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Levobupivacaine induces vasodilatation, but not vasoconstriction, in rat mesenteric artery

Levobupivacaína induz vasodilatação, mas não vasoconstrição em artéria mesentérica de rato

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Resumo

Introdução: Levobupivacaína pode ser uma nova alternativa para analgesia por apresentar baixa toxicidade e vasoconstrição, permitindo sua utilização em pacientes que apresentam contra-indicação no uso de vasoconstritores. **Objetivo**: Avaliar os efeitos da levobupivacaína utilizando a técnica de reatividade vascular em artéria mesentérica isolada de rato e comparar este efeito à lidocaína. **Material e método**: Anéis foram obtidos da artéria mesentérica de ratos machos *Wistar* e foram mantidos em cubas. Para o registro das contrações isométricas, cada anel foi suspenso por linhas de algodão fixadas a um transdutor de força acoplado a um sistema de aquisição. **Resultado**: Tanto a lidocaína como a levobupivacaína não apresentaram efeito vasocontritor sobre o tônus basal em anéis com endotélio functional. No entanto, quando os anéis foram pré-contraídos com fenilefrina, ambas as drogas induziram um vasorrelaxamento concentração-dependente. O efeito vasorrelaxante causado pela levobupivacaína não foi diferente após a remoção do endotélio, ou com o tetraetilamônio (1mM), um bloqueador não seletivo dos canais para. K^+. Em anéis sem endotélio funcional e pré-contraídos com solução despolarizante de Tyrode (KCl 80mM), o vasorelaxamento induzido pela levobupivacaína não foi significativamente diferente daquele observado em anéis pré-contraídos com fenilefrina e não apresentou um efeito adicional significativo sobre o relaxamento máximo da nifedipina. **Conclusão**: Este estudo demonstrou que a levobupivacaína produz efeito vasorrelaxante em artéria mesentérica de rato, que é endotélio independente. Este efeito parece envolver os bloqueadores de canais para Ca^{2+} em célula muscular vascular lisa.

Descritores: Lidocaína; artéria mesentérica; vasodilatação.

Abstract

Introduction: Levobupivacaine (LEVO) can replace analgesia because it exhibits low toxicity and causes minor vasoconstriction, enabling its use in patients in whom vasoconstrictors are contraindicated. **Objective**: We aimed to evaluate the effects of LEVO in isolated rat superior mesenteric artery by using the vascular reactivity technique and compare its effect to that of lidocaine. **Material and method**: Arterial rings were obtained from the mesenteric artery of male Wistar rats and kept in organ baths. For recording isometric contractions, each ring was suspended by cotton threads from a force transducer, which was connected to a data acquisition system. **Result**: Both lidocaine and LEVO did not show a vasoconstrictor effect on the basal tone of the arterial rings with functional endothelium. However, when the rings were pre-contracted with phenylephrine, both drugs were able to induce concentration-dependent vasodilatation. The vasodilator effect induced by LEVO did not change after removal of the endothelium, or with the addition of tetraethylammonium (1 mM), a non-selective K^+ channel blocker. In the rings without functional endothelium, which were pre-contracted with depolarizing Tyrode's solution (KCl 80 mM), LEVO-induced vasodilatation was not significantly different from that observed in the rings pre-contracted with phenylephrine. Moreover, it did not show a significant additional vasodilator effect compared to the maximal vasodilator effect of nifedipine. **Conclusion**: This study demonstrated that LEVO produces a vasodilator effect in the rat superior mesenteric artery in an endothelium-independent manner. This effect seems to be mediated *via* Ca^{2+} channel blockade in the vascular smooth muscle cells.

Descriptors: Lidocaine; mesenteric artery; vasodilatation.

INTRODUCTION

Advances in operation techniques and concerns about pain control have supported and sustained several pharmacological and clinical studies on local anesthetics[1]. Local anesthetics are widely used in dentistry to minimize pain, in order to provide a safe and effective dental treatment[2].

Local anesthetics are classified according to their chemical structure into ester and amide-types, the latter being used more frequently in clinical settings. Amide-type anesthetics include prilocaine, lidocaine, mepivacaine, articaine, ropivacaine, and bupivacaine (BUPI)[3]. BUPI is a long-acting anesthetic, which can be used in long surgeries without the need for anesthetic complementation. However, it exhibits a certain degree of cardiotoxicity, caused by the dextrorotatory enantiomer in the racemic mixture (S50-R50), which encouraged researchers to develop an anesthetic with a lower toxic potential[4,5].

Thus, levobupivacaine (LEVO), a local anesthetic with properties similar to those of BUPI but with less central and cardiac toxicity, was introduced. This difference is due to its predominant levorotatory enantiomer (S75-R25)[5-7].

LEVO is considered as a new alternative to analgesia, which is associated with low toxicity when applied in the dental area and with minor vasoconstriction[8-12]. Thus, it is a satisfactory option for subjects in whom the use of vasoconstrictors is contraindicated[13].

The present study aimed to evaluate the possible vasoconstrictor effect of LEVO in isolated rat superior mesenteric artery using the technique of vascular reactivity. The superior mesenteric artery is a resistant artery, which can reflect some possible effects on the vascular reactivity in smaller blood vessels such as those present in the area treated by local anesthetics in dentistry. We also compared the effect of LEVO to that of lidocaine (LIDO).

MATERIAL AND METHOD

Animals

Thirteen male Wistar normotensive rats (250-300 g) were obtained from the Department of Physiology in the Federal University of Sergipe, Sergipe, Brazil. They were maintained in a large cage under controlled conditions of temperature and light (lights on: 06:00-18:00), and were fed with rodent diet and tap water *ad libitum*. All procedures were approved by the Animal Research Ethics Committee of the Federal University of Sergipe (Protocol number 27/2012) and were carried out in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication 85-23, revised 1996).

Drugs

LEVO in enantiomeric excess 50% and lidocaine (LIDO) were purchased from Cristália and L-phenylephrine chloride (Phe), acetylcholine chloride (Ach), nifedipine (NIF), and tetraethylammonium (TEA) were purchased from Sigma-Aldrich.

Tissue Preparation

Rats were sacrificed by exsanguination under anesthesia and the superior mesenteric artery was removed, cleaned from the connective and fat tissues, and sectioned in rings (1-2 mm). These rings were suspended in organ baths containing 10 mL of Tyrode's solution, gassed with carbogen, and maintained at 37 °C under a resting tension of 0.75 g for 60 min (stabilization period). The isometric tension was recorded by a force transducer (Letica, Model TRI210, Barcelona, Spain) coupled to an amplifier-recorder (AECAD 0804, AVS, São Paulo – SP, Brasil). When necessary, the endothelium was removed with a fine steel wire and its functionality was assessed based on the ability of Ach (1 μM) to reduce more than 75% of the tone pre-induced by Phe (1 μM). The absence of Ach-induced relaxation was considered as evidence that the endothelium of the arterial rings became non-functional.

Characterization of the Effect of LIDO and LEVO on the Basal Tone of the Arterial Rings

After confirming the presence of functional endothelium and the complete recovery of the basal tone, LIDO at concentrations of 3×10^{-7}-3×10^{-4} M (n = 4) and LEVO at concentrations of 3×10^{-7}-3×10^{-4} M (n = 9) were cumulatively and separately added to the bath in order to construct a control concentration-response curve.

Characterization of the Effect of LIDO and LEVO on the Pre-contracted Arterial Rings

After verifying the presence of functional endothelium, intact arterial rings were pre-contracted again with Phe (1 μM). Then, during the tonic phase of contraction, LIDO at concentrations of 3×10^{-7}-3×10^{-4} M (n = 5) or LEVO at concentrations of 3×10^{-7}-3×10^{-4} M (n = 6) was cumulatively added to the bath to construct a concentration-response curve.

Assessment of the Role of the Vascular Endothelium in the Responses Induced by LEVO

After verifying the absence of functional endothelium, the rings were pre-contracted with Phe (1 μM) and during tonic phase of contraction, increasing concentrations of LEVO (3×10^{-7}-3×10^{-4} M; n = 4) were cumulatively added to the bath. The concentration-response curve obtained from this experiment was compared with that obtained from the experiment conducted on arterial rings with functional endothelium.

Assessment of the Role of Ca^{2+} in the Responses Induced by LEVO

The possible effect of LEVO on Ca^{2+} channels was investigated using the concentration-response curve for LEVO (3×10^{-7}-3×10^{-4} M; n = 4) in arterial rings without endothelium in the presence of a high concentration of potassium. In this protocol, the normal Tyrode's solution was replaced by a K^+ depolarizing Tyrode's solution containing 80 mM of KCl and the tissues were immersed in this solution until the end of the experiment.

The involvement of dihydropyridine-sensitive voltage-operated calcium channels (Cavs) was assessed *via* testing the response of the rings without endothelium, pre-contracted with Phe (1 μM) to the anesthetic (3 x 10^{-4} M; n = 6) in the absence or presence of NIF (10 μM), a selective blocker of the dihydropyridine-sensitive Cavs[14].

Assessment of the Contribution of K^+ Channels to the Responses Induced by LEVO

The possible effect of LEVO on K^+ channels was investigated using the concentration-response curve for LEVO (3 x 10^{-7}-3 x 10^{-4} M; n = 7) in arterial rings without endothelium incubated with 1 mM of TEA for 30 min, which is a non-selective K^+ channel blocker at this concentration[15]. The concentration-response curve for this experimental condition was compared with that obtained in the absence of the blocker.

Statistical Analysis

Values were expressed as mean ± S.E.M. The results were analyzed with one or two-way ANOVA followed by Bonferroni *post-hoc* test. All analyses were performed using GraphPad Prism™ 5.0. A value of $p<0.05$ was considered significant.

RESULT

As shown in Figure 1A, both LIDO and LEVO were unable to induce vasoconstriction of the blood vessel during basal tone. However, in rings with functional endothelium, which was pre-contracted with phenylephrine, both LIDO and LEVO were capable of inducing concentration-dependent relaxation (E_{max} = 74.5 ± 11%; n = 5 and 91.13 ± 9.8%; n = 6, respectively) (Figures 1B and 2).

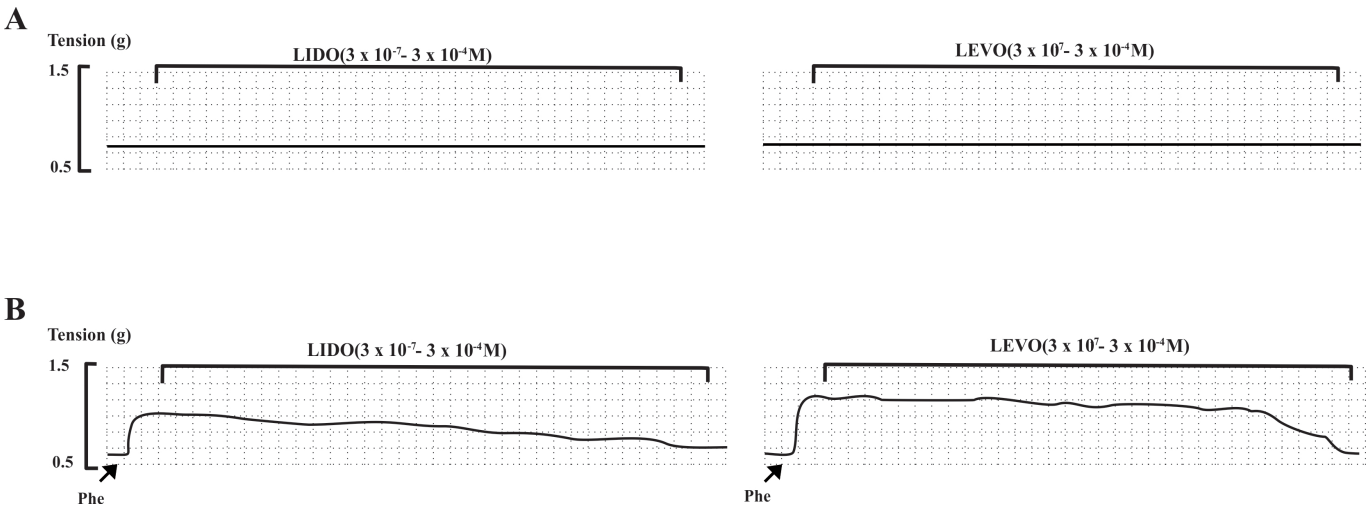

Figure 1. Original registration showing the effect of LIDO and LEVO in isolated arterial rings of the rat superior mesenteric artery on the basal tone **(A)** and in isolated arterial rings of the rat superior mesenteric artery pre-contracted with 1 μM of Phe **(B)**.

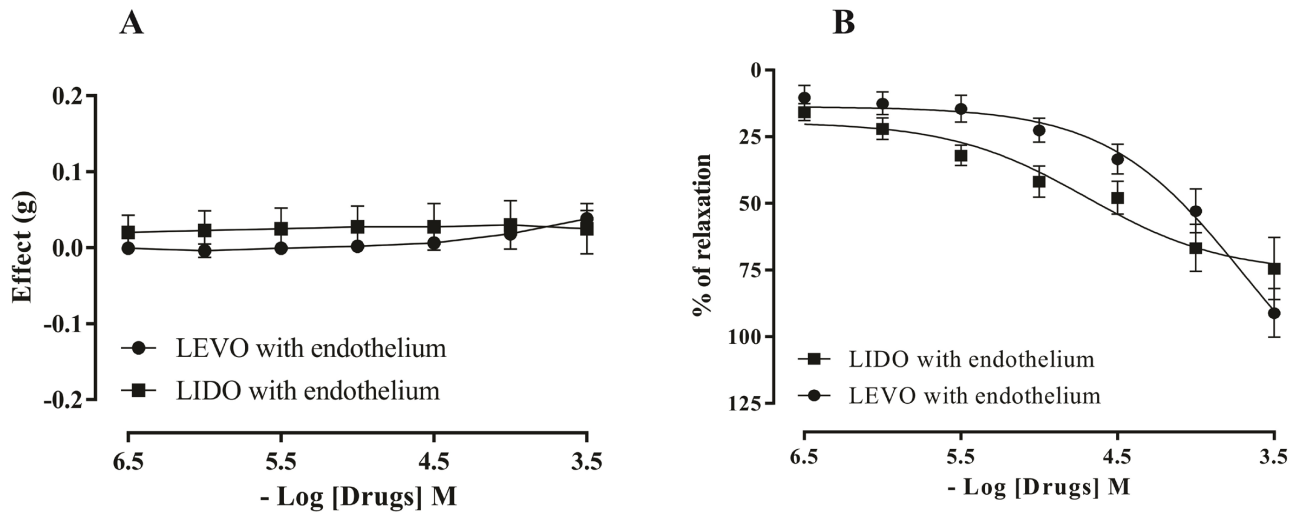

Figure 2. Concentration-response curves for LIDO (3 x 10^{-7}-3 x 10^{-4} M; n = 9) and LEVO (3 x 10^{-7}-3 x 10^{-4} M; n = 4) on the basal tone of *isolated rings of the rat superior mesenteric artery* with functional endothelium **(A)** and in isolated rings of the rat superior mesenteric artery with functional endothelium, pre-contracted with 1 μM Phe **(B)**. Values are expressed as mean ± S.E.M. The data were analyzed by two-way ANOVA followed by Bonferroni *post-hoc* test.

The concentration-dependent relaxation induced by LEVO in arterial rings without functional endothelium, which were pre-contracted with Phe (1 μM), was not significantly different from that obtained in rings with functional endothelium (E_{max} = 91.13 ± 9.8%; n = 6 and 90.4 ± 2.8%; n = 4, respectively) (Figure 3A).

The possible involvement of Ca^{2+} channels was investigated using the curves, in which the rings were pre-contracted with depolarizing Tyrode's solution (KCl 80 mM). LEVO was capable of inducing vasodilatation similar to that achieved in the rings without functional endothelium, which were pre-contracted with Phe (1 μM) (E_{max} = 92.5 ± 1.0%; n = 4 and 90.4 ± 2.8%; n = 4, respectively), as shown in Figure 4A. LEVO (3 x 10^{-4} M) and NIF (10 μM) were able to induce vasodilatation in the rings without endothelium, pre-contracted with Phe (89.3 ± 6.1%; n = 5 and 80.0 ± 4.6%; n = 6, respectively). However, LEVO did not induce a significant additional effect in the rings preincubated with NIF (97.0 ± 3.15%, n=6) (Figure 4B).

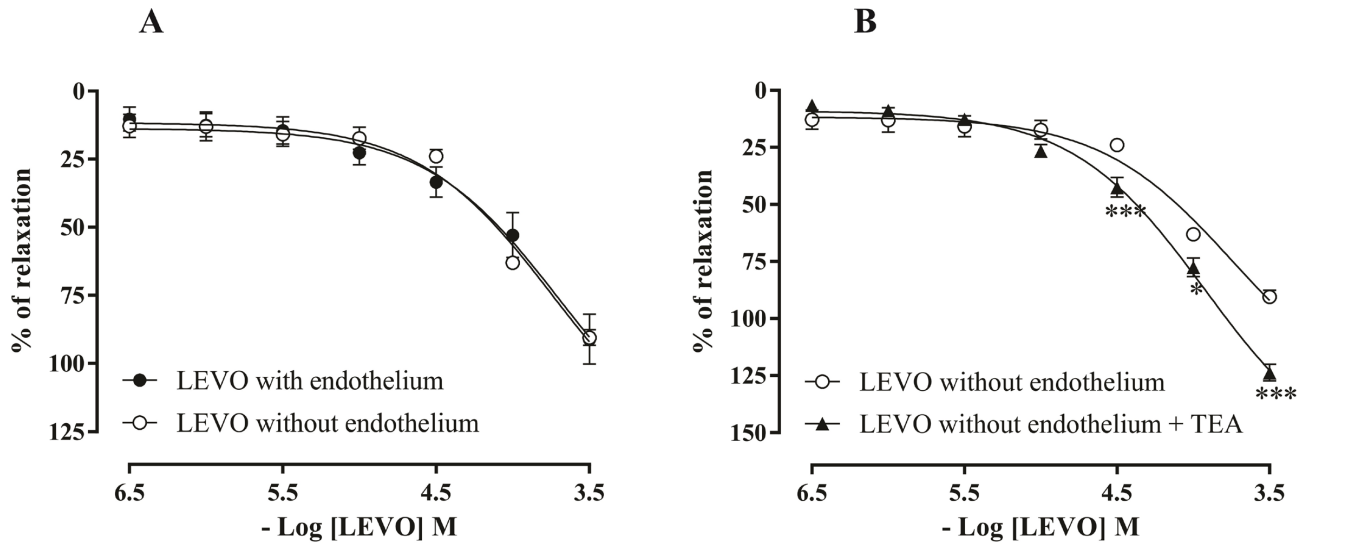

Figure 3. Concentration-response curves for LEVO (3 x 10^{-7}-3 x 10^{-5} M) in isolated rings of the rat superior mesenteric artery with (n = 6) and without (n = 4) functional endothelium, pre-contracted with 1 μM Phe **(A)**, and in isolated rings of the rat superior mesenteric artery without functional endothelium after TEA (1 mM) (n = 7) **(B)**. Values are expressed as mean ±S.E.M. The data were analyzed with two-way ANOVA followed by Bonferroni *post-hoc* test. *p < 0.05 and *** p < 0.001 *vs.* rings without the endothelium pre-contracted with Phe.

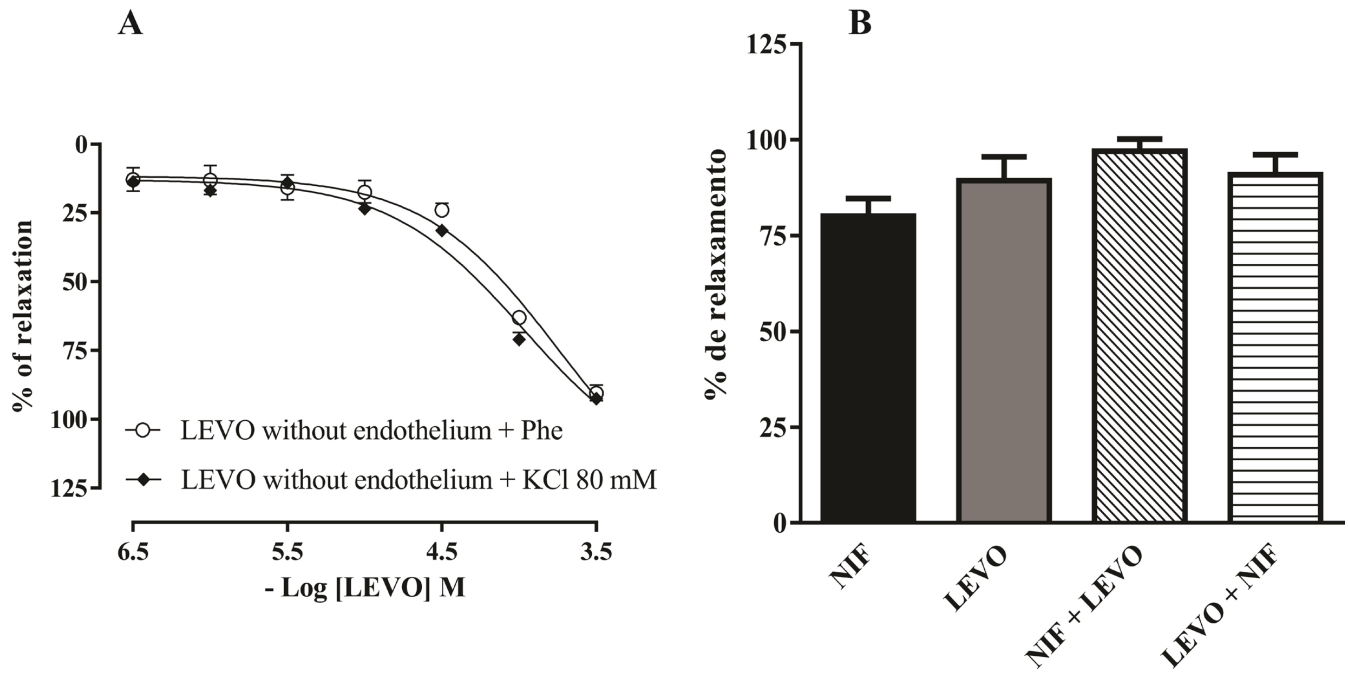

Figure 4. Concentration-response curves for LEVO (3 x 10^{-7}- 3 x 10^{-5} M; n = 6) in isolated rings of the rat superior mesenteric artery without functional endothelium pre-contracted with Phe (n = 4) or KCL 80 mM (n = 4) **(A)**, and the vasodilator effect of NIF (10 μM), LEVO (3 x 10^{-4} M), LEVO after the maximum relaxation of NIF and NIF after the maximum relaxation of LEVO in the rings of the rat mesenteric artery without endothelium pre-contracted with Phe (1 μM) **(B)**. Values are expressed as mean ± S.E.M. The data were analyzed with one or two-way ANOVA followed by Bonferroni *post-hoc* test.

To assess the possible contribution of K^+-channels to the vasodilator effect induced by LEVO, rings without functional endothelium were pre-incubated with 1 mM of TEA. At this concentration, TEA was able to non-selectively block K^+ channels[15]. In this protocol, the vasodilator effect induced by LEVO was found to be significantly higher as compared to that induced by the drug in the absence of the inhibitor (E_{max} = 90.4 ± 2.8%; n = 4 *vs* 123.7 ± 3.6%; n = 7) (Figure 3B).

DISCUSSION

Studies showed that LEVO in 50% enantiomeric excess induced certain intrinsic vasoconstriction *in vitro*[8-10,12,16] and *in* vivo[17-19]. Therefore, this study aimed to assess the vasoactivity of LEVO in *in vitro* experiments using arterial rings prepared from isolated rat superior mesenteric artery, a resistant artery, which can reflect the possible effects on the vascular reactivity in smaller blood vessels such as those present in the area treated by local anesthetic in clinical dentistry. Furthermore, this effect was compared to that of lidocaine, a standard local anesthetic used in dentistry.

In this study, it was shown that both LEVO and LIDO has no contractile effect on basal tone in the rat mesenteric artery. These results corroborate the findings of Chang et al.[20], who demonstrated that LEVO did not exhibit a contractile effect on the rat tracheal smooth muscles. In contrast, Iida et al.[21] and Mukozawa et al.[9,12] have shown that LEVO was able to induce vasoconstriction in studies on dog cerebral arterioles and rat thoracic aorta, respectively. These controversial results may be attributed to the differences in the structure of the chemical agents, the vascular bed, the experimental conditions, or the species used.

In addition, these opposite effects induced by LEVO can be justified because some anesthetics, including LEVO and BUPI, exhibit a biphasic activity depending on the concentration used. It was observed that these anesthetics cause vasodilatation at high concentrations, and vasoconstriction at smaller concentrations, both *in vivo* and *in vitro*[16-19].

Since no vasoconstrictor activity was observed on the basal tone, experiments were conducted to evaluate the possible vasodilator effect of LEVO and compare it to that of LIDO. The vasodilatation induced by LEVO was similar to that caused by the lidocaine.

Furthermore, we assessed the underlying mechanism responsible for the vasodilator effect of LEVO. Since the endothelium is an important regulator of the vascular tone *via* releasing endothelium-derived relaxing factors, mainly nitric oxide (NO) and products derived from the activation of cyclooxygenase (COX) enzyme, such as prostacyclins, experiments were carried out to assess the role of the endothelium in this response[22]. However the endothelium probably does not contribute to vasodilatador effect of LEVO.

In accordance with the results of the present study, LEVO showed an endothelium-independent effect on the rat thoracic aorta[12] as well as on isolated human umbilical artery and vein[11]. However, it was shown that the effect of LEVO on rat aorta was dependent on nitric oxide released by the endothelium[8]. These findings reinforce that the vascular effects of LEVO may differ depending on some variables, such as the vascular bed used.

We also evaluated whether the effects induced by LEVO are mediated *via* another endothelium-independent signaling pathway, such as Ca^{2+}-channel blockade. It is known that increased external K^+ concentration induces smooth muscle contraction through the activation of Cavs and subsequent release of calcium from the sarcoplasmic reticulum. Contractions induced by high concentrations of K^+ are inhibited by Ca^{2+} -channel blockers or by the removal of Ca^{2+} from the external environment because they are totally dependent on Ca^{2+} influx[23].

LEVO induced vasodilatation on pre-contracted rings with depolarizing Tyrode's solution (KCl 80 mM) and did not promote an additional vasodilator effect compared to the maximum effect induced by NIF, suggesting that LEVO may act mainly in a similar way as NIF, i.e., blocking dihydropyridine-sensitive Cavs.

Choi et al.[8], Baik et al.[10] and Mukozawa et al.[12] demonstrated that LEVO-induced vasoconstriction in the aorta is mediated mainly by the intracellular calcium and by Ca^{2+} influx through Cavs[8,10,12]. However, our results suggest that LEVO acts *via* inhibition of Ca^{2+} influx through these channels. These differences might be related to the different vascular beds used and different experimental conditions. Nevertheless, additional studies are needed for a better understanding of the underlying mechanism of action.

Moreover, there are reports in the literature that K^+ channels also play an important role in the regulation of the vascular tone[24]. K^+ channel opening in the smooth muscle cell membrane causes K^+ efflux, resulting in hyperpolarization that closes the Cavs, resulting in decreased influx of Ca^{2+} ions and thus, relaxation of the smooth muscles[25]. LEVO was able to induce vasodilatation in rings without functional endothelium with TEA, which suggests that these channels are not involved in LEVO-induced vasodilator effect.

CONCLUSION

The results of this study demonstrated that LEVO did not induce vasoconstriction of arterial rings prepared from rat superior mesenteric artery, however, it produced a vasodilator effect. This LEVO-induced vasodilatation was endothelium and K^+ channel-independent, however, it could be mediated *via* the blockade of Cavs in the vascular smooth muscle cells. We suggest that LEVO exhibits several vascular effects depending on the vascular bed used. Although LEVO did not display the expected vasoconstriction in our study, LEVO remains beneficial and can be widely used in dentistry as it is less cardiotoxic and less neurotoxic than BUPI, and it also provides long-lasting anesthesia.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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