Phentolamine mesylate to reverse oral soft-tissue local anesthesia

A systematic review and meta-analysis

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ABSTRACT

Background. Knowing that patients desire reduced duration of local anesthesia, the authors performed a meta-analysis to evaluate the efficacy of phentolamine mesylate (PM) in reducing anesthesia duration and the occurrence of adverse effects.

Types of Studies Reviewed. The authors searched studies in 4 electronic databases up to December 18, 2014. For each study, the methodological quality was assessed according to the Cochrane Collaboration's tool for assessing risk of bias. Randomized controlled trials (RCTs) that used PM met the inclusion criteria.

Results. Six RCTs met the inclusion criteria and were used to carry out a meta-analysis of the effectiveness of PM and a qualitative analysis of its adverse effects. The use of PM was more effective in reversing the anesthetic effect on the lower lip and tongue than was applying a placebo. Adverse effects reported in the studies were not statistically significant, the most frequent being headache, pain during injection, and postprocedure pain.

Conclusions and Practical Implications. Based on limited evidence, PM is effective in reducing the persistence of anesthesia duration on the lower lip and tongue, with infrequent adverse effects of little clinical significance.

JADA 2015:146(10):751-759

http://dx.doi.org/10.1016/j.adaj.2015.04.018

Local anesthetics have been extensively studied in the field of dentistry.[1] The techniques used with these substances cause a total or partial loss of sensation in the oral soft tissues, lasting between 3 and 5 hours.[2,3]

According to Saunders and colleagues[4] there is a willingness by patients to eliminate or reduce the use of anesthetics, or to discuss options for shortening the duration of the effects of local anesthetics, as they consider it an annoying and uncomfortable situation[5] that can alter their quality of life.[6,7] Therefore, agents for anesthetic reversal[3] have been developed such as phentolamine mesylate (PM) under the name of Oraverse (Septodont) as a local anesthesia antagonist.[8,9]

Supplemental material is available online.

PM bases its effect on vasodilation of the vascular system. It is administered in the same area as a local anesthetic, antagonizing the vasoconstrictor effect of sympathomimetic amines, producing a time reduction

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in soft-tissue anesthesia. Shortened effects of anesthesia increases the welfare and satisfaction of the patient.[10,11]

Moreover, it also offers the possibility to check the existence of a paresthesia (temporary or permanent) of the inferior alveolar nerve at an early stage.[12] Among the possible adverse effects, orthostatic hypotension, nausea, heart rhythm disorders (tachycardia and bradycardia being the most frequent[8]), pain at the injection site, and headache have been reported.[13] There are few studies in the scientific literature examining PM in the field of dentistry.

The aim of this systematic review was to evaluate the effectiveness of PM in reducing the anesthesia time of the lower lip and tongue, as well as determine in a qualitative way the occurrence of adverse effects derived from its administration.

METHODS

We prepared this systematic review by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist,[14] and the methodological quality was evaluated by following the Cochrane Collaboration's tool for assessing risk of bias,[15] which incorporates 7 domains:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- masking of participants and personnel (performance bias);
- masking of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- other bias.

The studies were classified in the following categories: low risk of bias—low risk of bias for all key domains; unclear risk of bias—unclear risk of bias for 1 or more key domains; high risk of bias—high risk of bias for 1 or more key domains.[15]

Inclusion criteria. The scientific studies

- included randomized controlled trials (RCTs);
- were published in any language;
- were published from January 1, 2008, to December 18, 2014;
- used an experimental model that consisted of humans of any age, who were undergoing dental procedures during which they received local anesthetic that was associated with vasoconstriction in the oral cavity, and PM was used as an antagonist;
- had results evaluating the reduction in anesthesia time and the occurrence of adverse effects.

Exclusion criteria. The exclusion criteria were:

- other types of studies that were not RCTs, such as observational studies, quasi-experimental studies, systematic reviews, and meta-analyses;
- studies before 2008, as PM was introduced in the same year for the purposes of this study;
- those not published in journals.

Search strategy. A comprehensive search of the literature was conducted up to December 18, 2014, in the following databases: MEDLINE, Scopus, Science Direct, and the Cochrane Central Register of Controlled Trials. The search strategy used was a combination of Medical Subject Headings (MeSH) terms and free text terms; (Oraverse OR "phentolamine mesylate [MeSH]" OR ("local anesthesia [MeSH]" AND reversal)) AND dentistry [MeSH]. Those terms were adjusted according to the requirements of each electronic base (Figure 1).

Study selection. Two independent researchers (J.G.-S., C.G.-S.) reviewed all the articles and rejected those that did not meet the inclusion criteria.

Synthesis of quantitative results. A meta-analysis was performed using statistical software (R version 3.1.3, metaphor package, R Foundation). We used random effects models to obtain the standardized mean difference with a confidence interval of 95% (CI) for the evaluation of the duration of the anesthetic effect on the lower lip and tongue. Heterogeneity was also assessed using the I^2 statistic and DerSimonian-Laird test (Q). A $P < .05$ was considered statistically significant.

We conducted sensitivity analysis to confirm the association by removing studies with a higher risk of introducing bias and assessed the contribution of each study to the heterogeneity by sequentially omitting 1 study and recalculating the combined results with the "leave1out" and "influence" functions on the R statistical program.

Finally, a funnel plot was constructed and Egger regression test was performed to assess possible publication bias using the "funnel" and "regtest" functions. A $P < .05$ was considered predictive of a statistically significant publication bias.

RESULTS

Study selection. The response to the search strategy yielded 465 results, of which 438 remained after removing those that were duplicated. We restricted the search to those articles published between January 1, 2008, and December 18, 2014, (inclusive) and excluded all results that were not published in journals, leaving a total of 104 references. Then, 2 independent researchers (J.G-S.) and (C.G-S.) reviewed all the titles and abstracts, obtaining 8 references. Finally, 2 were discarded for not being RCTs, and 6 articles were used, whose characteristics and variables are shown in Tables 1 and 2.[10,11,16-19]

Risk of bias within studies. Only one of the included RCTs did not indicate the method of randomization used.[18] None of the authors of the included trials indicated whether commercial financing was used for the study.

ABBREVIATION KEY. **C:** Combined. **FAB:** Functional assessment battery. **MeSH:** Medical Subject Headings. **PM:** Phentolamine mesylate. **RCT:** Randomized controlled trials. **STAR:** Soft-tissue anesthesia recovery. **U:** Unspecified. **W-B-PRS:** Wong-Baker FACES Pain Rating Scale.