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PHENTOLAMINE MESYLATE IN DENTAL PRACTICE: EFFICACY AND SAFETY FOR REVERSING SOFT TISSUE ANESTHESIA - A SYSTEMATIC REVIEW

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ABSTRACT

This systematic review assesses the efficacy and safety of Phentolamine Mesylate as a local anesthetic reversal agent in dental procedures. We conducted a comprehensive search for English-language articles from January 2008 to June 2022 in MEDLINE, PubMed, EBSCO, Web of Science, Scopus, Science Direct, and the Cochrane Central Register of Controlled Trials. After deduplication, 378 articles were identified. Following abstract screening, 306 articles were excluded, leaving 72 potentially relevant studies. Ultimately, 11 randomized controlled trials met the inclusion criteria, and their risk of bias was assessed using the Critical Appraisal Skills Programme tool and Cochrane Collaboration methodology. The findings consistently support Phentolamine Mesylate's therapeutic efficacy, significantly reducing the time needed to recover from residual soft tissue anesthesia across all studies, with high patient satisfaction. Promoting awareness of Phentolamine Mesylate as a local anesthetic reversal agent is crucial to mitigate residual anesthesia's adverse effects.

KEYWORDS: Lidocaine, Phentolamine Mesylate, Reversal of anesthesia, Soft tissue anesthesia, Self-inflicted injury

INTRODUCTION

The advent of local anesthetics has revolutionized dental practice, significantly improving the comfort of patients and the feasibility of various dental treatments. [1] Lidocaine, one of the most commonly used Local Anesthetic, provides soft tissue anesthesia that typically lasts for 3 to 5 hours [2-4]. However, this duration often exceeds the necessary timeframe for many essential dental procedures, leading to several clinical challenges and patient discomfort.[2-4] One notable issue arises when mandibular block injections are administered. In such cases, the tongue

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remains anesthetized longer than the lips, increasing the risk of self-inflicted injuries .[5] Patients frequently report difficulties in speaking, drinking, and eating normally due to persistent anesthesia, with drooling being a particularly distressing consequence of prolonged soft tissue anesthesia. Pediatric patients, in particular, are at risk, as they may inadvertently chew on a numb lower lip, potentially leading to ulcerations.[6]

To address these challenges, Phentolamine Mesylate, a non-selective alpha (1 and 2) adrenergic blocking agent, has been introduced as an anesthesia reversal drug. Phentolamine Mesylate counteracts the adverse effects of Local Anesthetic by opposing the vasoconstrictive properties of epinephrine. It accelerates the absorption rate of the anesthetic agent, acting as a competitive inhibitor of epinephrine, while also promoting smooth muscle relaxation and increased blood circulation.(5) Marketed under the name OraVerse, Phentolamine Mesylate received approval from the US Food and Drug Administration, Germany, and Canada in 2008, 2011, and 2014, respectively.(3,7) Dental practitioners commonly administer 1.7 ml of a packaged solution containing 0.4 mg of Phentolamine Mesylate for anesthesia reversal during dental procedures.[5,8-10]

Despite its potential benefits, Phentolamine Mesylate usage in dental settings, particularly its timing and safety considerations, remains a matter of concern. Clinical trials on the efficacy and safety of Phentolamine Mesylate, especially in specific patient populations, are limited. For instance, caution is advised when considering Phentolamine Mesylate for children under the age of six who weigh less than 15 kg to reverse lip and tongue numbness—a condition that typically resolves naturally within about an hour.[2, 5]

This systematic review aims to address key questions surrounding the effectiveness of Phentolamine Mesylate in reducing the duration of lip and tongue anesthesia following dental procedures, as well as assessing reported adverse events and relevant primary and secondary outcomes. Additionally, we will explore the associated challenges and unknown risks associated with Phentolamine Mesylate administration compared to traditional local anesthesias.

MATERIALS AND METHODS

In adherence to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11), we meticulously conducted this systematic review.[11]

Inclusion criteria

We applied the PICOS (Population-Intervention-Comparator-Outcome-Study Design) framework to identify eligible studies. Our review encompassed randomized controlled trials published in English from January 2008 to June 2022. We focused on an experimental model involving individuals of any age (Population) who received local anesthesia in combination with a vasoconstrictor (Comparator) and were administered Phentolamine Mesylate as an antagonist (Intervention) during dental procedures. Our primary outcomes of interest encompassed the reduction in anesthesia duration and the occurrence of adverse events (Outcome).

Exclusion criteria

We applied strict exclusion criteria to ensure the focus on intervention-specific research. The following types of studies were excluded: non-interventional studies, observational studies, quasi-experimental studies, systematic reviews, meta-analyses, animal studies, and in-vitro research.

Information sources and search strategy

For a comprehensive and thorough literature search, we accessed several renowned databases: MEDLINE, PubMed, EBSCO, Web of Science, Scopus, Science Direct, and the Cochrane Central

Register of Controlled Trials. Our search strategy was carefully crafted using a combination of Medical Subject Headings (MeSH), title/abstract keywords, truncations, and Boolean operators. The key search terms included: "Oraverse," "phentolamine mesylate [MeSH]," and ("local anesthesia [MeSH]" AND "reversal"). The search strategy was adapted to suit the unique requirements of each electronic database. We took into account both Phentolamine Mesylate and its relevance to dental and oral surgery aspects. To ensure the currency of the research, we restricted our results to studies published within the last 15 years.

Study selection and data collection process

Using both electronic and manual searches, the search technique produced 536 items, of which 378 remained after duplicates were eliminated. Then, after screening all of the titles and abstracts, 306 papers were removed by two independent reviewers. 72 studies were evaluated for full-text analysis based on the stated eligibility criteria. Finally, 11 studies[12–22] were deemed qualified for inclusion in the review for qualitative synthesis, whereas 61 articles were excluded for not being Randomized Control Trials. The heterogeneity of the studies precluded the performance of meta-analyses. Figure 1 shows the conceptual PRISMA flow chart for study selection.

The comprehensive search strategy, combining electronic and manual searches, yielded an initial pool of 536 items. After eliminating duplicates, 378 unique records remained. Subsequently, two independent reviewers conducted a meticulous review of titles and abstracts, resulting in the exclusion of 306 papers that did not meet the defined eligibility criteria. Seventy-two studies underwent a rigorous full-text analysis based on the specified criteria. Ultimately, 11 studies [12–22] qualified for inclusion in the review, facilitating a qualitative synthesis. Notably, 61 articles were excluded due to their non-randomized controlled trial design. The inherent heterogeneity among the selected studies precluded the possibility of conducting meta-analyses.

For a visual representation of the study selection process, please refer to Figure 1, illustrating the conceptual PRISMA flow chart.

Data extraction

Data extraction was performed meticulously using a custom-designed data extraction form in Microsoft Excel 2010. Both reviewers independently gathered relevant information from each of the included studies.

Table 1, provided in this review, presents a comprehensive overview of the extracted data from the included research. In instances where differences of opinion arose during the study selection and data extraction processes, a consensus was reached following consultation with a third reviewer.

Key data points retrieved from each study encompassed author and publication year, participant age, total participant count in the treatment and control groups, drug concentration employed, type of nerve block or infiltration, method employed for inducing numbness and reversing its effects, effectiveness evaluation, adverse outcomes, and primary and secondary endpoint measures.

Quality assessment

To ensure rigorous evaluation, two independent reviewers meticulously assessed the quality of the identified publications using the Critical Appraisal Skills Programme tool (CASP) [23], a well-recognized framework for critical appraisal.

Additionally, the Cochrane Collaboration tool for evaluating bias across trials in randomized controlled trials was employed to scrutinize potential sources of bias [24]. Various domains were considered, including randomization, allocation concealment, blinding procedures, dropout rates, selective reporting, and other potential sources of bias.

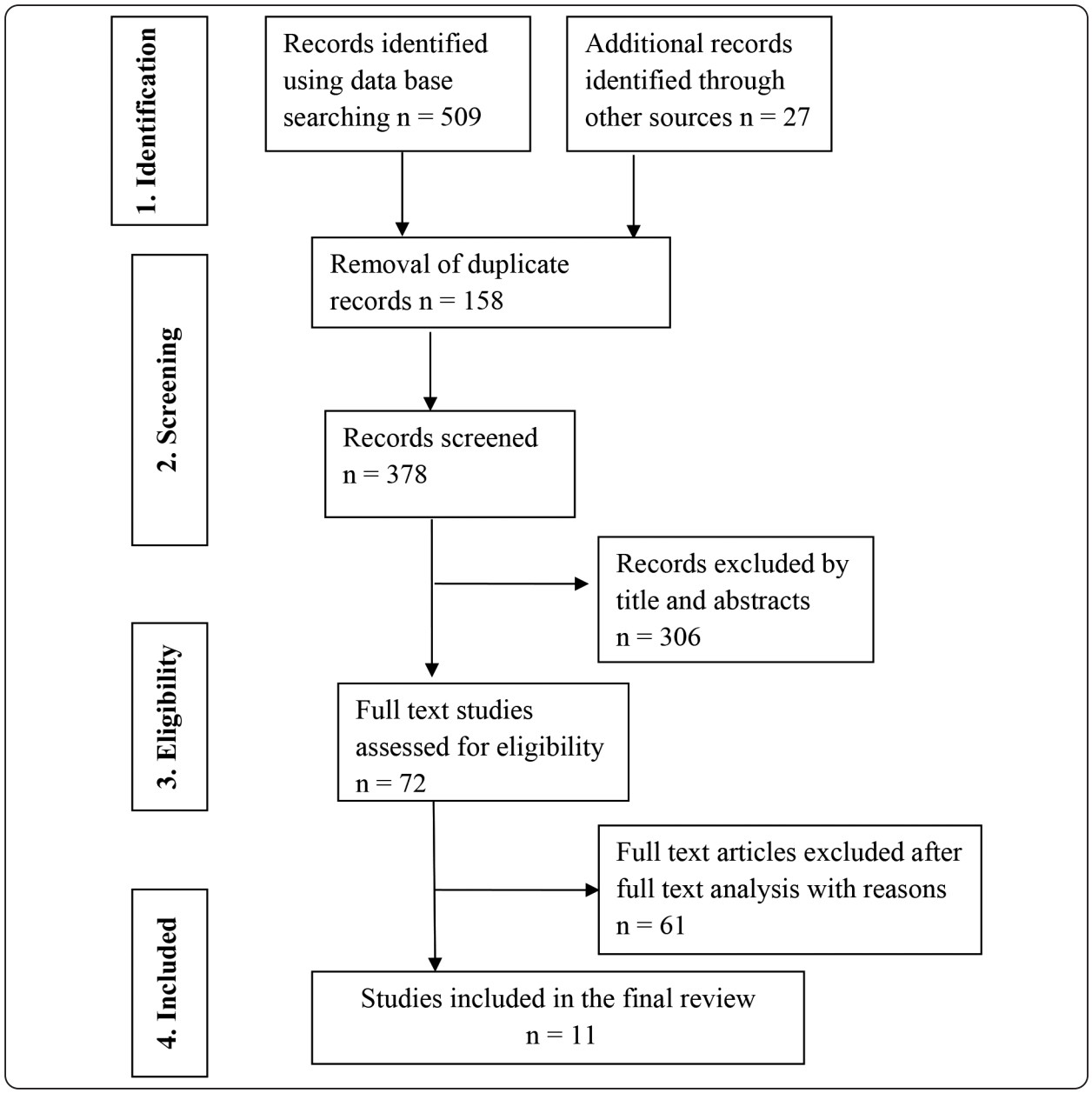

Fig. (1) Figure 1: PRISMA flow chart of the included studies (Adapted from Preferred Reporting Items for Systematic Reviews and Metaanalyses 2009 Flow Diagram)

For each domain assessed, the reviewers categorized the risk of bias into one of three levels: low (indicating that all domains were adequately satisfied), unclear (indicating that 1 or 2 domains were not entirely met), or high (indicating that 3 or more domains were unfulfilled).

Given the substantial heterogeneity among the included studies, conducting meta-analyses was not feasible.

RESULTS

This systematic review incorporates a total of 11 studies that met the predefined inclusion criteria (see Table 1).

TABLE (1) Summary of the included studies in the review

Author, Year	Mean Age (years)	weight (Kg)	Study design	Control group	Experimental group	Dental procedure	Local anesthesia	Nerve block or infiltration	Methods	Adverse effects
Vintanel-moreno et al., 2021	54.78 ± 11.34	NS	Prospective randomized double blind trial	n=30	n=30 PM	Implant surgery	4% articaine with adrenaline 1:100,000	Inferior alveolar, and Lingual nerve blocks followed by buccal nerve infiltration	VAS	Speech impairment, nausea, feeling of palpitation or dizziness, and head or neck pain were reported, but insignificant
Beshara et al., 2021	Study group: 6.60±1.15 Control group: 6.38±1.27	>15	Single blinded randomized controlled parallel group clinical trial	n=40	n=40 PM	Pediatric patients	2% lidocaine with 1:100,000 epinephrine	Inferior alveolar nerve block	pFAB, index finger palpation, and lip tapping	Insignificant occurrence of redness, swelling, and hematoma. Presence of ulcer was found to be significant
Gago-García et al., 2021	44.3±11	>30	A prospective randomized double-blind study	30	2groups (n=30 in each) Two cartridges of PM, and the proportion of anaesthesia to reversal agent was always 1:1	Restoration, extraction, full mouth disinfection, implant placement, and endodontic treatment.	Group 1: lidocaine 2% 1/80,000 Group 2: articaine 4% 1/200,000, and Group 3: bupivacaine 0.5% 1/200,000	Inferior alveolar nerve block	VAS	Pain at the site of the injection (11.1%), headaches (6.7%), tachycardia (1.1%), and heavy bleeding after treatment (3.3%) were observed
Michaud et al., 2018	>18	NS	Triple blinded Randomized placebo controlled trial	n=17 1.7 ml of normal saline n=19	1.7 ml of 0.4 mg PM in saline water (Oraverse)	Trained students of dental hygiene and dentistry	1.8 ml of 2% Lidocaine at 1:100,000	Inferior alveolar nerve block	Self-assessment of soft tissue anaesthesia using finger palpation and tapping with comparison with the non-anesthetized side	The only adverse events observed were post-injection discomfort or pain (63%) in the test group and 41% in the control group
Hersh et al., 2017	Study group: 4.20.8± Control group: 4.10.9±	>15	Randomized-double-blind study	n=51 Sham injection	n=99 PM	routine dental restorative procedures	2% Lidocaine at 1:100,000	submucosal injection (inferior alveolar blocks for the mandible)	pFAB, tapping of lip/ tongue on the anaesthetized side and compared it to that of the unanesthetized side. W-B PRS was also employed	A transient decreased blood pressure was noted in some cases. It induced rapid recovery of lip anaesthesia ($p<0.0001$) in four to five year old children

Elmore et al., 2013	26	NS	Prospective randomized cross over single blind	n=90 sham injection	n=90 PM	Not specified	2% lidocaine (36 mg) with 1:100,000 epinephrine	Inferior alveolar nerve block	Tapping lips and tongue, electric pulp tester to monitor pulpal anesthesia, VAS	Tenderness (4%–6%) at the injection site, headache (2%–4%), and soreness on opening the jaw (3%), tongue paresthesia (1%) that persisted for around 5 months were reported.
Nourbakhsh et al., 2012	4 to 11	≥15	Randomized-double-blind, controlled clinical trial	n=43 Sham injection	n=43 PM	Routine dental treatment	lidocaine 2% and epinephrine 1:80,000	NS	VAS	19% of patient traumatized their lips after treatment without PM injection than PM group (2%)
Fowler et al., 2011	Study group: 382.3± Control group: 342.3±	NS	Prospective single blind randomized trial	n=39 Sham	n=46 PM	Asymptomatic endodontic cases	0.2 mL of 20% benzocaine topical anesthetic gel, followed by 1.8 ml of lidocaine 2% and epinephrine 1:100,000	Inferior alveolar nerve block	Tapping cheek, lips, and tongue; VAS	Postoperative pain of the tooth, and injection site, subjective intraoral swelling with PM were reported with no serious AE
Hersh et al., 2008	>12	>30	Two randomized controlled, double- blinded Phase III clinical trials: involving the mandible and the maxilla	n=122 sham	n=122 PM	a restorative or crown preparation procedure or a dental scaling and root planing	2% lidocaine with 1:100,000 epinephrine, 4% Articaine with 1:100,000 epinephrine, 4% Prilocaine with 1:200,000 epinephrine, and 2% Mepivacaine with 1:20,000 levonordefrin	inferior alveolar nerve block, the Gow-Gates block, the Vazirani-Akinosi block, the mental incisive block for mandible and supraperiosteal injection of the anterior teeth, the superior anterior alveolar nerve block and the infraorbital nerve block.	lip and tongue palpation, the Soft Tissue Anaesthesia Recovery (STAR) questionnaire, pFAB, and VAS	Injection site pain 6.6 and 6.7% at mandibular and maxillary sites respectively; 5.7% and 1.7% respectively, for the sham group. Post procedural pain and headache also reported
Laviola et al., 2008	2712±	>30	Double blind, randomized, multicenter, study	n=61 saline	n=61 PM	routine periodontal maintenance, restorative procedures, or single crowns	2% lidocaine with 1:100,000 epinephrine, 4% articaine with 1:100,000 epinephrine, 2% mepivacaine with 1:20,000 levonordefrin, and 4% prilocaine with 1:200,000 epinephrine.	Supraperiosteal infiltration or middle or anterior superior alveolar nerve injection (maxilla). Inferior alveolar/lingual nerve block (mandible)	Tapping, for lips, and the tongue; pressing with the forefinger for the chin. VAS was also carried out	Tachycardia was reported at similar rates in both the groups.
Tavares et al., 2008	4 to 11	>30	Double blind, randomized,	n=43 Sham injection	n=72 PM	Restorative or periodontal	lidocaine 2% and epinephrine 1:80,000	Supraperiosteal injection in 54.6%, inferior alveolar nerve blocks in 28.9% , and 13.2% received Gow-Gates nerve blocks	Tapping of lips and tongue, intraoral pain measured by the W-B PRS were performed. Vital signs was also monitored	Pain at the injection site, increased blood pressure, and post-procedural pain were frequently reported

NS - Not specified; PM - Phentolamine Mesylate; VAS - Visual analogue scale; WB-PRS - Wong-Baker Faces Pain-Rating Scale ; pFAB - Pediatric functional assessment battery

TABLE (2) Outcome measures and the mean difference in the duration of the anesthetic effect between the groups

	Duration of anaesthetic effect in the lips			Duration of anesthetic effect in the tongue				
	Control group (minutes)	Experimental group (minutes)	Mean difference	Control group (minutes)	Experimental group (minutes)	Mean difference	Primary outcome	Secondary outcome
Vintanel-moreno et al., 2021	190.05 ± 49.99	87.14 ± 53.36	102.91	180.21 ± 61.63	78.27 ± 44.92	101.94	Monitoring of systolic and diastolic BP, and Oxygen saturation. Systolic blood pressure increased significantly in study group, without any serious AE.	Duration of the reversal of anaesthetic effect on the tongue and lip showed a significant reduction in the PM group and improved patient satisfaction.
Beshara et al., 2021	30	60	30	NS	NS	NS	The incidence of self-inflicted STA and return to normal function in PM group were efficacious post-operatively and STI was followed up after 24 hours.	The pFAB included evaluation of smiling, speaking, drinking and the presence or absence of drooling which was quicker in PM group
Gago-García et al., 2021	Group 1: 59.6 Group 2: 88.5 Group 3: 249	Group 1: 116 to 125 min Group 2: 157 to 182 Group 3: 190 to 230	Group 1: 12.13 Group 2: 33.97 Group 3: 52.05	Group 1: 52.5 Group 2: 84.5 Group 3: 214.5	Group 1: 122 to 132 min Group 2: 161 to 185 min Group 3: 221 to 270	Group 1: 13.50 Group 2: 32.36 Group 3: 64.51	Patients were monitored for numbness, tingling, or normal sensation after injection of the reversal agent using VAS and a questionnaire	Patient satisfaction (100%) and likelihood of recommending (98.9%)
Michaud et al., 2018	104.4±13.4	170.1±13.8	65.7	83.1±11.7	133.9±12.4	50.8	Reversal of normal sensation in the lip and tongue as well as normal speaking, drinking and smiling was enhanced by around 60 minutes compared to the controls	The only adverse events observed were post- operative pain and discomfort
Hersh et al., 2017	61	109	48	60	91	31	A statistically significant rapid reversal of lip sensation was determined compared to controls	PM was safe and well-tolerated in three- to five-year-old children
Elmore et al., 2013	97±18	73±21	24	91±19	66±14	27	Reversal of pulpal anesthesia were elicited ($p<0.05$)	Return-to-normal sensation of the lip and tongue was observed ($p<0.05$)

Nourbakhsh et al., 2012	Group 1: 135.52 min Group 2 (PM): 106.04 min	Group 1: 29.47 min Group 2 (PM): 33.12 min	Group 1: 106.05 min Group 2 (PM): 72.92	NS	NS	NS	A statistically significant difference ($p < 0.001$) in reversal of normal lip sensation was reported between case and control groups and also between the groups ($p< 0.003$)	incidence of soft tissue trauma after mandibular block injection showed a statistically significant difference ($p<0.04$)
Fowler et al., 2011	220.5	153	67.5	169	142	27	Return-to-normal sensation for the maxillary lip/cheek and mandibular lip and tongue were found to be statistically significant.	Frequency of patient reported postoperative complications such as intraoral swelling, nausea, ringing in the ears, and feeling of dizziness were found to be statistically insignificant
Hersh et al., 2008	143.75	60	83.75	125	60	65	Median recovery times in the lower lip and tongue for PM group was 70 and 60 minutes respectively	Recovery from actual functional deficits and subject-perceived altered function, sensation and appearance showed significant difference ($p<0.0001$)
Laviola et al., 2008	155	70	85	105	73.5	31.5	The difference in median recovery of normal sensation in the lip was reported to be 85 minutes	PM treatment significantly decreased recovery times for normal sensation in the chin and tongue with median reductions of 59.5 and 32min respectively
Tavares et al., 2008	135	60	75	112.5	45	67.5	Evaluation of the safety and tolerability of a formulation of PM revealed a favourable result	PM accelerated the return of normal soft tissue sensation

NS - Not specified; pFAB - Pediatric functional assessment battery; VAS - Visual analogue scale; PM - Phentolamine Mesylate; STA - Soft tissue anesthesia; STI - Self-afflicted soft tissue injury; AE - Adverse events

Table 3: Risk of bias assessment within the studies

S.No	Section A: Validity of basic study design valid for a RCT	Vintanel-moreno et al., 2021	Beshara et al., 2021	Gago-García et al., 2021	Michaud et al., 2018	Hersh et al., 2017	Elmore et al., 2013	Nourbakhsh et al., 2012	Fowler et al., 2011	Hersh et al., 2008	Laviola et al., 2008	Tavares et al., 2008
1	Did the study address a clearly focused research question?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Was the assignment of participants to interventions randomized?	C	Y	N	Y	C	Y	N	C	C	C	C
3	Were all participants who entered the study accounted for at its conclusion?	N	C	Y	Y	N	N	N	N	Y	Y	Y
	Section B: Aspects of sound methodology											
4	Blinding/Masking											
	Were the participants 'blind' to intervention?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Were the investigators 'blind' to the intervention to be given?	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y
	Were the people assessing/analyzing outcome 'blinded'?	N	Y	N	Y	N	N	N	N	N	N	N
5	Were the study groups similar at the start of the RCT?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	Did each study group receive the same level of care/treated equally?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Section C: Results											
7	Were the effects of intervention reported comprehensively?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	Was the precision of the estimate of the intervention/treatment effect reported?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N
9	Do the benefits of the intervention outweigh the harms and costs?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Section D: Application of results to the local population											
10	Can the results be applied to your local population/in your context?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11	Would the intervention be of greater value to the people than any of the existing interventions?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y - Yes; N - No; C - Cannot tell

TABLE (4) Risk of bias (RoB) assessment across the studies

Author, year	Selection bias (random sequence generation)	Selection bias (allocation concealment)	Performance bias (blinding)	Detection bias (outcome assessment)	Attrition bias (incomplete data of outcome)	Reporting bias (selective reporting)	Other bias	Level of RoB
Vintanel-moreno, 2021	?	+	+	?	-	?	?	High
Beshara, 2021	+	+	+	+	-	?	?	High
Gago-García, 2021	-	+	+	?	+	+	?	High
Michaud, 2018	+	+	+	+	+	+	?	Moderate
Hersh, 2017	?	-	+	?	-	?	?	High
Elmore, 2013	+	+	+	+	-	?	?	High
Nourbakhsh, 2012	-	-	+	?	+	+	?	High
Fowler, 2011	+	-	-	?	--	?	?	High
Hersh, 2008	?	-	+	?	+	+	?	High
Laviola, 2008	+	?	+	+	+	+	?	Moderate
Tavares, 2008	?	-	+	?	+	+	?	High

High RoB: +

Low RoB : -

Unclear RoB: ?

Study characteristics

In the electronic database searches, we initially identified 509 articles, and an additional 27 studies were discovered through manual searches. Among the 11 included studies, one by Laviola et al.[19] featured participants spanning a wide age range from 10 to 65. Notably, five of the selected trials involved participants under the age of 12 [15, 18, 19, 21, 22]. Five studies primarily focused on assessing the safety and efficacy of Phentolamine Mesylate in expediting the recovery from (soft tissue anesthesia).[12,14,15,18,19]

Funding for the studies conducted by Michaud et al.[16] and Nourbakhsh et al.[21] was provided by the Dalhousie Faculty of Dentistry and the Department of Research and Technology of the Isfahan University of Medical Sciences, respectively. Hersh et al.[15] received support from a grant awarded by Septodont Inc., Cambridge, and the National Institutes of Health (NIH) for their investigation. Additionally, the research conducted by Hersh et al.[13], Tavares et al.[18], and Laviola et al.[19] was funded by Novalar Pharmaceuticals, San Diego.

While many studies support the clinical use of Phentolamine Mesylate as an anesthetic reversal agent in pediatric patients and conservative dentistry, Vintanel-Moreno et al.[14] addressed the current need for research to evaluate the reversing effects of Phentolamine Mesylate in dental implant surgery. They suggested its potential utility in the adult population undergoing implant therapy. Elmore et al.[17] also reported a significant reduction in pulpal anesthesia following a 30-minute interval between Phentolamine Mesylate and sham injections, in addition to a reduction in soft tissue anesthesia . The studies included in this review primarily investigated the anesthetic reversal effect of Phentolamine Mesylate compared to that of a placebo or sham injection administered after delivering local anesthesia. Notably, the investigations by Laviola et al.[19] and Michaud et al.[16] stood out as they assessed the effectiveness of Phentolamine Mesylate using a genuine control injection of saline, in contrast to the sham injections used in other trials.

Synthesis of results

Types of local anesthesia

With the exception of the studies by Gago-Garcia et al. [12], Tavares et al. 18, and Nourbakhsh et al. [21], which employed a concentration of 1:80,000, Lidocaine was the exclusive anesthetic agent used in all other studies with epinephrine at a 1:100,000 concentration. Notably, in two trials conducted by Laviola et al. [19] and Hersh et al. [13], the reversal effect was assessed using four different anesthetic agents: Lidocaine 2% and epinephrine 1:100,000, Articaine 4% and epinephrine 1:100,000, Prilocaine 4% and epinephrine 1:200,000, and Mepivacaine 2% and Levonordefrin 1:20,000.Of particular interest, Gago-Garcia et al. conducted a randomized controlled trial using Bupivacaine and found that the duration of anesthesia was significantly shorter in the Bupivacaine group compared to the Lidocaine/ Articaine group. However, it's worth noting that the majority of studies primarily utilized Lidocaine and Articaine in combination with a vasoconstrictor to assess the efficacy of Phentolamine Mesylate as a reversal agent. Moreover, Vintanel-Moreno et al. employed 4% Articaine with 1:100,000 epinephrine, highlighting the potential use of Phentolamine Mesylate in dental implant placement, which garnered high levels of patient satisfaction.[14]

This synthesis illustrates the diverse array of local anesthetic agents employed in the included studies and underscores the potential applicability of Phentolamine Mesylate across various clinical scenarios, particularly in the context of dental implant procedures.

Phentolamine Mesylate effectiveness

Table 2 illustrates the duration of lip and tongue numbness following Phentolamine Mesylate and sham injections, along with the time difference between the two groups. Patients who received Phentolamine Mesylate experienced a notable reduction in the duration of soft tissue anesthesia compared to those receiving sham injections,

thereby reducing the risk of self-inflicted injuries. In a cross-over clinical trial, Elmore et al. found that when Phentolamine Mesylate was administered at 30 minutes instead of 60 minutes, the time required for the lips and tongue to return to normal was significantly reduced by 24 minutes[17].

Following Phentolamine Mesylate injection, Laviola et al. observed that lip and tongue numbness lasted for 70 and 73.5 minutes, respectively[19]. Fowler et al. reported differences in the recovery times for the lip and tongue between the experimental and control groups, with durations of 67.5 minutes and 27 minutes, respectively[20]. Notably, Vintanel-Moreno found that the largest disparity in recovery times between the lips and tongue was observed across all included studies, with average recovery times of 102.9 minutes for the lips and 101.9 minutes for the tongue[14]. Additionally, Gago-Garcia et al. reported high patient satisfaction levels and a strong inclination to recommend Phentolamine Mesylate to others[12]. These findings collectively highlight the effectiveness of Phentolamine Mesylate in reducing the duration of soft tissue anesthesia , offering a valuable clinical benefit in dental procedures, particularly in terms of patient comfort and safety.

Evaluation methods

The operator/investigator was instructed on how to compare the anesthetized side against the non-anesthetized side to determine the degree of lip numbness. Utilizing the Pediatric functional assessment battery (pFAB), functional deficits were estimated by taking measurements of drooling, speaking, smiling, and drinking three ounces of water at varying points throughout the trial. These functional assessments were scored as normal when all functional tests were positive and abnormal when one or more of these functions were rated as aberrant in the assessment. pFAB was used in children in three of the clinical trials in the review[13,15,22]. The Soft Tissue Anesthesia Recovery (STAR) questionnaire, the Functional Assessment Battery (FAB), and Heft-Parker visual analog scale (H-P VAS) ascertained how the individual felt about their altered function, sensation, and appearance in adults.[13]

Outcome measures

The Heft-Parker Visual Analog Scale (VAS) and the Wong-Baker FACES Pain Rating Scale (W-B PRS) were used to assess pain. The W-B PRS is used to measure intraoral pain, with zero representing no pain and five being the "worst possible pain[18] and was employed in seven of the included studies in the review.[12,14,15,17,19–21] The VAS scale was used to measure patient satisfaction with Phentolamine Mesylate administration and discomfort experienced postoperatively; the score of which ranges from 0 to 10, representing no pain to extreme pain, respectively. The VAS was utilized in the study conducted by Hersh et al.,[13] and Tavares et al.[18]

Adverse effects

The monitoring of vital signs periodically, appropriate evaluations of pain at the injection and surgical sites, the requirement for analgesics, clinical evaluations of the oral cavity, and reporting of adverse effects were the safety precautions employed in the included studies. The following vital signs were observed: breathing rate, body temperature, heart rate, and blood pressure. Mild tachycardia, headaches, pain during injections, subjective feelings of inflammation, nausea, elevated body temperature, and slight changes in blood pressure were recorded. Importantly,no significant variations in vital signs, pain, or adverse events between Phentolamine Mesylate and sham-treated patients were seen during any of the trials, nor were any serious side effects.[14,25]

isk of bias within studies

In accordance with the CASP tool for RCT, table 3 displays the comprehensive risk of bias assessment for each of the 11 clinical trials that were part of the review. The instrument evaluates

the validity of the study design, sound methodology, outcome measure, and relevance of its application to the local community. The precision estimate of the outcome measures and the randomization strategy was not disclosed in studies by Tavares et al.,[18] and Nourbakhsh et al.[21] Four further trials did not disclose the randomization procedure.[12–15]

Risk of bias across the studies

Table 4 depicts an overview of the risk of bias for each of the included studies. Nine trials (82%) had a high risk of bias for at least one bias domain. Allocation concealment and attrition bias were the most commonly observed high-risk bias domains. Nine included studies used double-blind trials, while Fowler et al.,[20] and Michaud et al.[16] used single-blind and triple-blind trials respectively. Two of the studies[16,19] had a moderate level of risk using the preset seven domains for RoB assessment, whereas the other nine studies had a high risk of bias.[12–15,17,18,20–22]

DISCUSSION

Despite the limited number of available RCTs, the data from this review provide valuable insights for delivering high-quality dental care. Patients place great importance on their dental experience, and the transient reduction in their quality of life due to negative anesthetic effects cannot be overlooked. Notably, the control group with residual soft tissue anesthesia appeared to experience a higher incidence of post-operative self-inflicted injuries compared to the Phentolamine Mesylate group [22]. The persistent soft tissue anesthesia not only hampers essential functions such as speech, smiling, and drinking but also alters individuals' perceptions of their physical appearance [8, 25]. Of particular concern is the potential for self-inflicted injuries in the lips, tongue, and cheeks due to the enduring numbness, which can manifest as erythema, hematoma, puffiness, or ulcer. Several studies have suggested a possible link between the reversal of soft tissue anesthesia and a reduction in self-inflicted injuries, underscoring the clinical significance of promptly addressing residual anesthesia. Moreover, several of the included studies reported high levels of patient satisfaction with Phentolamine Mesylate administration. Patients appreciated the faster recovery from anesthesia, which contributed to a positive overall dental experience [22, 26]

While the available RCTs are relatively limited in number, the findings emphasize the importance of incorporating interventions like Phentolamine Mesylate to mitigate the negative impact of soft tissue anesthesia and enhance the overall dental experience for patients. Further research and broader clinical adoption of such interventions may lead to improved patient outcomes and satisfaction in dental procedures.

It's important to note that subjects should be older than 6 years to accurately assess the efficacy of the intervention. Nonetheless, safety was evaluated in all reported trials, regardless of participant profiles or ages, consistent with the findings of Verma et al.[3] Phentolamine Mesylate reversal has only been explored in children as young as 4 years old, weighing 15 kg; the FDA has not yet authorized its usage in children under the age of 6 [1, 6]. According to Tavares et al., Phentolamine Mesylate was well-tolerated and safe in children between the ages of 4 and 11.[18]

The duration of local anesthesia can vary depending on the type of anesthetic agent and administration technique. Lidocaine with epinephrine (1:100,000) is the most widely used anesthetic in dental offices, with a duration of soft tissue anesthesia ranging from 180 to 300 minutes following a nerve block [27]. Laviola et al. [19] observed a one-hour reduction in the time required to restore normal lip sensation after administering Phentolamine Mesylate immediately following dental therapy, where local anesthesia was given beforehand. This reduction in soft tissue anesthesia duration was consistent regardless of the type of treatment, age, or gender. In another study by Tavares et al. [18], the reversal times for normal

sensation of the tongue and lip were reduced by 60% and 55.6%, respectively, in pediatric patients.

When Hersh et al.[13] utilized Lidocaine rather than Articaine, the anesthetic effect on the lower lip and tongue was significantly reduced. Because Articaine 4% (1:100,000 epinephrine) is a stronger and longer-lasting local anesthesia than Lidocaine 2% (1:100,000 epinephrine) and the action of Phentolamine Mesylate is more constrained, the reduction in anesthesia time is larger when employing 2% Lidocaine (1:100,000 epinephrine).[8] In contrast to the Lidocaine and Articaine group, Gago-Garcia et al. found that Bupivacaine significantly reduced the reversal effect from 460 minutes to 230 minutes for the lip and 270 minutes for the tongue. It is advisable to use anesthetics with a longer duration for treatments that are anticipated to last longer than usual rather than giving numerous doses.[12]

Interestingly, when Hersh et al.[13] utilized Lidocaine instead of Articaine, the anesthetic effect on the lower lip and tongue was significantly reduced. This observation highlights the influence of the type of anesthetic agent on the efficacy of Phentolamine Mesylate. Articaine 4% (1:100,000 epinephrine) is a stronger and longer-lasting local anesthesia compared to Lidocaine 2% (1:100,000 epinephrine), and the action of Phentolamine Mesylate is more constrained, resulting in a larger reduction in anesthesia time when using 2% Lidocaine [8]. In contrast to the Lidocaine and Articaine group, Gago-Garcia et al. [12] found that Bupivacaine significantly reduced the reversal effect from 460 minutes to 230 minutes for the lip and 270 minutes for the tongue. Therefore, it is advisable to use anesthetics with longer durations for treatments expected to last longer than usual, rather than administering multiple doses. [12]

Many authors concur that the most accurate way to determine the impact of Phentolamine Mesylate on soft tissues is to palpate the lips and tongue. The palpation of the chin is also observed by a few other investigators. The pFAB and STAR recovery questionnaires, developed specifically for the study, were nevertheless added in several investigations, including those by Hersh et al.[13] and Elmore et al.[17] The latter also employed an electric pulp tester to assess the impact of Phentolamine Mesylate on dental pulp.[8]

It's important to note that Phentolamine Mesylate counteracts the vasoconstriction-inducing effects of epinephrine associated with the anesthetic agent; however, it is not an antagonist of the anesthetic itself. Therefore, it cannot be employed to reverse anesthesia without a vasoconstrictor [14, 29]. None of the included clinical trials were deemed to have a low risk of bias, which aligns with the reports of Prados-frutos et al.[8]. More high-quality RCTs are necessary to estimate the median duration of soft tissue anesthesia and quantify any adverse effects.

CONCLUSION

In the context of local anesthetic treatments, our systematic review consistently reveals a noteworthy reduction in residual soft tissue anesthesia recovery time across all included studies with the use of Phentolamine Mesylate. This emerges as a promising strategy for mitigating postoperative complications linked to prolonged anesthesia in dental procedures. The integration of Phentolamine Mesylate into standard protocols offers dental professionals an opportunity to enhance patient experience, minimize self-inflicted injuries, and reduce functional impairments. Moreover, raising awareness among practitioners about the safe and effective use of Phentolamine Mesylate for local anesthesia reversal is imperative to maximize its benefits. Future research avenues may explore specific patient profiles, dental procedures, and dosage optimization to further refine Phentolamine Mesylate's application in dental practice, always in compliance with regional regulatory guidelines. Patient education plays a pivotal role in fostering comprehension and acceptance of Phentolamine Mesylate, ultimately leading to improved outcomes and patient satisfaction in dental procedures.

In conclusion, Phentolamine Mesylate emerges as a prudent addition to the dental armamentarium for addressing the challenges associated with residual soft tissue anesthesia. Embracing this innovation and promoting its responsible use can empower dental professionals to deliver enhanced patient care and a more comfortable dental experience.

LIMITATION

Despite its potential benefits, this systematic review has some limitations. Firstly, the availability of relevant studies may be limited, as research on this specific topic could be scarce. This limitation could result in a small pool of eligible studies, which might impact the generalizability of the findings. Additionally, the quality of the included studies can vary, potentially introducing bias or affecting the overall strength of the evidence. Furthermore, there might be heterogeneity among the studies in terms of patient populations, dosage protocols, and the outcome measures, making it challenging to effectively compare and combine the results. These variations could impede the establishment of definitive conclusions regarding the efficacy and safety of Phentolamine Mesylate for the reversal of residual local anesthesia in dental procedures. Lastly, publication bias could be a concern, as studies reporting positive outcomes are more likely to be published, while those with negative or inconclusive results might remain unpublished. This bias can influence the validity of the conclusions drawn from the systematic review. Therefore, while the systematic review provides valuable insights, it is important to consider these limitations when interpreting and applying its findings.

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CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest related to this study.

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