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.

Using the predetermined 7 domains for risk of bias assessment, we determined that 2[10,16] of the 6 RCTs had a high risk of bias, 4[11,17,18,19] had an uncertain risk of bias, and none of them to had a low risk of bias. Table 3 shows a more detailed description of the RCTs included.

Types of local anesthetics used. Several local anesthetics were used in the reviewed RCTs. Lidocaine was the only anesthetic evaluated in every study. All the authors used an epinephrine concentration of 1:100,000, excepting Nourbakhsh and colleagues,[19] who used a concentration of 1:80,000. Laviola and colleagues[16] and Hersh and colleagues[17] evaluated the same 4 anesthetic agents (lidocaine 2% and epinephrine 1:100,000, articane 4% and epinephrine 1:100,000, prilocaine 4% and epinephrine 1:200,000, mepivacaine 2% and levonordefrin 1:20,000), these being the 2 studies in which the largest number of local anesthetic agents were evaluated.

Tavares and colleagues[18] and Nourbakhsh and colleagues[19] only used lidocaine 2% in their studies, using different concentrations of epinephrine (Table 2).

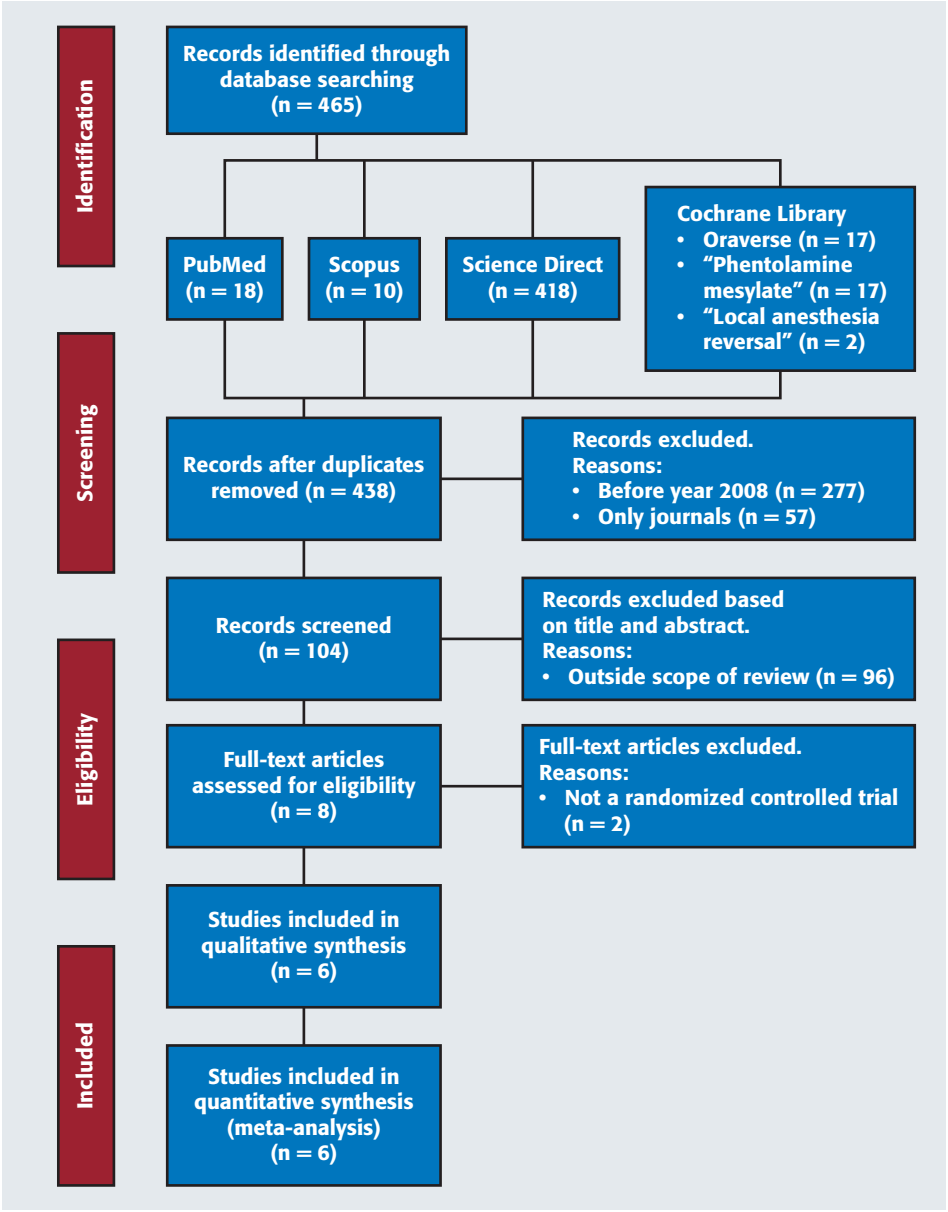

Figure 1. Flow diagram of the literature search, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

PM effectiveness. The recovery time for lip and tongue sensitivity after administration of PM and placebo, as well as the time difference between the 2 groups, is contained in Table 2. The duration of anesthesia in the lower lip and tongue were evaluated for the meta-analytic study as the only parameters susceptible to quantitative analysis.

Primary analysis. For the development of the meta-analysis, the mean (standard deviation [SD]) of each of the identified RCTs were grouped. However, 4 of the studies only report the median (m), the minimum and maximum range (a and b, respectively), and the sample size of the trial. An estimation of the mean was performed by the following formula[20]: $\overline{x} \approx \frac{a+2m+b}{4}$ and the SD[20] by $SD = \frac{1}{12}\left(\frac{(a-2m+b)^2}{4} + (b-a)^2\right)$. Table 4 shows the data used and its estimation. For those cases in which the sample size $n > 25$, the best estimator for the mean was the median.

Test of heterogeneity. A random effects model was used to test for heterogeneity in the studies on the lower

TABLE 1

Description of identified studies.

VARIABLE	LAVIOLA AND COLLEAGUES,[16] 2008	HERSH AND COLLEAGUES,[17] 2008	TAVARES AND COLLEAGUES,[18] 2008	FOWLER AND COLLEAGUES,[10] 2011	NOURBAKHSH AND COLLEAGUES,[19] 2012	ELMORE AND COLLEAGUES,[11] 2013
Type of Study	RCT* (double masked)	RCT (double masked)	RCT (double masked)	RCT (simple masked)	RCT (double masked)	RCT (simple masked)
Title	Randomized study of PM† for reversal of local anesthesia	Reversal of soft-tissue local anesthesia with PM in adolescents and adults	Reversal of soft-tissue local anesthesia with PM in pediatric patients	Reversal of soft-tissue anesthesia in asymptomatic endodontic patients: a preliminary, prospective, randomized, single-blind study	Effect of PM on duration of soft tissue local anesthesia in children	Reversal of pulpal and soft tissue anesthesia by using phentolamine: a prospective randomized, single-blind study
Journal	Journal of Dental Research	The Journal of the American Dental Association	The Journal of the American Dental Association	Journal of Endodontics	Journal of Research in Pharmacy Practice	Journal of Endodontics
Sample Used to Evaluate Efficacy	122	244	152	85	43	90
	Cases 61 / Controls 61	Cases 122 / Controls 122	Cases 72 / Controls 43	Cases 46 / Controls 39	Cases 43 / Controls 43	Cases 90 / Controls 90
Age, y	10-65	≥ 12	4-11	≥ 18	4-11	≥ 18
Dental Procedure	Restorative, periodontal, or prosthetic	Restorative, periodontal, or prosthetic	Restorative or periodontal	Endodontic (asymptomatic)	Not specified, no extractions	Any
Local Anesthetic	Lidocaine 2% per epinephrine 1:100,000 Articane 4% per epinephrine 1:100,000 Prilocaine 4% per epinephrine 1:200,000 Mepivacaine 2% per levonordefrin 1:20,000	Lidocaine 2% per epinephrine 1:100,000 Articane 4% per epinephrine 1:100,000 Prilocaine 4% per epinephrine 1:200,000 Mepivacaine2% per levonordefrin 1:20,000	Lidocaine 2% per epinephrine 1:100,000	Benzocaine 20% and lidocaine 2% per epinephrine 1:100,000	Lidocaine 2% per epinephrine 1:80,000	Benzocaine 20% and lidocaine 2% per epinephrine 1:100,000
Experimental Group	PM	PM	PM	PM	PM	PM
Control Group	Placebo (saline)	Sham (without injection)	Sham (without injection)	Sham (without injection)	Sham (without injection)	Sham (injection without infiltration)
Method	Tapping lips, tongue, and chin; intra- and extraoral exploration; vital signs monitorization	Tapping lips, tongue, and chin; FAB‡ STAR§ questionnaire, intra- and extra-oral exploration, vital signs monitorization, Heft-Parker VAS¶	Tapping lips and tongue, intra- and extraoral exploration, vital signs monitorization, W-B-PRS#	Tapping cheek, lips, and tongue; intra- and extraoral exploration, Heft-Parker VAS	Tapping, vital signs, trauma incidence	Tapping lips and tongue, electric pulp tester, intra- and extraoral exploration, Heft-Parker VAS
Significant Adverse Effects	No	No	No	No	No	No

* RCT: Randomized controlled trial.
† PM: Phentolamine mesylate.
‡ FAB: Functional assessment battery.
§ STAR: Soft-tissue anesthesia recovery.
¶ VAS: Visual analog scale.
# W-B-PRS: Wong-Baker FACES Pain Rating Scale.

lip and tongue. In both cases, significant heterogeneity ($P < .05$) was observed.

Figure 2 shows a forest plot comparing the duration of anesthesia in the experimental and the control groups, showing that in the group in which PM was applied, the duration was shorter than in the control group. The study by Nourbakhsh and colleagues[19] used 2 groups in which each group served as case and control, evaluating

TABLE 2

Average recovery times with phentolamine mesylate and sham groups and their differences.

AUTHOR, YEAR	AVERAGE RECOVERY TIME WITH PM*		AVERAGE RECOVERY TIME WITH SHAM		TREATMENT DIFFERENCE	
	Lip	Tongue	Lip	Tongue	Lip	Tongue
Laviola and Colleagues,[16] 2008	Lower lip: 101 min Upper lip: 50 min C†: 70 min	73.5 min	Lower lip: 150 min Upper lip: 155.5 min C: 155 min	105 min	Lower lip: 49 min Upper lip: 105.5 min C: 85 min	31.5 min
Hersh and Colleagues,[17] 2008	Lower lip: 70 min Upper lip: 50 min C: ± 60 min‡	60 min	Lower lip: 155 min Upper lip: 132.5 min C: ± 143.75 min‡	125 min	Lower lip: 85 min Upper lip: 82.5 min C: ± 83.75 min‡	65 min
Fowler and Colleagues,[10] 2011	Lower lip: 170 min Upper lip: 136 min C: ± 153‡	142 min	Lower lip: 217 min Upper lip: 224 min C: ± 220.5 min‡	169 min	Lower lip: 47 min Upper lip: 88 min C: ± 67.5 min‡	27 min
Tavares and Colleagues,[18] 2008	Lower lip: U§ Upper lip: U C: 60 min	45 min	Lower lip: U Upper lip: U C: 135 min	112.5 min	Lower lip: 120 min Upper lip: 52.5 min C: 75 min	67.5 min
Nourbakhsh and Colleagues,[19] 2012	Unspecified lip: Group 1: 29.47 min Group 2: 33.12 min	Not evaluated	Unspecified lip: Group 1: 135.52 min Group 2: 106.04 min	Not evaluated	Unspecified lip: Group 1: 106.05 min Group 2: 72.92 min	Not evaluated
Elmore and Colleagues,[11] 2013	Lower lip: PM* applied after 30 min and sham applied after 60 min, with a mean of 73 min duration	PM applied after 30 min and sham applied after 60 min, with a mean of 66 min duration	Lower lip: Sham applied after 30 min and PM applied after 60 min, with a mean of 97 min duration	Sham applied after 30 min and PM applied after 60 min, with a mean of 91 min duration	24 min	25 min‡

* PM: Phentolamine mesylate.
† C: Combined (upper and lower lip).
‡ Estimated value.
§ U: Unspecified.

them as 2 studies with the same characteristics. There was a high degree of heterogeneity among the RCTs included ($I^2 = 94.74\%$).

Figure 3 shows a forest plot comparing the duration of anesthesia in the experimental and control groups, showing that in the group in which PM was applied, the duration was shorter than in the control group. Not all the included studies evaluated the recovery of tongue sensitivity. A high degree of heterogeneity was identified among the RCTs included ($I^2 = 91.80\%$).

Sensitivity analysis. A sensitivity analysis for studies that evaluated the anesthetic duration on the lower lip showed that Fowler and colleagues[10] (standard error [SE] = −1.43; 95% CI, −1.63 to −1.23; $I^2 = 30.91\%$) contributed the most to homogeneity. eFigure 1 (available online at the end of this article) displays a plot of the sensitivity analysis that shows all the remaining studies have an unduly great impact on the fit of the model, the outlier being the study by Fowler and colleagues.[10] There were no statistically significant differences in effect sizes and confidence intervals of 95% with the random effects of the standardized mean difference (data not shown).

A sensitivity analysis for studies that evaluated anesthetic duration on the tongue displayed wide heterogeneity, being lowest for those of Laviola and colleagues[16] (SE = −1.84; 95% CI, −2.45 to −1.24; $I^2 = 83.34\%$) and Fowler and colleagues[10] (SE = −1.32; 95% CI, −1.91 to −0.73; $I^2 = 86.78\%$), but not enough to generate a great impact on the model. eFigure 2 (available online at the end of this article) displays a plot of the sensitivity analysis that shows all the remaining studies had an unduly great impact on the fit of the model, the outliers being the studies of Fowler and colleagues[10] and Laviola and colleagues.[16] There were no statistically significant differences in effect sizes and confidence intervals of 95% with the random effects of the standardized mean difference (data not shown).

Publication bias. A funnel plot for evaluating the duration of anesthesia on the lower lip had a more asymmetric distribution (eFigure 3, available online at the end of this article), whereas a funnel plot for the duration of anesthesia on the tongue had an almost symmetrical distribution (eFigure 4, available online at the end of this article). The Egger regression test suggested no significant asymmetry of the funnel plots ($P = .17$ and $P = .99$,

TABLE 3

Risk-of-bias assessment of the included trials.

AUTHOR, YEAR	POSSIBLE SOURCE OF BIAS (TYPE OF BIAS)						
	Random Sequence Generation (Selection)	Allocation Concealment (Selection)	Masking of Participants and Personnel (Performance)	Masking of Outcome Assessment (Detection)	Incomplete Outcome Data (Attrition)	Selective Reporting (Reporting)	Other Bias
Laviola and Colleagues,[16] 2008	Low risk	Low risk	High risk	Low risk	Low risk	Unclear risk	Low risk
Hersh and Colleagues,[17] 2008	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Tavares and Colleagues,[18] 2008	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Fowler and Colleagues,[10] 2011	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk	Unclear risk
Nourbakhsh and Colleagues,[19] 2012	High risk	High risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Elmore and Colleagues,[11] 2013	Low risk	Unclear risk	High risk	Low risk	Low risk	Unclear risk	Unclear risk

TABLE 4

Grouping of data for evaluation of standardized mean difference and timing of recovery of the lower lip and tongue.

AUTHOR, YEAR	DURATION OF SOFT-TISSUE ANESTHESIA IN THE LOWER LIP (MIN)									
	Phentolamine Mesylate Group					Control Group				
	Sample size	Median	Range	Mean	Standard error	Sample size	Median	Range	Mean	Standard error
Laviola and Colleagues,[16] 2008	61	70	0-240	70*	60*	61	155	0-240	155*	60*
Fowler and Colleagues,[10] 2011	46	–†	–	170	11.9	39	–	–	217	10.8
Elmore and Colleagues,[11] 2013	90	–	–	73	21	90	–	–	97	18
Hersh and Colleagues,[17] 2008	122	70	0-300	70*	50*	122	155	0-300	155*	50*
Tavares and Colleagues,[18] 2008	72	60	0-240	60*	40*	43	135	0-240	135*	60*
Nourbakhsh and Colleagues,[19] 2012	21	29.47	0-140	49.735*	35*	21	135.52	0-140	102.760*	35*
	22	33.12	0-140	51.56*	35*	22	106.04	0-140	88.02*	35*
AUTHOR, YEAR	**DURATION OF SOFT-TISSUE ANESTHESIA IN THE TONGUE (MIN)**									
	Phentolamine Mesylate Group					Sham Group				
	Sample size	Median	Range	Mean	Standard error	Sample size	Median	Range	Mean	Standard error
Laviola and Colleagues,[16] 2008	30	73.5	0-240	73.5*	60*	31	105	0-240	105*	60*
Fowler and Colleagues,[10] 2011	46	–	–	142	10.5	39	–	–	169	8.9
Elmore and Colleagues,[11] 2013	90	–	–	66	14	90	–	–	91	19
Hersh and Colleagues,[17] 2008	93	60	0-200	60*	33.333*	103	125	0-200	125*	33.333*
Tavares and Colleagues,[18] 2008	32	45	0-180	45*	45*	16	112.5	0-180	101.25*	45*

* Estimated value. The study only reported the median, range, and the sample size.
† Dashes indicate that no data are available.

respectively), indicating no evidence of substantial publication bias.

Adverse effects evaluation. Adverse effects were evaluated by extra- and intraoral exploration[10,11,16-19]; vital signs motorization using body temperature, heart rate, blood pressure, and breathing rate[16,18,19]; and pain assessment through 2 scales: the Heft-Parker Visual Analog Scale[10,11,16,19] and the Wong-Baker FACES Pain Rating Scale.[18] Adverse effects were similar in both groups. Some of the adverse effects reported were mild tachycardia,[16] headache,[11,16,17] pain during the injection,[17,18] postprocedure pain,[11,17,18] blood pressure increase,[18] subjective sensation of inflammation,[10] nausea, and increased temperature.[19]

DISCUSSION

This systematic review included 6 RCTs for which only the time duration of anesthesia on the lower lip and tongue of the experimental and control groups could be

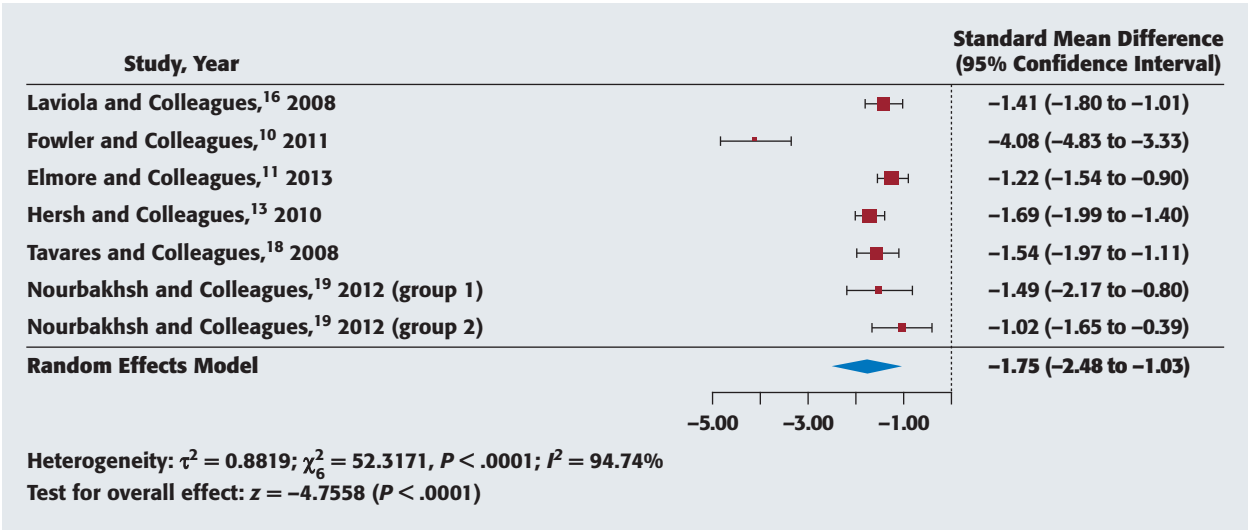

Figure 2. Forest plot comparing the duration of lower lip anesthesia in the phentolamine mesylate and sham groups.

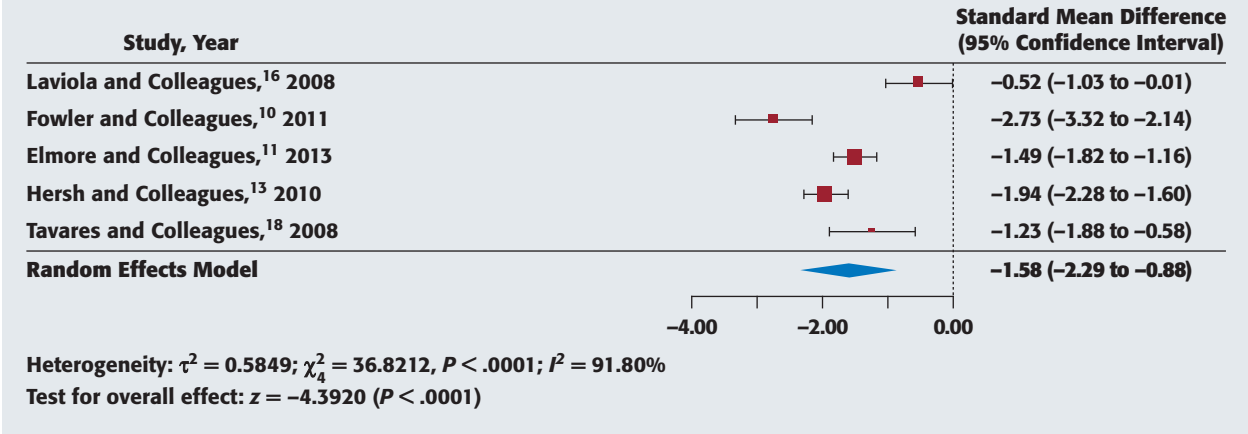

Figure 3. Forest plot comparing the duration of tongue anesthesia in the phentolamine mesylate and sham groups.

evaluated by meta-analysis. Despite the small number of RCTs available, use of data provided by this meta-analysis is justified because patients demand high quality dental care accompanied by the best quality of life possible. Some patients perceive the undesirable effects of anesthesia as a temporary decline in their quality of life.[17] Moreover, patients believe that residual soft-tissue numbness interferes with their normal daily activities in 3 specific areas: perceptual (perception of altered physical appearance), sensory (lack of sensation), and functional (diminished ability to speak, smile, drink, and control drooling).[7]

This review of RCTs available in the literature helps determine whether it is justified to use PM to reduce the time duration of anesthesia and, thus, improve the welfare and quality of life of our patients.

The evidence obtained was consistent with the clinical success of the experimental group to which the PM was applied, in which the duration of anesthesia was significantly shorter in all studies. Thus, with use of PM patients would recover functions such as talking, smiling, and drinking faster.

In group 2 of the study by Nourbakhsh and colleagues,[19] however, the use of PM was not as effective as in group 1 and in the rest of the included studies. Although several of the RCTs analyzed[10,16-18] agree on the absence of an influence of age on the effect of PM, there could be a reduced efficiency for children younger than 6 years, because this study included ages between 4 and 11 years in both groups; this may be the reason for the result. We cannot forget that the use of PM is not recommended by the manufacturer in children younger than 6 years.[21]

Although the number of RCTs was less than 10, we used a funnel plot and Egger regression test to assess publication bias and Cochrane Collaboration's tool for assessing risk of bias.[15] The resulting heterogeneity of the meta-analytic study could be due to the quality of the trials, which was generally poor, because none of the studies met all domains and, therefore, none was estimated as possessing a low risk of bias. Most of the trials[11,17-19] were judged to have an unclear risk of bias because of the lack of information. The rest[10,16] were cataloged as high risk of bias. However, the statistical analysis suggests that the most suitable methodology for conducting future studies, as they are inadequate, would follow that of the studies of Fowler and colleagues[10] and Laviola and colleagues.[16]

Numerous authors agree on the use of palpation of the lips and tongue[10,11,16-19] as the most reliable method to assess the effect of PM in soft tissues. Other authors[16] palpate the chin as well. Nevertheless, some studies, such as those conducted by Hersh and colleagues[17] and Elmore and colleagues,[11] added the Functional Assessment Battery and soft-tissue anesthesia recovery questionnaires, specially designed for the study. In addition, the latter included the use of an electric pulp tester to evaluate the effect of PM on dental pulp.

Despite the existing uniformity in the included studies in the method used to determine recovery of sensitivity by palpation of the area numbed, it is possible that the results may have varied among the different studies owing to the inherent subjectivity of the test. Therefore, it would be advisable to use objective methods to analyze sensitivity.

Owing to the small number of included studies and the heterogeneity of the sample, it was only possible to perform a qualitative analysis of the adverse effects produced by the use of PM. None of the studies obtained statistically significant values compared with the control group.

All studies used a placebo in the control group: either injecting saline,[16] simulating without an injection,[10,17,18,19] or simulating with an injection without infiltration.[11] Authors such as Fowler and colleagues[10] advocate simulation without injection or simulation with injection and without infiltration, because they refer to possible alterations in the duration of anesthesia due to dilution of the local anesthetic through saline or other substances used as placebo.

Although our study focuses on analyzing the effect of PM on the lower lip and tongue, 3 of the RCTs included[10,16,17] reported greater effectiveness in the maxilla. On the other hand, Tavares and colleagues[18] obtained better results in the mandible. Elmore and colleagues[11] only evaluated the mandible, and Nourbakhsh and colleagues[19] did not specify between the maxilla and mandible. In addition, studies that evaluated the recovery time in both the lip and tongue obtained a faster recovery time in the tongue.[10,11,16-18]

The studies by Laviola and colleagues[16] and Hersh and colleagues[17] revealed no significant differences either in terms of the dental procedure performed (restorative, periodontal, or prosthetic) or in the type of local anesthetic used whenever a locoregional block (truncal) of the inferior alveolar and lingual nerve was performed. Moreover, authors such as Fowler and colleagues[10] obtained similar results using 20% benzocaine as a topical anesthetic before the local anesthetic injection.

Laviola and colleagues[16] determined that the recovery time in the upper lip, lower lip, and tongue after applying PM was lower when lidocaine was used as a local anesthetic compared with articaine. Hersh and colleagues[17] also showed a greater reduction in the anesthetic effect on the lower lip and tongue when he used lidocaine instead of articaine. However, in the upper lip recovery time was reduced by 69% with articaine versus 63% with lidocaine, a fact that can be attributed to the small number of participants receiving articaine as a local anesthetic. Therefore, it appears that the reduction of anesthesia time is greater when using 2% lidocaine (1:100,000 epinephrine) as a local anesthetic agent, which could be because articaine 4% (1:100,000 epinephrine) is a more powerful and longer lasting local anesthetic than lidocaine 2% (1:100,000 epinephrine) and the effect of PM is more limited.

CONCLUSION

None of the RCTs analyzed were estimated to have a low risk of bias. Based on limited evidence, we found that the group that had PM applied showed greater efficacy in reducing the anesthetic time in the lower lip and tongue than in the control groups. The appearance of adverse effects is rare. We believe that to infer the average recovery time and quantify any adverse effects, more high-quality RCTs are needed. Those RCTs should have a lower risk of bias and an appropriate methodology to establish an objective method to assess the recovery of sensation. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at http://dx.doi.org/10.1016/j.adaj.2015.04.018.

Disclosure. None of the authors reported any disclosures.

Drs. Prados-Frutos and Rojo equally contributed as co-first authors.

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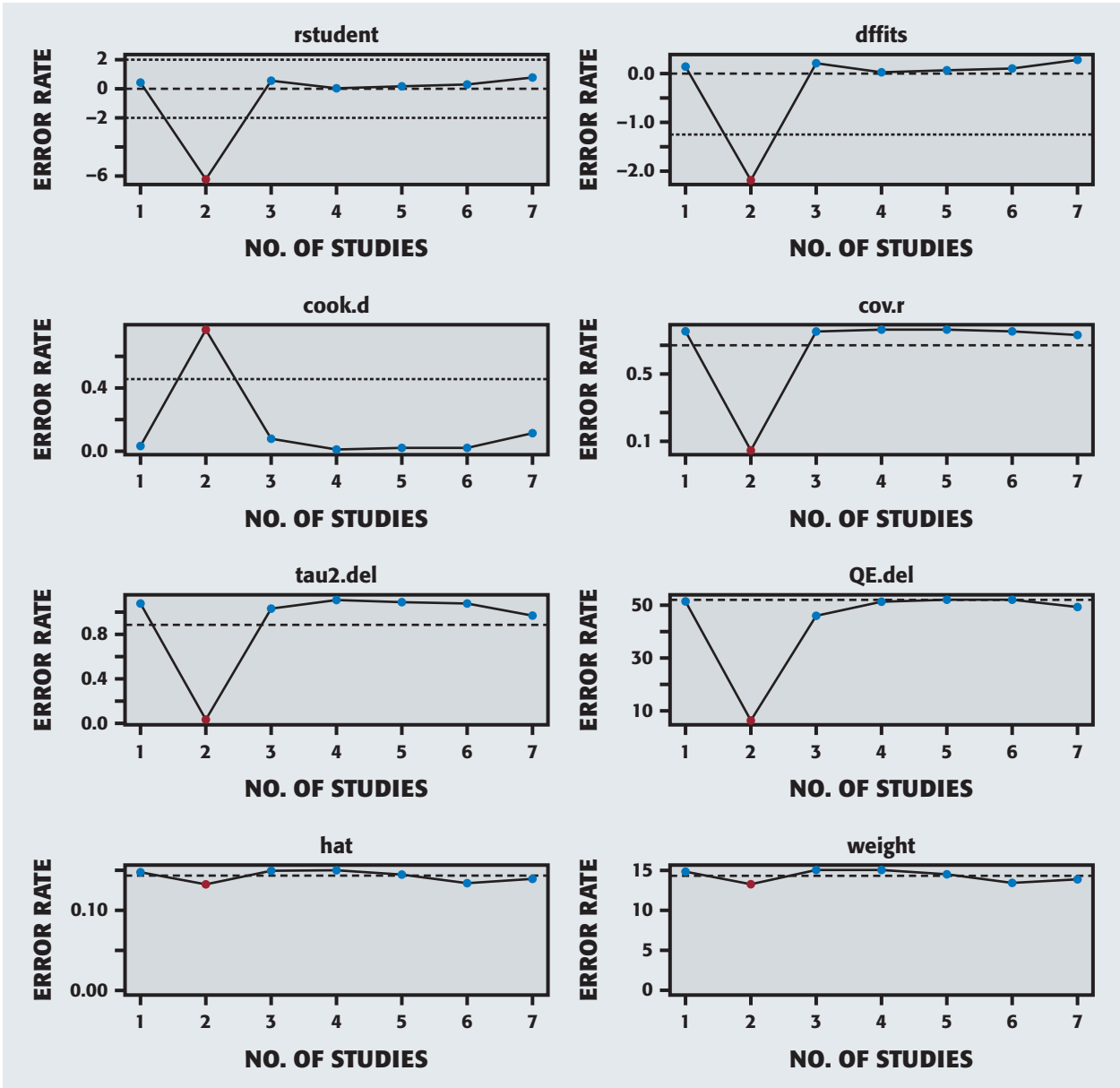
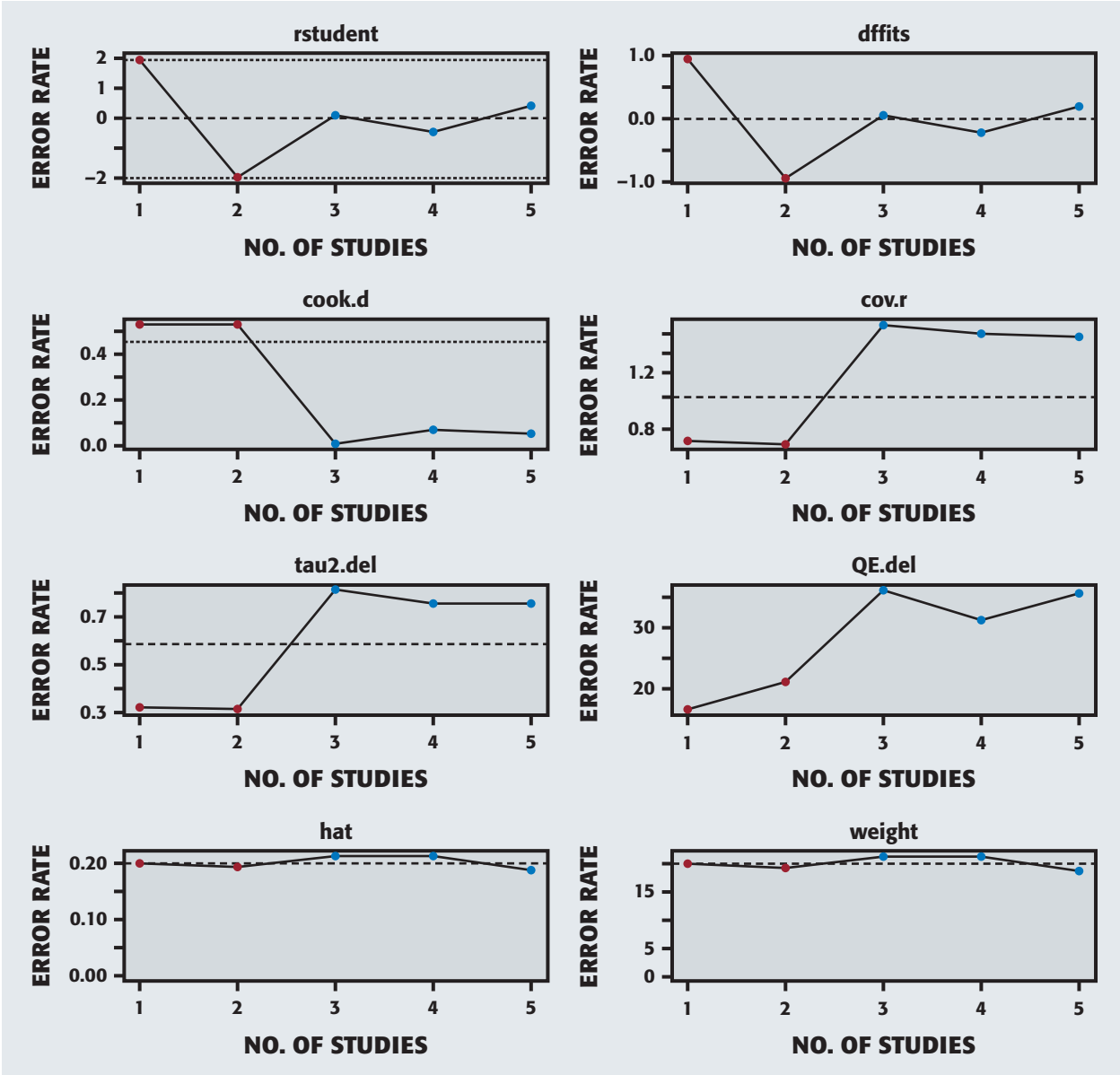
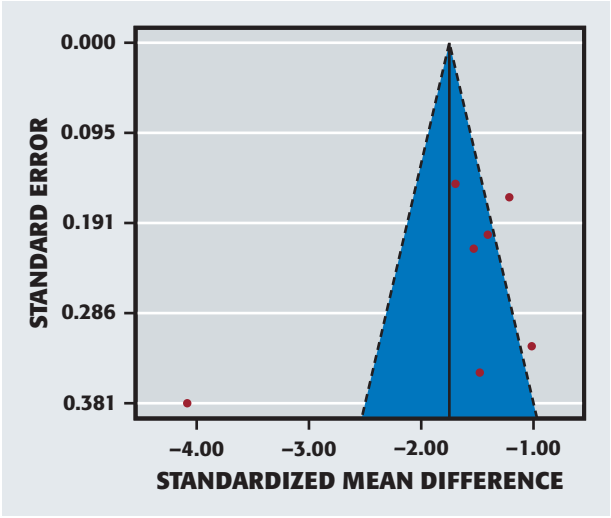


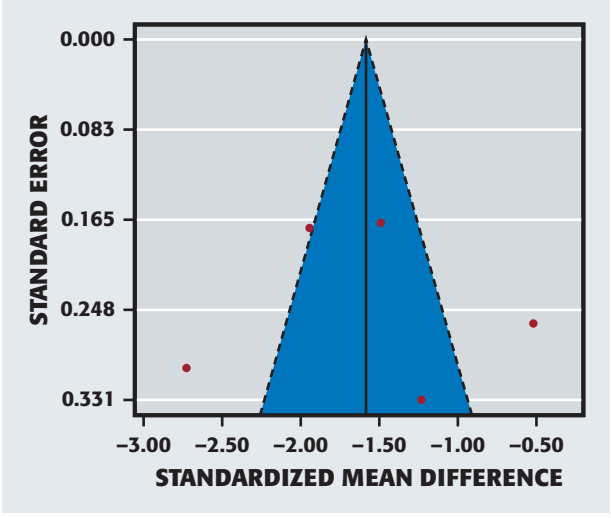
eFigure 1. Plot of sensitivity analysis of studies comparing the duration of lower lip anesthesia in the phentolamine mesylate and sham groups. cook.d: Cook's distances. cov.r: Covariance ratios. dffits: DFFITS values. hat: Hat values. QE.del: Leave-one-out values of the test statistics for heterogeneity. rstudent: Externally standardized residuals. tau2.del: Leave-one-out estimates of the amount of heterogeneity.



eFigure 2. Plot of sensitivity analysis of studies comparing the duration of tongue anesthesia in the phentolamine mesylate and sham groups. cook.d: Cook's distances. cov.r: Covariance ratios. dffits: DFFITS values. hat: Hat values. QE.del: Leave-one-out values of the test statistics for heterogeneity. rstudent: Externally standardized residuals. tau2.del: Leave-one-out estimates of the amount of heterogeneity.



eFigure 3. Funnel plot (with pseudo 95% confidence intervals) to detect possible publication bias of studies comparing the duration of lower lip anesthesia in the phentolamine mesylate and sham groups.



eFigure 4. Funnel plot (with pseudo 95% confidence intervals) to detect possible publication bias of studies comparing the duration of tongue anesthesia in the phentolamine mesylate and sham groups.