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Anaesthetic efficacy of intraoral topical lidocaine and prilocaine in nanostrusctured lipid nanocarriers: a randomized clinical trial

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SUMMARY

This randomized placebo-controlled crossover trial evaluated if nanostructured lipid nanocarriers (NLC) could improve the topical anaesthetic efficacy of lidocaine and prilocaine (L+P) incorporated in a xanthan-hydrogel applied in the oral cavity. There were no differences among topical formulations regarding the primary endpoints of pain intensity during needle insertion or local anaesthetic injection. Nonetheless, exploratory analyses indicate that individuals with low mechanical pain sensitivity were more susceptible to placebo effects which could also interfere with the anaesthetic effects of the topical formulations. Thus, mechanical pain sensitivity can be an interesting approach to increase assay sensitivity in clinical trials of topical anaesthesia.

INTRODUCTION

Topical anaesthetics are used to reduce pain and discomfort caused by needle insertion and local anaesthetic injection in Dentistry. However, the efficacy of the commercially available formulations has shown conflicting results when applied in the orofacial region (Franz-Montan et al., 2017). The greatest challenge in formulation development is to overcome the oral mucosa epithelium barrier, wrongly considered a highly permeable tissue. The properties of lipid nanoparticles can potentially increase the efficacy of topical applications for the oral mucosa due to the enhanced permeation ability of the nanometric particles, high interface contact, biocompatibility biodegradability, and sustained delivery of active agents (Ribeiro et al., 2016). Our group developed and characterized an optimized nanostructured lipid nanocarriers (NLC) co-loading lidocaine and prilocaine (L+P) (Ribeiro et al., 2016) and demonstrated pre-clinically that a hybrid xanthan-hydrogel quadrupled the topical anaesthetic effect in a mice model (Ribeiro et al., 2018). Therefore, we designed a clinical trial to evaluate if the NLC could improve the intraoral topical anaesthetic efficacy of L+P incorporated in a hybrid xanthan-hydrogel applied in healthy volunteers.

MATERIALS AND METHODS

This randomized placebo-controlled crossover trial included 40 healthy individuals (approved by Ethical Committee of Piracicaba Dental School under the Protocol # 45317521.9.0000.5418). Four formulations, i.e., L+P, 5% encapsulated in NLC + xanthan (A); L+P, 5% + xanthan (B); commercial L+P 5% EMLA® (EMLA); and placebo xanthan (PLACEBO), were topically applied (2 min) at the palatal mucosa on the 2nd pre-molar region at right and left sides, in two different sessions, followed by 0.3 mL injection of a local anaesthetic solution. The order of application and side were randomized. Pain intensity after needle insertion (puncture pain) and local

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anaesthetic injection (injection pain) were evaluated in visual analogue scales (0-10 cm VAS). Mechanical pain threshold (MPT) was evaluated at each region prior to topical application with von-Frey filaments. Moreover, the participants were divided in two groups based on the average MPT Z-scores according to the following: Z-score = (Indidivual $_{value}$ - Mean $_{group}$) / SD $_{group}$. Values below -1.0 indicated a baseline low mechanical pain sensitivity and values above -1.0 indicated normal or high mechanical pain sensitivity. Mixed ANOVA with the within-factor formulation (4 levels) and the between-factor mechanical pain sensitivity (2 levels) was applied to the data. The significance level was set at 5% (p=0.050).

RESULTS AND DISCUSSION

Overall, there were no differences among the formulations on the pain intensity ($p<0.05$) (Table 1).

Table 1. *Mean and standard deviation (SD) of pain intensity during puncture and injection.*

Formulations	Puncture pain	Injection pain
A	1.8 (1.6) [a]	0.7 (1.0) [b]
B	2.1 (1.6) [a]	1.0 (1.3) [b]
EMLA	1.9 (1.8) [a]	0.9 (1.3) [b]
PLACEBO	1.8 (1.4) [a]	1.0 (1.3) [b]

The same lowercase letters within the same column indicates no differences between the formulations (p>0.050). A = L+P, 5% encapsulated in NLC + xanthan. B = L+P, 5% + xanthan.

On the other hand, it was observed that individuals with higher MPT values, i.e., Z-scores below -1.0, reported lower pain intensities during puncture regardless of the formulation ($F_{1,38}$=12.2, p=0.001). Interestingly, it was also found that individuals with higher MPT values presented a greater placebo response when compared with individuals with a normal or lower MPT values, i.e., Z-scores above -1.0 (Fig. 1). Moreover, multiple comparisons analyses showed that pain intensity during puncture under the effect of formulation B was significantly more painful in individuals with a normal or lower MPT when compared with individuals with higher MPT (Tukey: p=0.031). Such differences were not observed for the other formulations or pain intensity during injection (Tukey: p>0.050).

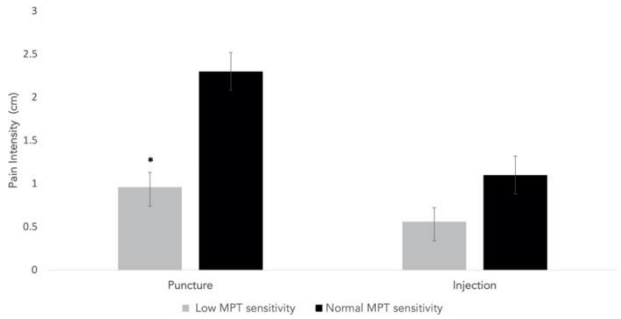

Fig. 1. *Mean of pain intensity during puncture and injection following the placebo formulation. Error bars indicate the standard error of the mean. * = significant between-group differences (p=0.015).*

CONCLUSIONS

This randomized crossover trial is inconclusive regarding the additional anaesthetic effects of administering dental topical anesthesia using nanocarriers, as they did not improve the anaesthetic efficacy of L+P on pain intensity due to intraoral injections. Nonetheless, exploratory analyses indicate that individuals with low mechanical pain sensitivity might be more susceptible to placebo effects which could also interfere with the anaesthetic effects of the topical formulations. Thus, mechanical pain sensitivity can be an interesting approach to increase assay sensitivity in clinical trials of topical anaesthesia.

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