. *Clin J Pain*. 1989;5:239–44.
27. Tremont-Lukats IW, Hutson PR, Backonja MM. A randomized, double-masked, placebo-controlled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. *Clin J Pain*. 2006;22:266–71.
28. Nasser R, Yadla S, Maltenfort MG, et al. Complications in spine surgery. *J Neurosurg Spine*. 2010;13:144–57.
29. Mitchell SJ, Pellett O, Gorman DF. Cerebral protection by lidocaine during cardiac operations. *Ann Thorac Surg*. 1999;67:1117–24.
30. Mathew JP, Mackensen GB, Phillips-Bute B, et al. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke*. 2009;40:880–7.
31. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology*. 2000;93:858–75.