Can local anesthesia with ropivacaine provide postoperative analgesia in extraction of impacted mandibular third molars? A randomized clinical trial

Klinger de Souza Amorim, DDS, MSc,[a] Anne Caroline Gercina, DDS,[a] Filipe Mazar Santos Ramiro, DDS,[b] Leonardo de Araújo Medeiros, DDS,[b] Jaiza Samara Macena de Araújo, DDS, MSc,[a] Francisco Carlos Groppo, DDS, PhD,[a] and Liane Maciel de Almeida Souza, DDS, PhD[b]

Objective. The aim of this study was to compare the local anesthesia efficacy of ropivacaine 0.75% compared to lidocaine 2% with 1:100,000 epinephrine for postoperative analgesia following extraction of impacted mandibular third molars.

Study Design. In this randomized, double-blind crossover clinical trial, 30 participants underwent surgical removal of bilateral impacted mandibular third molars under local anesthesia using ropivacaine 0.75% or lidocaine 2% with 1:100,000 epinephrine. The pain was recorded on a visual analog scale at 4, 8, 12, 24, and 48 h postoperatively. The use of analgesics and the presence of adverse effects were recorded.

Results. The duration of soft tissue anesthesia in the ropivacaine group was significantly longer than that in the lidocaine group. The lidocaine group recorded significantly higher visual analog scale scores at all postoperative time intervals, except in the final 48-h period. Analgesic use was higher in the lidocaine group. Rescue medication was used by 2 patients in each group (6.7%). Significantly more postoperative bleeding was seen in the ropivacaine group.

Conclusion. Ropivacaine 0.75% injection before the surgical procedure may be associated with preventive analgesia for extraction of impacted mandibular third molars. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:512−518)

The concept of preventive analgesia considers the fact that the stimulation of nociceptive fibers promotes neural and behavioral changes, which may persist even after cessation of the noxious stimulus. Preventive analgesia can be used to reduce or prevent pain during the perioperative period and reduce the use of analgesics for the control of postoperative pain (POP), thereby reducing the patient's morbidity and discomfort.[1]

POP is an inherent and unavoidable consequence of most dental treatments, especially surgeries. Pain management can be performed through block anesthesia and the use of anti-inflammatories before the tissue injury. The intensity of pain might vary according to the duration of the procedure and individual pain. Oral surgical procedures usually result in acute POP, which, if not well managed, may increase morbidity and patient discomfort.[2]

Currently, in dentistry, there are 4 main classes of drugs that can be used to control POP, acting at different stages of the etiopathogenesis of pain: local anesthetics, nonsteroidal anti-inflammatory drugs, corticosteroids, and analgesics (central and peripheral acting).[3] Local anesthetics are widely utilized for their ability to block sensation in a limited area, and they are also among the class of pharmacologic compounds used to attenuate or eliminate pain. They are used in regional blocks, in the induction of intra-operative and/or postoperative analgesia, and for the management of acute and chronic pain.[4] A systematic literature review showed that block anesthesia has shown potential for postoperative analgesia; that is, beyond the initial purpose of intra-operative anesthesia.[5]

Recent studies involving local anesthetics have shown that ropivacaine can be considered safer than bupivacaine, due to its decreased neurotoxic and cardiotoxic effects. Ropivacaine has a short latency period and a long duration of action, for both infiltrative and nerve block anesthesia; these aspects offer safety and predictability during the procedure. Ropivacaine is an amide local anesthetic that is chemically homologous to bupivacaine, commercially available as a pure levorotatory isomer for medical use, and less toxic than bupivacaine in its racemic form. Therefore, ropivacaine is an effective and safe alternative to bupivacaine, when a prolonged duration of anesthesia is required.[6]

Numerous studies that compare a variety of local anesthetics used lidocaine 2% with 1: 100,000 epinephrine as the gold standard.[4] The purpose of this study was to evaluate and compare the efficacy of

Statement of Clinical Relevance

Third molar extraction presents peak pain on the day of surgery. Ropivacaine 0.75% as a local anesthetic may present advantages such as long-lasting anesthesia, low toxicity, no vasoconstriction, and less analgesic use, leading to less postoperative pain.

[a]Pharmacology, Anesthesiology and Therapeutics Department of the Piracicaba Dental School, University of Campinas, Piracibaba, São Paulo, Brazil.
[b]Federal University of Sergipe, Oral Surgery and Anesthesiology Area of Dentistry Department, Aracaju, Sergipe, Brazil.
Received for publication Mar 24, 2020; returned for revision Aug 2, 2020; accepted for publication Sep 23, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.09.010

ropivacaine 0.75% without a vasoconstrictor compared to lidocaine 2% with 1:100,000 epinephrine in the management of the postoperative pain after extraction of impacted mandibular third molars.

MATERIALS AND METHODS

This randomized, double-blind crossover clinical trial was approved by the Human Health Research Ethics Committee (Protocol: 02988812.3.0000.5546) and approved by the Brazilian registry of clinical trials (Registration Number RBR-99S7WV). It complied with the principles of the Declaration of Helsinki 1964 and amendments thereafter. Informed consent was obtained from all patients included in the study. Study patients were those who sought dental services and required the surgical removal of bilateral impacted mandibular third molars. Patients with mesioangular impactions classified as class II-B according to Pell and Gregory's classification[7] on panoramic radiographic examination were selected for the study.

Volunteers aged between 18 and 35 years, both male and female, without any significant medical conditions and with physical status ASA (American Society of Anesthesiologists) I[4] (verified before each treatment session) were included in the study. Exclusion criteria included alcoholism, use of drugs that affect the central nervous system (stimulants, relaxants, depressants, or sedatives), use of anti-inflammatories or any kind of analgesics within 15 days before the surgery, and pregnancy, lactation, anxiety related to dental treatment, or hypersensitivity to local anesthetics.

The study was conducted by 3 investigators, with well-defined roles, without any collaborative communication between them. The first investigator was responsible for anamnesis and clinical examination for evaluation of inclusion and exclusion criteria, randomization of the first stage of surgery, and anesthetic used in each procedure. Randomization was performed using a random draw of cards with the letter R or L from an envelope, allocating patients into the R group (ropivacaine hydrochloride 0.75% solution for injection) or L group (lidocaine hydrochloride 2.0% + epinephrine hemitartrate 1:100,000).

Thereafter, 3 Luer lock syringes were prepared to contain 1.8, 0.9, and 0.9 mL of the same anesthetic solution. The syringes were prepared immediately before the surgical procedure to ensure freshness of the solution. In order to control postoperative edema and trismus, a single dose of intramuscular dexamethasone (4 mg) was administered[4] to all study participants 30 min before surgery. Subsequently, the patients underwent local anesthetic injection, via the direct technique for inferior alveolar nerve block (1.8 mL), buccal nerve block (0.9 mL), and buccal mandibular infiltration (0.9 mL), according to the preestablished protocol.[6] Subsequently, they underwent the surgical procedure of mandibular third molar extraction. The surgical technique was standardized to all patients, with osteotomies with a rotary instrument under irrigation with physiologic solution (NaCl 0.9%) until the tooth was exposed at its cementoenamel junction plus odontosection.

Each patient underwent 2 surgical procedures performed by the second investigator was K.S.A., on 2 separate days to remove the impacted mandibular third molars from each side. All procedures were performed in the morning (to avoid circadian interferences in pain threshold)[3] and the minimum interval between the first and second surgeries was 2 weeks. Each procedure was carried out with a different anesthetic protocol according to the previous randomization.

After the procedure, sodium dipyrone (12 tablets, 500 mg each, 1 every 6 h) was prescribed as the postoperative analgesic drug, only to be used in case of pain or discomfort. Patients were familiarized with the 10 cm visual analog scale (VAS, a descriptive pain scale)[2] and instructed to assess and document pain at 4, 8, 12, 24, and 48 h after surgery. The rescue medication prescribed was paracetamol (12 tablets, 750 mg each, 1 every 6 h) in case of inadequate analgesia after taking sodium dipyrone.

The duration of anesthesia was recorded during the procedure and postoperatively, at home, with the lower lip pinprick test (using a blunt needle), where the patients were instructed to record the exact time when numbness of the lower lip ceased (assumed as the end of soft tissue anesthesia).[8] To prevent subjective bias in case of voluntary or involuntary noncompliance, a third investigator contacted the patients by phone every 30 min to ensure that accurate data regarding the exact time when the anesthetic effect receded was recorded. Information regarding the intake of prescribed analgesic medication, the time interval between the intake of medications, and the number of tablets taken during the first 72-h postoperative period, as well as any postoperative complications, including bleeding in the first 24-h postoperative period, were obtained by contacting the patients by phone at the end the first 3 postoperative days.

Sample Size Calculation

Evaluation of POP was one of this study's most important objectives. Considering the results with 10 patients in the previous pilot study for POP in 24 h (mean ± standard deviation, L group: 11.93 ± 14.3; R group: 2.06 ± 4.21, in millimeters on the VAS), 30 patients would be needed to achieve a 95% test power with a significance level of 5%, because this is a crossover study with an equal proportion of patients in both groups (*t* test; BioEstat 5.0 Mamirauá institute, Tefé. Amazonas, Brazil).

Statistical Analysis

Friedman, Fisher's exact, chi-square, and paired *t* tests were performed to analyze the data. For all tests, the level of significance was set at 5%. (GraphPad 7.0, GraphPad Software. San Diego, California, United States of America) and BioEstat 5.0 were used to perform analyses.

RESULTS

A total of 42 patients required surgical removal of mandibular third molars. Ten did not meet the inclusion criteria and 2 declined to participate in the study; therefore, 30 participants were included in this study, and all completed the study (Figure 1). Male participants were between 18 and 35 years old (mean ± SD, 25.23 ± 5.05) and female participants were between 19 and 33 years old (mean ± SD, 21.7 ± 3.24), and the difference in sex distribution was not statistically significant (female patients, 56.7%; male patients, 43.3%).

It can be observed in Figure 2 that the duration of anesthesia was significantly different between the study groups. The L group recorded a significantly shorter duration, ranging from 108 to 360 min (mean ± SD, 213.8 ± 41 min), whereas the R group recorded a duration of 342 to 618 min (mean ± SD, 445.7 ± 58 min).

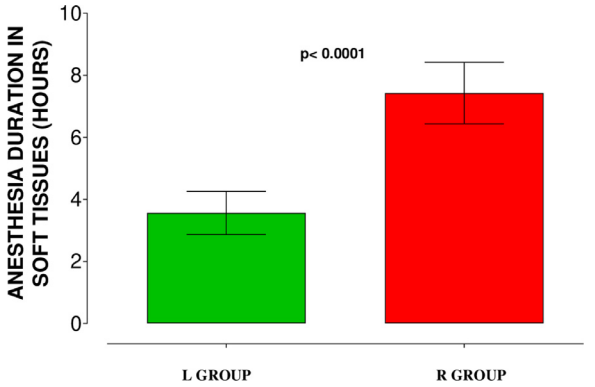

Fig. 2. Mean ± standard deviation of duration of soft tissue anesthesia (paired *t* test, $P < .0001$).

Patients in the L group displayed higher VAS scores in all postoperative periods, except 48 h, at which time

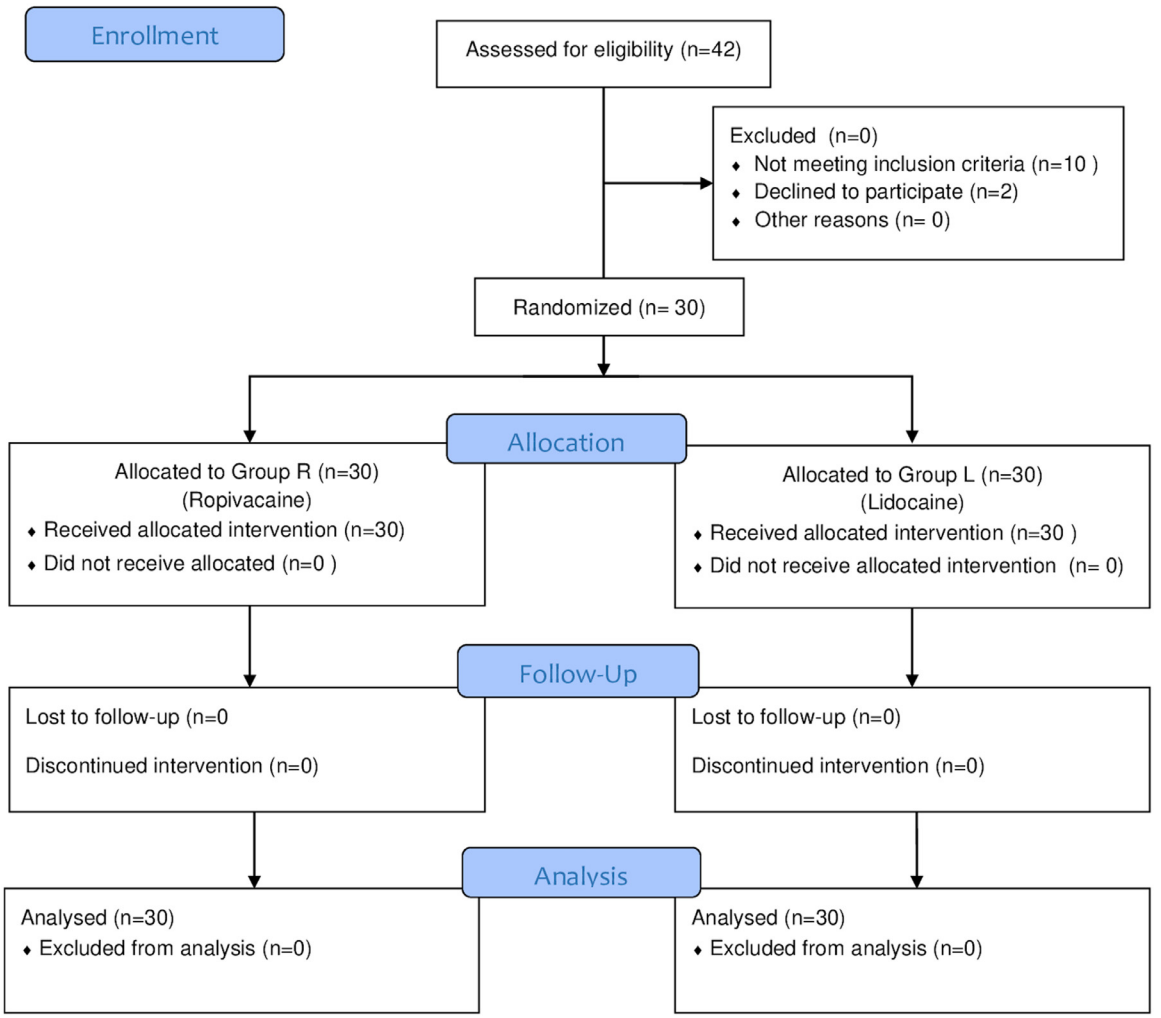

Fig. 1. Flow diagram of the study.

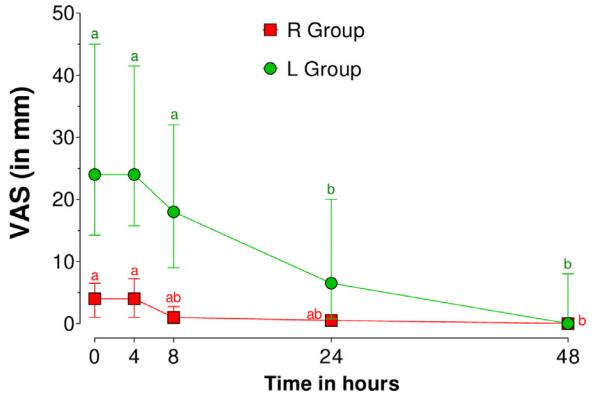

Fig. 3. Visual analog scale score means (± interquartile range) according to postoperative time. Different letters represent statistically significant difference between periods, considering each local anesthetic individually.

point none of the patients reported pain (Figure 3). There was a statistically significant difference within the R group only when comparing 0 and 4 h to 48 h. There was a statistically significant difference within the L group comparing the periods 0, 4, and 8 h to 24 and 48 h.

In all postoperative periods, patients in the L group consumed more analgesic medications compared to those in the R group (Figure 4), and the difference was found to be statistically significant. The average amount of analgesic used by patients in the R group was 0 12 h postoperatively as well, although it was not the mean value. There was a statistically significant difference in medication use between the 2 groups; see Table I.

The prescribed rescue medication was used by 2 patients (6.7%) in each group for whom the analgesic drug prescribed by the investigator did not have the desired effect. Table II shows that the number of patients with postoperative bleeding in the first 24-h postoperative period was higher in the R group (12

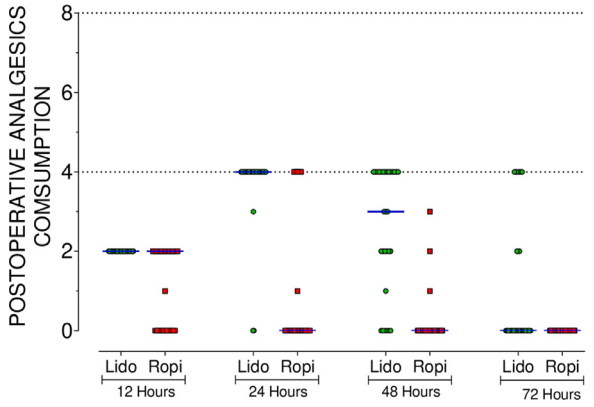

Fig. 4. Distribution (geometric forms) and mean (blue central line) of analgesic use according to postoperative time. Individuals in group L are represented by green circles and individuals in group R are represented by red squares.

Table I. Number of participants by group and use of analgesic medication over time

		L group	*R group*	*P value**
12 h	No	0	13	<.0001
	Yes	30	17	
24 h	No	2	22	<.0001
	Yes	28	8	
48 h	No	6	27	<.0001
	Yes	24	3	
72 h	No	20	30	.0008
	Yes	10	0	

*Fisher's exact test.

Table II. Postoperative bleeding observed in both the groups after injection of local anesthetics (chi-square, $P = .0233$)

	L group, n (%)	*R group, n (%)*
Yes	4 (13.3)	12 (40)
No	26 (86.7)	18 (60)

patients) compared to the L group (4 patients), and the difference was found to be statistically significant.

DISCUSSION

Third molar extraction is a commonly used model for the evaluation of analgesic efficacy in the control of POP,[1] which usually presents as acute pain of moderate to severe intensity. Current literature presents conflicting opinions regarding the efficacy of preventive analgesia in the control of POP. A literature review revealed a meta-analysis that indicated that there is no clinical evidence to support the use of preventive analgesia.[9] However, another meta-analysis reported that the use of local anesthetic wound infiltration resulted in a reduction of analgesic use and increased the time until the use of rescue analgesics.[10] These conflicting results may be related to diverse pharmacologic approaches, the complex and multifactorial nature of pain, and the ethical constraints involved when studying pain in human subjects.[11]

Ropivacaine is a long-lasting local anesthetic, and its elimination from the body is delayed due to its higher plasma protein binding capacity compared to lidocaine, which has a faster rate of elimination. The high protein binding capacity also indicates that the drug would remain bound to sodium channel proteins in the axon membrane for longer periods, blocking the conduction of the nerve impulses for a longer duration, which justifies the longer duration of action of ropivacaine,[4,6] as found in the present study. Similarly, a previous study showed that ropivacaine 0.75% induced soft tissue anesthesia of up to 9 h after the inferior alveolar nerve block,[12] in agreement with our findings.

When investigating the duration of action of a long-lasting local anesthetic, accurate documentation might be a limitation, especially because data collection is dependent on subject compliance, as established by previous studies involving ropivacaine.[8] In order to eliminate this subjective bias F.M.S.R, one of the investigators involved in our study contacted the study participants by phone every 30 min postoperatively to enquire about the pain perception from the pinprick, inferring the duration of anesthesia and registering the exact time that anesthesia wore off. Moreover, other parameters in the study are difficult to evaluate because they depend on patient compliance, subjective POP, and intake of analgesic pills.

It has been established that maximum POP after third molar extraction presents on the day of surgery.[13] Previous studies have also reported that POP reaches its peak between 6 and 12 h after the procedure, when patients would still be under the anesthetic effect of ropivacaine when it is used as local anesthetic. This may be a reason for the lower use of analgesics among some patients in the R group who did not take analgesic tablets during the first 12 h, unlike the L group, in which all of the patients took analgesic tablets. The same studies have also reported that although milder in nature, pain is expected within the first 72 h after surgery.[14,15] Therefore, the use of analgesics can be suspended after this period, in the absence of any postoperative complications.[16]

On the other hand, lower concentrations of ropivacaine may also have a selective analgesic effect, because clinically they block thin Aδ and C nerve fibers more readily than large Aβ fibers,[17] which is also associated with a greater duration of anesthesia, and thus greater patient comfort, and also contributes to the need for less analgesics during the postoperative period.

In vitro studies have also demonstrated the anti-inflammatory activity of ropivacaine.[18] Ropivacaine reduces leukocyte migration and the release of lipoxygenase products, which are important components of the inflammatory response[19,20]; however, these effects were not found for lidocaine.[21,22] This finding supports the preventive analgesic effects of ropivacaine 0.75% injection, also displayed by pain intensity reports, up to 24 h after incision for inguinal herniorrhaphies.[23] These properties may have contributed to the lower postoperative use of analgesics reported in the R group and suggest its preventive analgesic effect. This was observed throughout the 72-h postoperative period, in which there was a greater analgesic use in the L group compared to the R group, but it was especially clear in the 72 h refers only to the 72h period of postoperative (the third day of postoperative). The use of dexamethasone to modulate inflammatory effects during the postoperative period[4] does not affect the study outcomes, because it was uniformly applied to both study groups.

The use of analgesics between 12 and 72 h postoperatively is also compatible with the findings of VAS. The VAS scores decreased over time, in accordance with the number of study participants per group who used analgesic medication, as presented in Table I. Our results are supported by studies that affirm the efficacy of the injection of local anesthetic for control of acute POP in different types of surgeries, because it decreases pain and reduces use of opioids.[23,24] Furthermore, in a previous study, when preventive and postoperative injections of ropivacaine 0.75% were compared, the time until patients requested the first dose of rescue analgesic was longer in the group that received preventive ropivacaine 0.75% infiltration.[25] These findings contribute to our results, which suggest the efficacy of the preventive infiltration of ropivacaine 0.75% in managing POP.

Regarding adverse effects, ropivacaine 0.75% is a safe drug with acceptable toxicity, similar to lidocaine 2% with 1:100,000 epinephrine. Animal models used to study the toxicity of ropivacaine have established the low toxicity of ropivacaine 0.75%, because higher doses of ropivacaine 0.75% were necessary to cause toxic reactions in both the cardiovascular and central nervous systems in rats.[12,26]

Long-lasting anesthesia, on the other hand, can also present some disadvantages, such as residual soft tissue anesthesia. Although it was not a significant problem in the present study, it can lead to postanesthetic soft tissue trauma, most frequently noted in younger children and patients with mental and physical disabilities.[27] Because young children and patients with disabilities were not included in the present study, complication like tissue trauma was not encountered. However, the comfort provided by ropivacaine 0.75% long-lasting anesthesia in the R group could be related to the incidence of more cases of postoperative bleeding.[28]

Postoperative bleeding aspect is understudied in the literature. Although some studies mention the presence or absence of bleeding, there are no explanations or discussions as to why and how it occurs during the postoperative period.[29-31] Literature states that most local anesthetics (LAs) have a certain degree of vasodilator activity. The addition of vasoconstrictors increases the duration of the LA effect, decreases intraoperative bleeding, and reduces the total volume of anesthetic solution required during surgical procedures.[4] Although it has been established that ropivacaine 0.75% has vasoconstrictor properties,[8,32] patients in the R group experienced more postoperative bleeding than patients in the L group; thus it may not be

directly linked to the vasoactivity of the local anesthetic solution.

Epinephrine itself presents a greater action in $\beta 2$ adrenergic receptors in low concentrations, which results in vasodilation in the peripheral vasculature.[33] If that activity could directly influence postoperative bleeding, local anesthetics associated with epinephrine (and patients in the R group in the present study) should present more cases of postoperative bleeding. Thus, postoperative bleeding may be related to the comfort promoted by ropivacaine 0.75%, which could lead to less postoperative care; an earlier return to normal stomatognathic functions, such as consumption of solid foods; and more postoperative bleeding.[28] Though this was not the main focus of the postoperative comfort promoted by the ropivacaine, we believe that it could lead to increased postoperative bleeding, but a methodology focused on this could be applied in future studies.

It is also known that the use of vasoconstrictors can augment the duration of local anesthesia, especially in the case of LA with short or intermediate duration of action, but this increment is found to be shorter for long-lasting anesthetics.[34,35] The use of plain ropivacaine 0.75% solution as a local anesthetic is of particular interest, considering the aforementioned facts, because it has vasoconstrictor properties that improve the surgical field and offers long-lasting anesthesia. Moreover, plain ropivacaine 0.75% solution may be a good option for patients in whom the use of local anesthetic solutions with vasoconstrictors is contraindicated.

This study compared ropivacaine with lidocaine, the gold standard in dentistry, but this could present a limitation of the study. Although our results are interesting, questions arise such as if ropivacaine was compared with bupivacaine instead of lidocaine, would postoperative analgesic use be different? In addition, the association of ropivacaine with epinephrine in oral surgery and the use of plain ropivacaine in patients with limitations on the use of vasoconstrictors should be explored. Indeed, more studies are needed to bring those and other responses about the use of ropivacaine in oral surgery and dentistry in general.

In conclusion, ropivacaine 0.75% as LA promoted a longer duration of soft tissue anesthesia compared to lidocaine 2% with epinephrine 1:100,000. Compared to the L group, patients in the R group used less analgesic medication and had lower postoperative VAS scores. Therefore, it can be suggested that ropivacaine 0.75% injection the surgery provides preventive analgesia for extraction of impacted mandibular third molars.

ACKNOWLEDGEMENTS

Klinger de Souza Amorim acknowledges the Dentistry Department of the Federal University of Sergipe.

REFERENCES

1. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia II: recent advances and current trends. *Can J Anesth*. 2001;48:1091-1101.
2. de Almeida MCS, de Figueiredo Locks G, Gomes HP, Brunharo GM, Kauling ALC. Postoperative analgesia: comparing continuous epidural catheter infusion of local anesthetic and opioid and continuous wound catheter infusion of local anesthetic. *Braz J Anesthesiol*. 2011;61:293-303.
3. Andrade ED. *Therapy in Dentistry*. 3rd ed. Sao Paulo, Sao Paulo-Brazil: Medical Arts; 2014.
4. Malamed SF. *Handbook of Local Anesthesia*. 7th ed. St. Louis, Missouri-USA: Elsevier; 2019.
5. Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics. *Anesth Analg*. 2013;116:1141-1161.
6. Kuthiala G, Chaudhary G. Ropivacaine: a review of its pharmacology and clinical use. *Indian J Anaesth*. 2011;55:104-110.
7. Pell GJ, Gregory GT. Impacted mandibular third molars: classification and modified techniques for removal. *Dent Dig*. 1933;39:330-338.
8. Brković B, Andrić M, Ćalasan D, et al. Efficacy and safety of 1% ropivacaine for postoperative analgesia after lower third molar surgery: a prospective, randomized, double-blinded clinical study. *Clin Oral Investig*. 2017;21:779-785.
9. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief. *Anesthesiology*. 2002;96:725-741.
10. Ong CK-S, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg*. 2005;100:757-773.
11. Hariharan S, Moseley H, Kumar A, Raju S. The effect of preemptive analgesia in postoperative pain relief—a prospective double-blind randomized study. *Pain Med*. 2009;10:49-53.
12. Ernberg M, Kopp S. Ropivacaine for dental anesthesia: a dose-finding study. *J Oral Maxillofac Surg*. 2002;60:1004-1010. discussion 1010-1011.
13. Mozzati M, Gallesio G, Russo A, Staiti G, Mortellaro C. Third-molar extraction with ultrasound bone surgery. *J Craniofac Surg*. 2014;25:856-859.
14. Fisher SE, Frame JW, Rout PG, McEntegart DJ. Factors affecting the onset and severity of pain following the surgical removal of unilateral impacted mandibular third molar teeth. *Br Dent J*. 1988;164:351-354.
15. Khorshidi Khiavi R, Pourallahverdi M, Pourallahverdi A, Ghorani Khiavi S, Ghertasi Oskouei S, Mokhtari H. Pain control following impacted third molar surgery with bupivacaine irrigation of tooth socket: a prospective study. *J Dent Res Dent Clin Dent Prospects*. 2010;4:105-109.
16. Sato FRL, Asprino L, de Araújo DES, de Moraes M. Short-term outcome of postoperative patient recovery perception after surgical removal of third molars. *J Oral Maxillofac Surg*. 2009;67:1083-1091.
17. El-Sharrawy E, Yagiela JA. Anesthetic efficacy of different ropivacaine concentrations for inferior alveolar nerve block. *Anesth Prog*. 2006;53:3-7.
18. De Iuliis A, Zanatta L, Vincenti E, Galzigna L. Differences of ropivacaine and bupivacaine relevant to antiinflammatory actv-ity, platelet aggregation and antioxidant activity in vitro. *Farmaco*. 2001;56:153-157.
19. Babbs CF. Oxygen radicals in ulcerative colitis. *Free Radic Biol Med*. 1992;13:169-181.
20. Martinsson T, Oda T, Fernvik E, Roempke K, Dalsgaard CJ, Svensjö E. Ropivacaine inhibits leukocyte rolling, adhesion and CD11b/CD18 expression. *J Pharmacol Exp Ther*. 1997;283:59-65.

21. Goel RK, Tavares IA, Nellgard P, Jonsson A, Cassuto J, Bennett A. Effect of lignocaine on eicosanoid synthesis by pieces of human gastric mucosa. *J Pharm Pharmacol*. 1994;46:319-320.
22. Martinsson T, Haegerstrand A, Dalsgaard C-J. Effects of ropivacaine on eicosanoid release from human granulocytes and endothelial cells in vitro. *Inflamm Res*. 1997;46:398-403.
23. de Carvalho AL, Castellana FB, Gatto BEO, et al. Preemptive activity of incision infiltration with 0.75% ropivacaine in patients submitted to inguinal hernia repair. *Rev Dor*. 2011;12:321-326.
24. Chen MA, Davidson TM. Scar management: prevention and treatment strategies. *Curr Opin Otolaryngol Head Neck Surg*. 2005;13:242-247.
25. Johansson B, Hallerbäck B, Stubberöd A, et al. Preoperative local infiltration with ropivacaine for postoperative pain relief after inguinal hernia repair. A randomised controlled trial. *Eur J Surg*. 1997;163:371-378.
26. Dony P, Dewinde V, Vanderick B, et al. The comparative toxicity of ropivacaine and bupivacaine at equipotent doses in rats. *Anesth Analg*. 2000;91:1489-1492.
27. Tavares M, Goodson JM, Studen-Pavlovich D, et al. Reversal of soft-tissue local anesthesia with phentolamine mesylate in pediatric patients. *J Am Dent Assoc*. 2008;139:1095-1104.
28. Hupp JR, Ellis E. III, Tucker MR. *Contemporary Oral and Maxillofacial Surgery*. 6th ed. St. Louis, Missouri-USA: Elsevier; 2015.
29. Jerjes W, El-Maaytah M, Swinson B, et al. Experience versus complication rate in third molar surgery. *Head Face Med*. 2006;2:14.
30. Modanloo H, Eftekharian H, Arabiun H. Postoperative pain management after impacted third molar surgery with preoperative oral lamotrigine, a randomized, double-blind, placebo-controlled trial. *J Dent (Shiraz)*. 2018;19:189-196.
31. Malkawi Z, Al-Omiri MK, Khraisat A. Risk indicators of postoperative complications following surgical extraction of lower third molars. *Med Princ Pract*. 2011;20:321-325.
32. Brkovic BMB, Zlatkovic M, Jovanovic D, Stojic D. Maxillary infiltration anaesthesia by ropivacaine for upper third molar surgery. *Int J Oral Maxillofac Surg*. 2010;39:36-41.
33. Smiley RM, Kwatra MM, Schwinn DA. New developments in cardiovascular adrenergic receptor pharmacology: molecular mechanisms and clinical relevance. *J Cardiothorac Vasc Anesth*. 1998;12:80-95.
34. Schoenmakers KPW, Fenten MGE, Louwerens JW, Scheffer GJ, Stienstra R. The effects of adding epinephrine to ropivacaine for popliteal nerve block on the duration of postoperative analgesia: a randomized controlled trial. *BMC Anesthesiol*. 2015;15:100.
35. Cederholm I, Anskär S, Bengtsson M. Sensory, motor, and sympathetic block during epidural analgesia with 0.5% and 0.75% ropivacaine with and without epinephrine. *Reg Anesth*. 1994;19:18-33.

Reprint requests:

Klinger de Souza Amorim
Pharmacology
Anesthesiology and Therapeutics Department of the Piracicaba Dental School
University of Campinas
901 Limeira Avenue
Piracibaba
São Paulo 13414-903
Brazil
Klinger.amorim@outlook.com