

# Phentolamine mesylate to reverse oral soft-tissue local anesthesia

## A systematic review and meta-analysis

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**L**ocal anesthetics have been extensively studied in the field of dentistry.<sup>1</sup> 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.<sup>2,3</sup>

According to Saunders and colleagues<sup>4</sup> 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<sup>5</sup> that can alter their quality of life.<sup>6,7</sup>

Therefore, agents for anesthetic reversal<sup>3</sup> have been developed such as phentolamine mesylate (PM) under the name of Oraverse (Septodont) as a local anesthesia antagonist.<sup>8,9</sup>

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

### 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.

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in soft-tissue anesthesia. Shortened effects of anesthesia increases the welfare and satisfaction of the patient.<sup>10,11</sup>

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.<sup>12</sup> Among the possible adverse effects, orthostatic hypotension, nausea, heart rhythm disorders (tachycardia and bradycardia being the most frequent<sup>8</sup>), pain at the injection site, and headache have been reported.<sup>13</sup> 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,<sup>14</sup> and the methodological quality was evaluated by following the Cochrane Collaboration's tool for assessing risk of bias,<sup>15</sup> 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.<sup>15</sup>

**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 “leaveout” 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.<sup>10,11,16-19</sup>

**Risk of bias within studies.** Only one of the included RCTs did not indicate the method of randomization used.<sup>18</sup> 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<sup>10,16</sup> of the 6 RCTs had a high risk of bias, 4<sup>11,17,18,19</sup> 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,<sup>19</sup> who used a concentration of 1:80,000. Laviola and colleagues<sup>16</sup> and Hersh and colleagues<sup>17</sup> evaluated the same 4 anesthetic agents (lidocaine 2% and epinephrine 1:100,000, articaine 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.

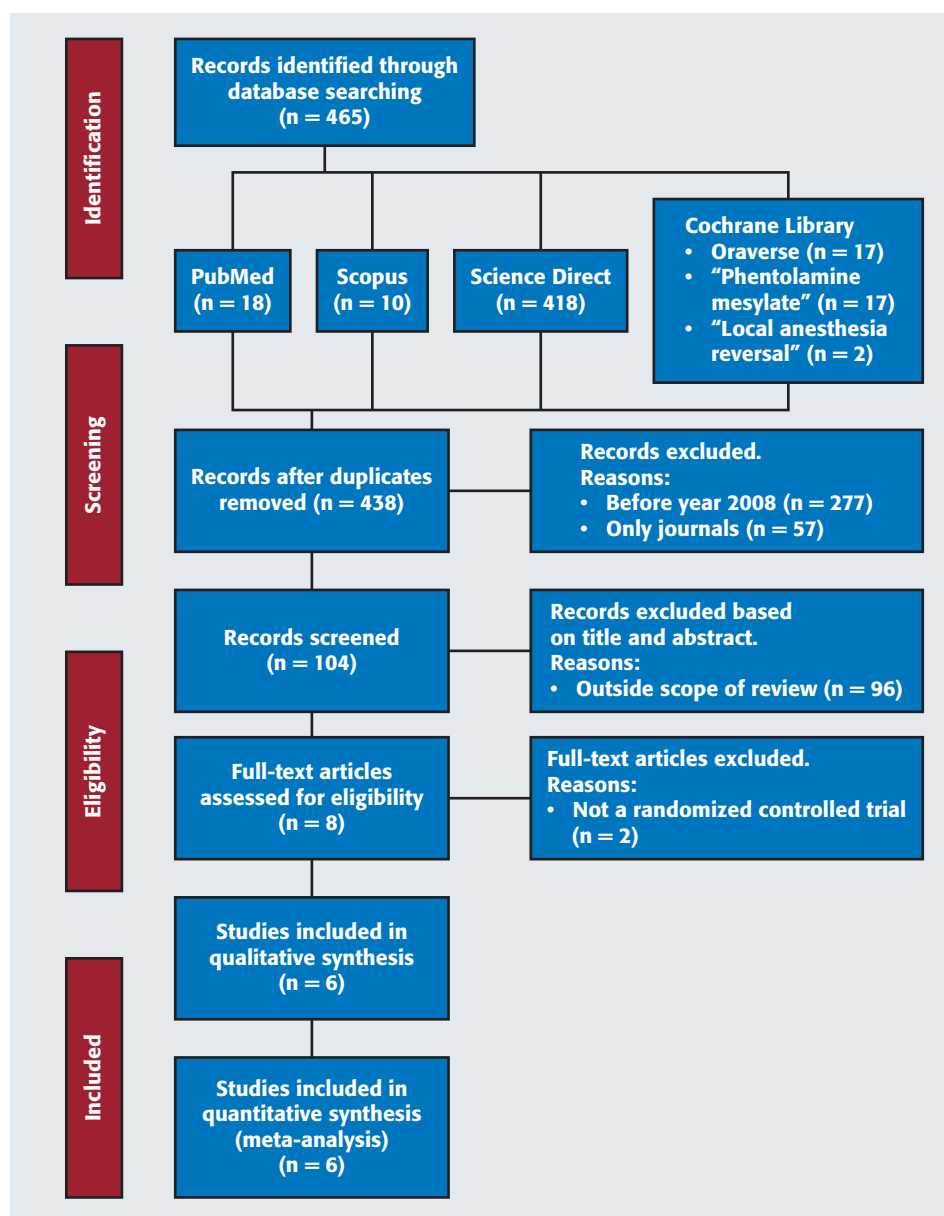
Tavares and colleagues<sup>18</sup> and Nourbakhsh and colleagues<sup>19</sup> only used lidocaine 2% in their studies, using different concentrations of epinephrine (Table 2).

**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<sup>20</sup>:  $\bar{x} \approx \frac{a+2m+b}{4}$  and the SD<sup>20</sup> 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



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

TABLE 1

| Description of identified studies.                                                                                                                                                                                                        |                                                                                              |             |                                                                                                                                           |              |                                                                                                 |             |                                                                                                                                    |             |                                                                      |             |                                                                                                                   |             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------------------------------------------------------------------------------------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------|-------------|----------------------------------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------------------|-------------|
| VARIABLE                                                                                                                                                                                                                                  | LAVIOLA AND COLLEAGUES, <sup>16</sup><br>2008                                                |             | HERSH AND COLLEAGUES, <sup>17</sup><br>2008                                                                                               |              | TAVARES AND COLLEAGUES, <sup>18</sup><br>2008                                                   |             | FOWLER AND COLLEAGUES, <sup>10</sup><br>2011                                                                                       |             | NOURBAKHSH AND COLLEAGUES, <sup>19</sup><br>2012                     |             | ELMORE AND COLLEAGUES, <sup>11</sup><br>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                                                       |             | Lidocaine 2% per epinephrine 1:100,000                                                                                                    |              | 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                                                         |             |
|                                                                                                                                                                                                                                           | Articane 4% per epinephrine 1:100,000                                                        |             | Articane 4% per epinephrine 1:100,000                                                                                                     |              |                                                                                                 |             |                                                                                                                                    |             |                                                                      |             |                                                                                                                   |             |
|                                                                                                                                                                                                                                           | Prilocaine 4% per epinephrine 1:200,000                                                      |             | Prilocaine 4% per epinephrine 1:200,000                                                                                                   |              |                                                                                                 |             |                                                                                                                                    |             |                                                                      |             |                                                                                                                   |             |
|                                                                                                                                                                                                                                           | Mepivacaine 2% per levonordefrin 1:20,000                                                    |             | Mepivacaine2% per levonordefrin 1:20,000                                                                                                  |              |                                                                                                 |             |                                                                                                                                    |             |                                                                      |             |                                                                                                                   |             |
| 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.<br>† PM: Phentolamine mesylate.<br>‡ FAB: Functional assessment battery.<br>§ STAR: Soft-tissue anesthesia recovery.<br>¶ VAS: Visual analog scale.<br># 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<sup>19</sup> 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, <sup>16</sup> 2008    | Lower lip: 101 min<br>Upper lip: 50 min<br>C†: 70 min                                             | 73.5 min                                                                              | Lower lip: 150 min<br>Upper lip: 155.5 min<br>C: 155 min                                         | 105 min                                                                               | Lower lip: 49 min<br>Upper lip: 105.5 min<br>C: 85 min        | 31.5 min      |
| Hersh and Colleagues, <sup>17</sup> 2008      | Lower lip: 70 min<br>Upper lip: 50 min<br>C: ± 60 min‡                                            | 60 min                                                                                | Lower lip: 155 min<br>Upper lip: 132.5 min<br>C: ± 143.75 min‡                                   | 125 min                                                                               | Lower lip: 85 min<br>Upper lip: 82.5 min<br>C: ± 83.75 min‡   | 65 min        |
| Fowler and Colleagues, <sup>10</sup> 2011     | Lower lip: 170 min<br>Upper lip: 136 min<br>C: ± 153‡                                             | 142 min                                                                               | Lower lip: 217 min<br>Upper lip: 224 min<br>C: ± 220.5 min‡                                      | 169 min                                                                               | Lower lip: 47 min<br>Upper lip: 88 min<br>C: ± 67.5 min‡      | 27 min        |
| Tavares and Colleagues, <sup>18</sup> 2008    | Lower lip: U§<br>Upper lip: U<br>C: 60 min                                                        | 45 min                                                                                | Lower lip: U<br>Upper lip: U<br>C: 135 min                                                       | 112.5 min                                                                             | Lower lip: 120 min<br>Upper lip: 52.5 min<br>C: 75 min        | 67.5 min      |
| Nourbakhsh and Colleagues, <sup>19</sup> 2012 | Unspecified lip:<br>Group 1: 29.47 min<br>Group 2: 33.12 min                                      | Not evaluated                                                                         | Unspecified lip:<br>Group 1: 135.52 min<br>Group 2: 106.04 min                                   | Not evaluated                                                                         | Unspecified lip:<br>Group 1: 106.05 min<br>Group 2: 72.92 min | Not evaluated |
| Elmore and Colleagues, <sup>11</sup> 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<sup>10</sup> (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.<sup>10</sup> 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<sup>16</sup> (SE = -1.84; 95% CI, -2.45 to -1.24;  $I^2 = 83.34\%$ ) and Fowler and colleagues<sup>10</sup> (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<sup>10</sup> and Laviola and colleagues.<sup>16</sup> 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, <sup>16</sup> 2008    | Low risk                               | Low risk                           | High risk                                           | Low risk                                  | Low risk                            | Unclear risk                    | Low risk     |
| Hersh and Colleagues, <sup>17</sup> 2008      | Low risk                               | Unclear risk                       | Low risk                                            | Low risk                                  | Unclear risk                        | Unclear risk                    | Unclear risk |
| Tavares and Colleagues, <sup>18</sup> 2008    | Unclear risk                           | Unclear risk                       | Low risk                                            | Low risk                                  | Low risk                            | Unclear risk                    | Unclear risk |
| Fowler and Colleagues, <sup>10</sup> 2011     | Low risk                               | High risk                          | High risk                                           | Low risk                                  | Low risk                            | Unclear risk                    | Unclear risk |
| Nourbakhsh and Colleagues, <sup>19</sup> 2012 | High risk                              | High risk                          | Low risk                                            | Unclear risk                              | Low risk                            | Unclear risk                    | Unclear risk |
| Elmore and Colleagues, <sup>11</sup> 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, <sup>16</sup> 2008    | 61                                                        | 70             | 0-240 | 70*     | 60*            | 61            | 155    | 0-240 | 155*     | 60*            |
| Fowler and Colleagues, <sup>10</sup> 2011     | 46                                                        | — <sup>†</sup> | —     | 170     | 11.9           | 39            | —      | —     | 217      | 10.8           |
| Elmore and Colleagues, <sup>11</sup> 2013     | 90                                                        | —              | —     | 73      | 21             | 90            | —      | —     | 97       | 18             |
| Hersh and Colleagues, <sup>17</sup> 2008      | 122                                                       | 70             | 0-300 | 70*     | 50*            | 122           | 155    | 0-300 | 155*     | 50*            |
| Tavares and Colleagues, <sup>18</sup> 2008    | 72                                                        | 60             | 0-240 | 60*     | 40*            | 43            | 135    | 0-240 | 135*     | 60*            |
| Nourbakhsh and Colleagues, <sup>19</sup> 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, <sup>16</sup> 2008    | 30                                                        | 73.5           | 0-240 | 73.5*   | 60*            | 31            | 105    | 0-240 | 105*     | 60*            |
| Fowler and Colleagues, <sup>10</sup> 2011     | 46                                                        | —              | —     | 142     | 10.5           | 39            | —      | —     | 169      | 8.9            |
| Elmore and Colleagues, <sup>11</sup> 2013     | 90                                                        | —              | —     | 66      | 14             | 90            | —      | —     | 91       | 19             |
| Hersh and Colleagues, <sup>17</sup> 2008      | 93                                                        | 60             | 0-200 | 60*     | 33.333*        | 103           | 125    | 0-200 | 125*     | 33.333*        |
| Tavares and Colleagues, <sup>18</sup> 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.

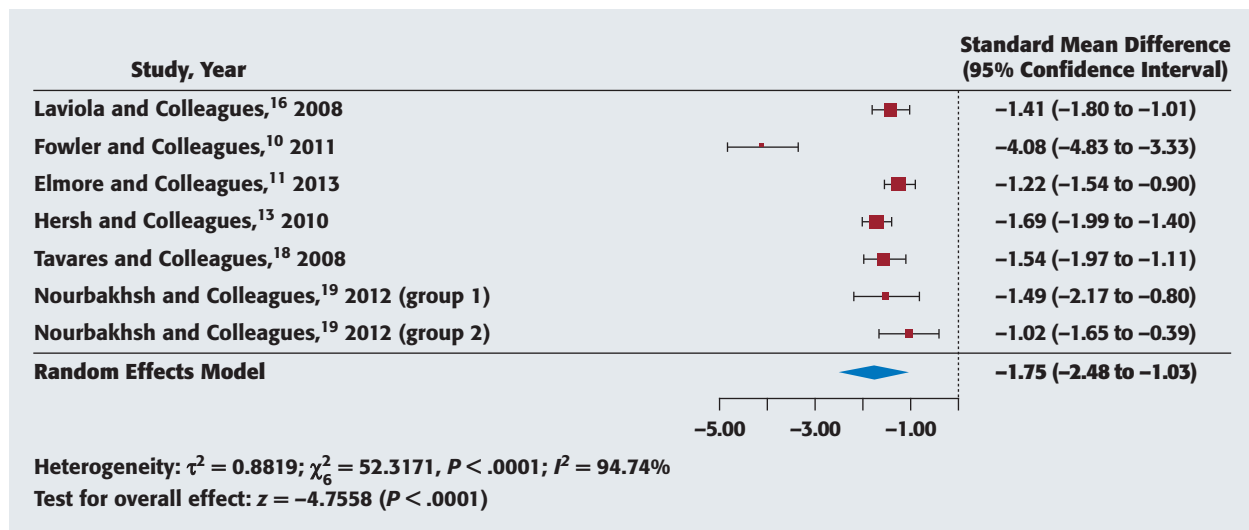
**Adverse effects evaluation.** Adverse effects were evaluated by extra- and intraoral exploration<sup>10,11,16-19</sup>; vital signs motorization using body temperature, heart rate, blood pressure, and breathing rate<sup>16,18,19</sup>; and pain assessment through 2 scales: the Heft-Parker Visual Analog Scale<sup>10,11,16,19</sup> and the Wong-Baker FACES Pain Rating Scale.<sup>18</sup> Adverse effects were similar in both groups. Some

of the adverse effects reported were mild tachycardia,<sup>16</sup> headache,<sup>11,16,17</sup> pain during the injection,<sup>17,18</sup> postprocedure pain,<sup>11,17,18</sup> blood pressure increase,<sup>18</sup> subjective sensation of inflammation,<sup>10</sup> nausea, and increased temperature.<sup>19</sup>

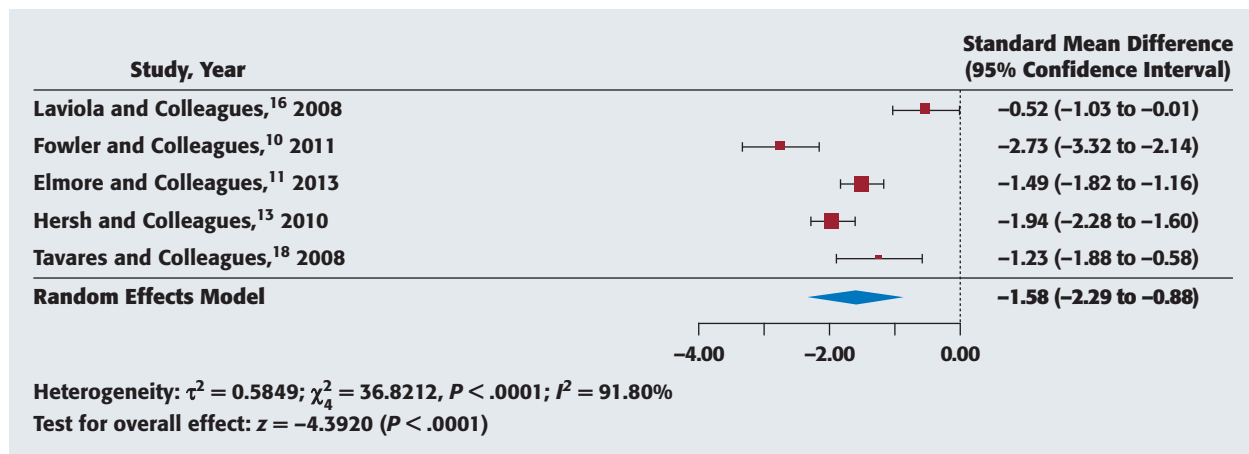
## DISCUSSION

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.<sup>17</sup> 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).<sup>7</sup>

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,<sup>19</sup> 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<sup>10,16-18</sup> 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.<sup>21</sup>

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.<sup>15</sup> 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<sup>11,17-19</sup> were judged to have an unclear risk of bias because of the lack of information. The rest<sup>10,16</sup> 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<sup>10</sup> and Laviola and colleagues.<sup>16</sup>

Numerous authors agree on the use of palpation of the lips and tongue<sup>10,11,16-19</sup> as the most reliable method to assess the effect of PM in soft tissues. Other authors<sup>16</sup> palpate the chin as well. Nevertheless, some studies, such as those conducted by Hersh and colleagues<sup>17</sup> and Elmore and colleagues,<sup>11</sup> 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,<sup>16</sup> simulating without an injection,<sup>10,17,18,19</sup> or simulating with an injection without infiltration.<sup>11</sup> Authors such as Fowler and colleagues<sup>10</sup> 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<sup>10,16,17</sup> reported greater effectiveness in the maxilla. On the other hand, Tavares and colleagues<sup>18</sup> obtained better results in the mandible. Elmore and colleagues<sup>11</sup> only evaluated the mandible, and Nourbakhsh and colleagues<sup>19</sup> 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.<sup>10,11,16-18</sup>

The studies by Laviola and colleagues<sup>16</sup> and Hersh and colleagues<sup>17</sup> 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<sup>10</sup> obtained similar results using 20% benzocaine as a topical anesthetic before the local anesthetic injection.

Laviola and colleagues<sup>16</sup> 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<sup>17</sup> 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>.

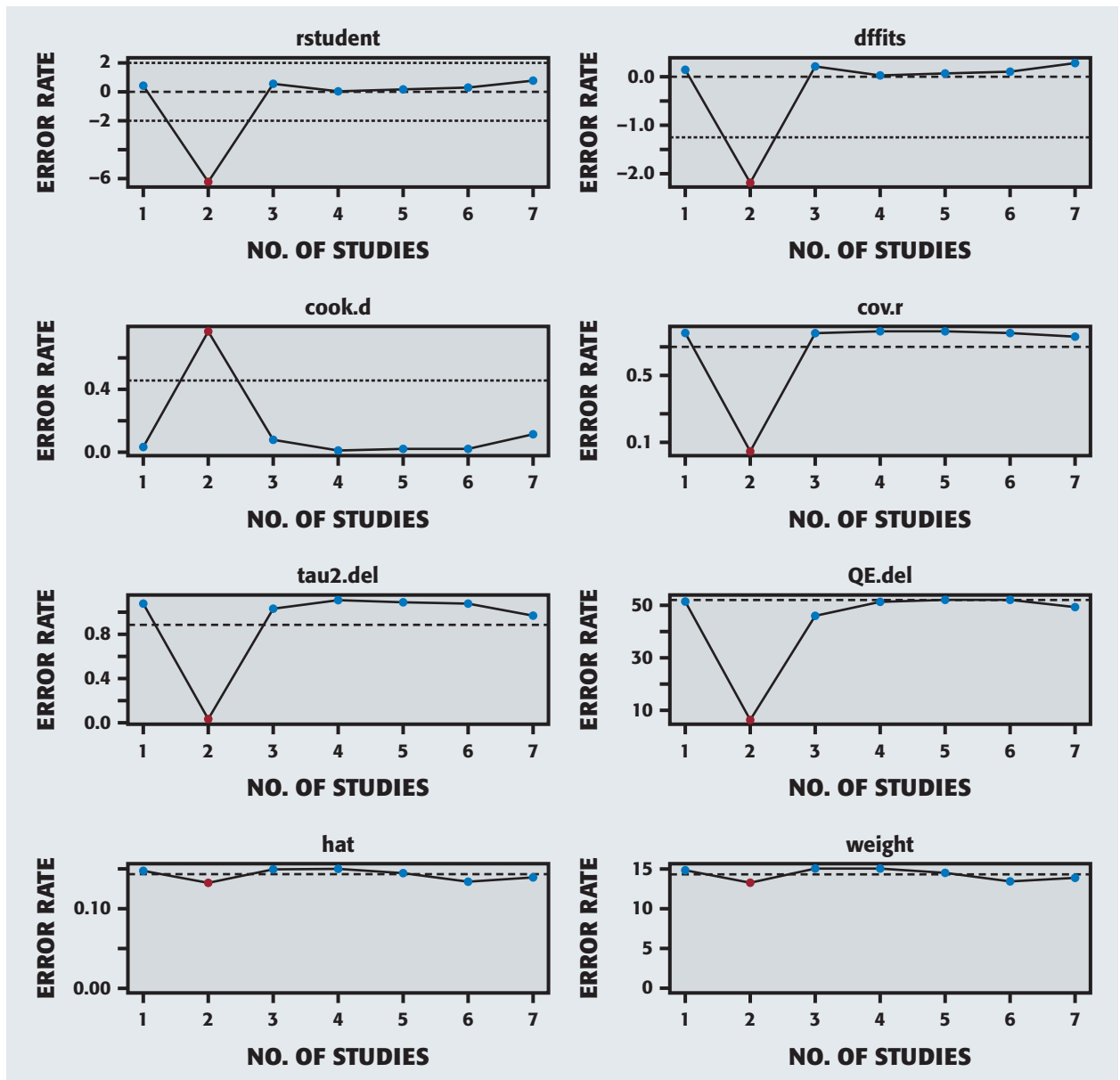
**Disclosure.** None of the authors reported any disclosures.

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

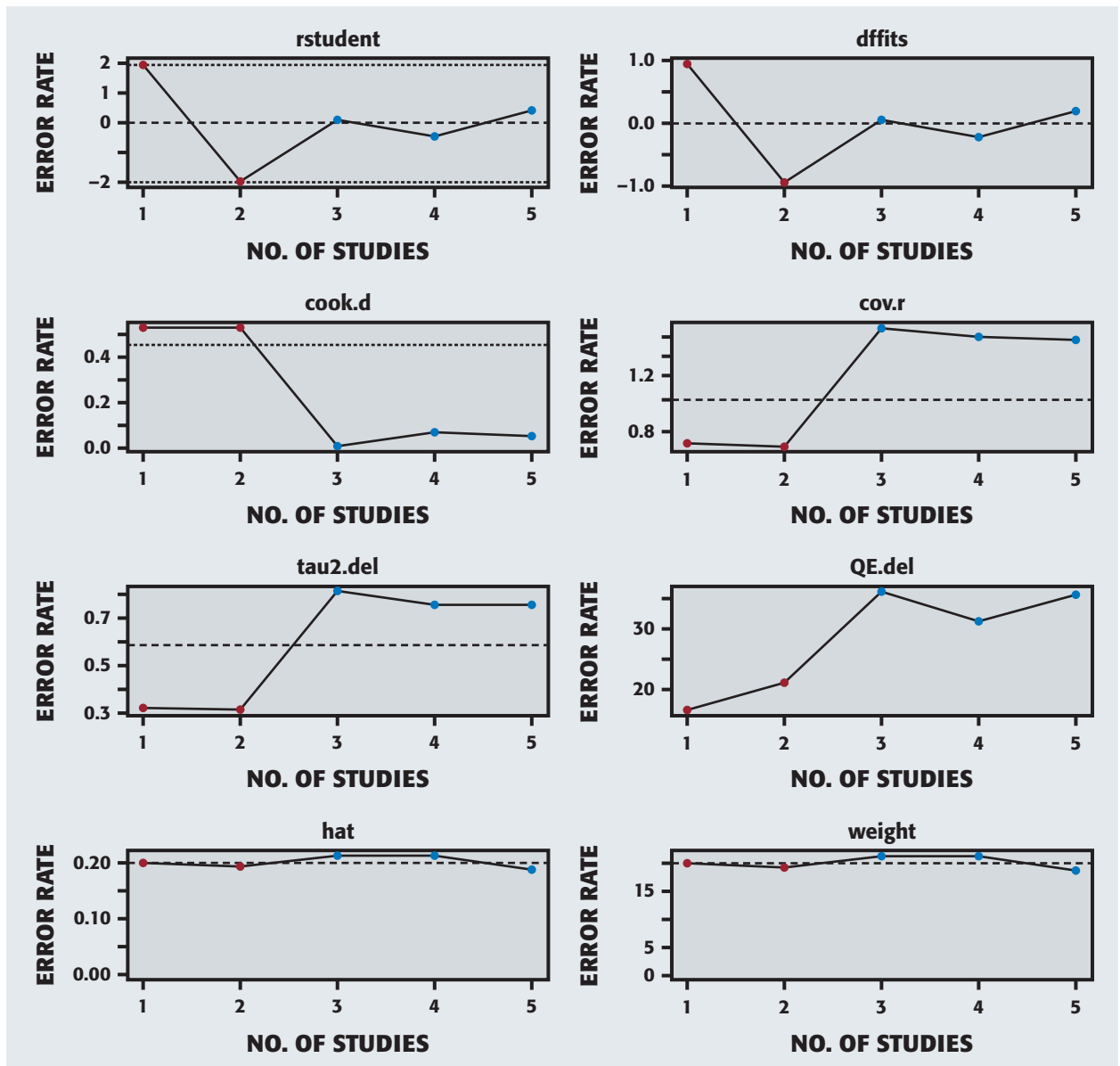
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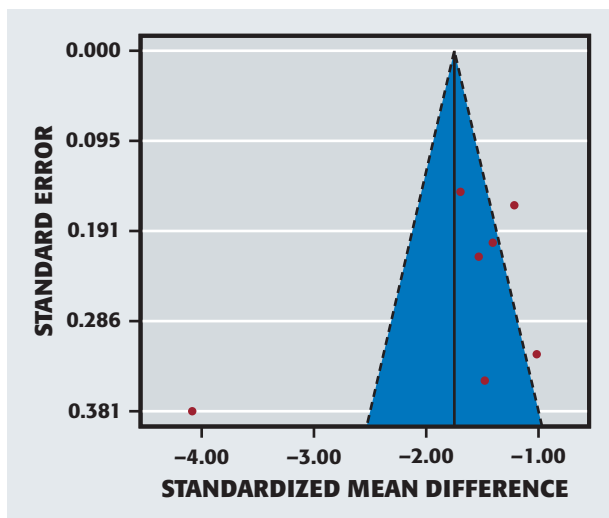
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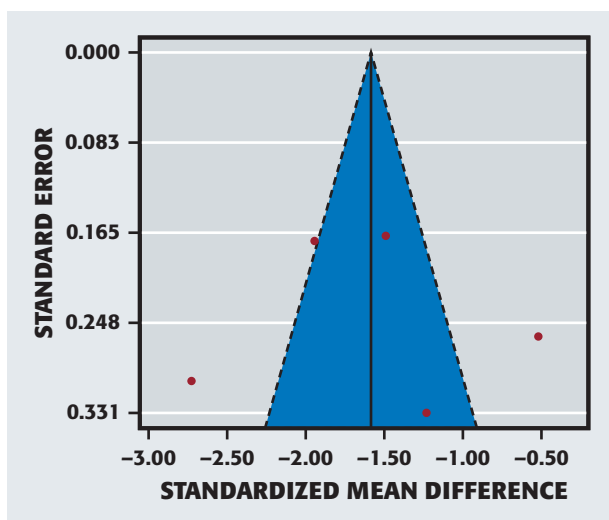
**eFigure 1.** Plot of sensitivity analysis of studies comparing the duration of lower lip anesthesia in the phentolamine mesylate and sham groups. cook.d: Cook's distances. cov.r: Covariance ratios. dffits: DFFITS values. hat: Hat values. QE.del: Leave-one-out values of the test statistics for heterogeneity.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