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Original Article

Effect of phentolamine mesylate on duration of soft tissue local anesthesia in children

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ABSTRACT

Objective: Addition of vasoconstrictors to local anesthesia results in prolonged pain control. However, associated soft-tissue anesthesia (STA) of the lips and tongue typically lasts 3-5 hours which is longer than required time for pain control after routine dental procedures can lead to inadvertent biting of the soft tissue, particularly in children. The present study aimed to evaluate phentolamine mesylate (PM) effect on duration of STA and incidence of soft-tissue trauma after mandibular block injection.

Methods: This randomized, double-blinded, controlled clinical trial included 54 patients with the age of 4-11 years. In group 1 at the first visit, the children received ordinary local anesthetic (LA) consisting of lidocaine 2% and epinephrine 1:80,000 and the PM injection was performed 30 minutes later. At the second visit, the contralateral side received LA injection then the dental procedure was done and a sham injection was performed. In group 2 at the first visit, patients received control injection and at the second visit received PM injection. Then the reversal time for normal sensation of soft tissue, the vital signs, and the incidence of soft-tissue trauma in a period of 3-5 hours after injection were evaluated.

Findings: There was a statistically significant difference ($P < 0.001$) in recovery time of normal lip sensation between case and control groups and also between two groups ($P < 0.003$). Incidence of soft-tissue trauma between case and control groups showed a statistically significant difference ($P < 0.039$).

Conclusion: PM can be considered as a safe and effective drug for reduction of reversal time of STA after dental procedures.

Keywords: Local anesthesia; mandibular block injection; phentolamine mesylate; soft-tissue anesthesia; soft-tissue trauma

INTRODUCTION

Local anesthetics, being the most commonly used drugs in dentistry are the safest and most efficient drugs for the prevention and management of pain in the preoperative period.[1,2] Addition of vasoconstrictors in local anesthesia increases the frequency of complete nerve blockage at low concentrations of the anesthetic's solution, moreover higher concentrations of vasoconstrictors results in prolonged pain control.[3] However, associated soft-tissue anesthesia (STA) of the lips and tongue typically lasts 3-5 hours which is longer than required time for pain control after routine restorative and periodontal procedures.[1] Prolonged STA can lead to inadvertent biting of the lips, tongue and cheeks, particularly in children[4] One recent study measured a 13% incidence of injury after mandibular anesthesia in Pediatric patients.[4] More commonly, however, residual STA is more of an inconvenience or annoyance to the patient and doctor than a risk. Patients feel that residual STA interferes with their normal daily activities in three areas: Perceptual (Perception of altered physical appearance), sensory (lack of sensation), and functional (diminished ability to speak, smile, drink, and control drooling,[5] and many patients complain about lingering numbness of residual STA following completion of a dental procedure.[5-7]

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The use of a substance which accelerates recovery from STA with no effect on duration of hard tissue anesthesia was one of the main objectives of the present study. Up to now, no drug has been developed for faster recovery of STA except phentolamin mesylate (PM). Accelerated recovery from STA could reduce the side effects of STA which is possible with the use of PM.

PM is a nonselective, competitive, α-adrenergic antagonist that has been used for more than 50 years in both animal and human studies to reverse the effects of extravasated adrenergic antagonists such as epinephrine.[8,9] PM is a vasodilator which blocks the effects of endogenous vasoconstrictors in oral tissues of cats, including the dental pulp and oral mucosa.[10] This drug was developed in 1952 and has been used for blockage and reversal of the effects of extravasated epinephrine and norepinephrine. Also it has been used for diagnosis and treatment of pheochromacytoma.[11] Moreover, it has been prescribed for prevention or treatment of dermal necrosis due to intravenous administration of norepinephrine.[12,13]

A specific formulation of PM (Oraverse, Novalar pharmaceuticals, San Diego) was approved by the FDA in May 2008.[14] Since there is no investigation evaluating the safety and tolerability of this drug in pediatrics with the ages of 4 years, the present study aimed to evaluate the PM effects on duration of STA and incidence of soft-tissue trauma after mandibular block injection in children with the ages of 4-11 years.

METHODS

This randomized, double-blind, controlled clinical trial which was registered in the Iranain clinical trial registry (#IRCT201102285934N1) included 54 patients with the age of 4-11 years who referred to the Pediatric department of the school of Dentistry, Isfahan University of Medical Sciences (IUMS). The study protocol was approved by the institutional board of Human studies (IUMS registration code #390348) and has no conflict with Helsinki declaration [Flow diagram].

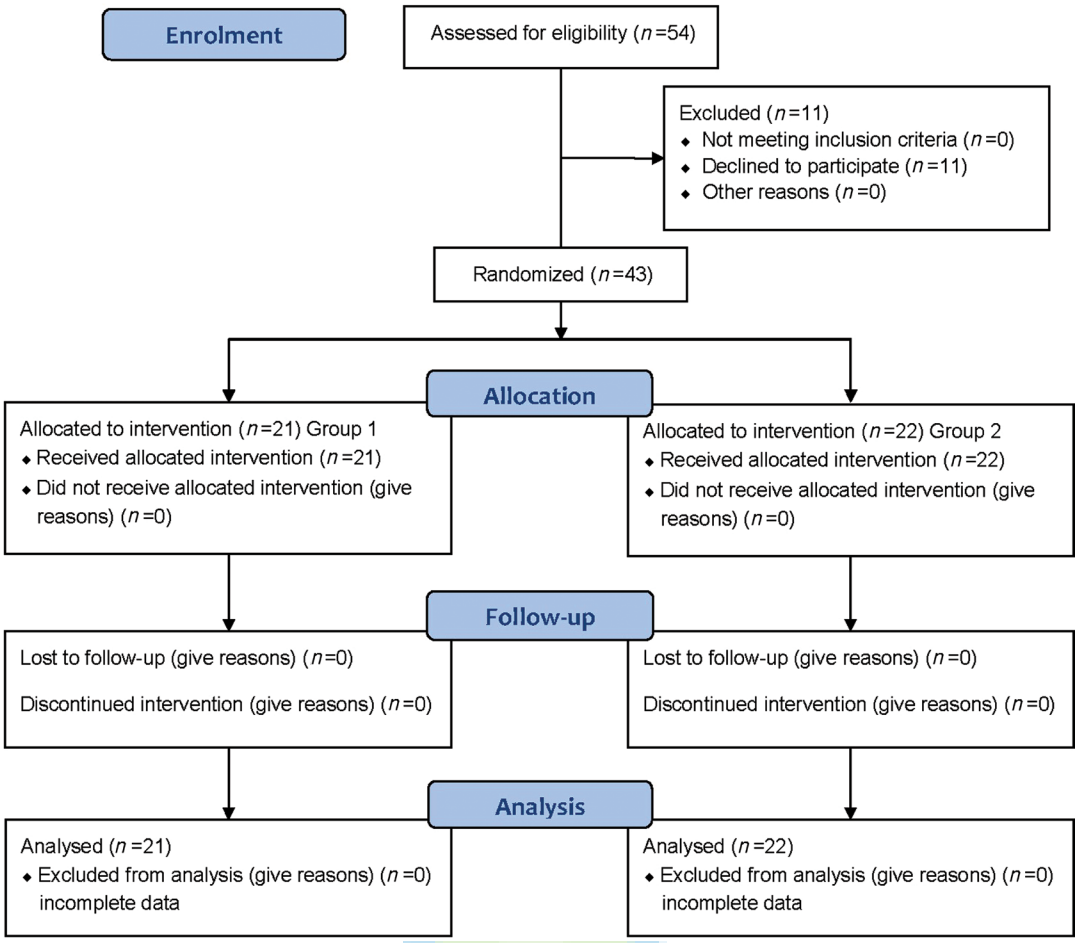
Inclusion criteria of the subjects of this study were as follows: Healthy children requiring routine dental treatment especially without know history of hypersensitivity to drugs such as epinephrine and PM, patients that needed bilateral dental procedure (except extraction) requiring local anesthetics (LA) with 2% lidocaine with 1: 80,000 epinephrine and patient with weight greater than or equal to 15 kg. All of the included children were taught to be able for understanding the difference between normal lip sensation and lip numbness at the beginning of the procedures. Patients who required other types of local anesthesia, patients who needed more than 1 cartridge of lidocain for numbness, patients whom weight was less than 15 kg, patients who required sedation or patients with maxillofacial anomalies were excluded from the study. After describing the process of this study to the parents, an informed consent which was approved by Ethical Committee of Isfahan University of Medical Sciences was gained from parents.

Patients were randomly divided into two groups based on odd or even ID card number by the dental hygienist who was blind to the study. The dental hygienist also measured vital signs such as blood pressure, pulse rate using a digital barometer, respiratory rate, temperature using an alcoholic thermometer, and also patients' weight. Before performing the dental procedure the children were trained how to distinct the soft-tissue numbness by soft tapping with the use of a rounded-tip explorer or finger. Then the local anesthetic was injected and patients were evaluated to diagnose the injected site from the side of their mouth that did not receive an injection. Children who could not learn to distinct numbness side from the other side were excluded.

In group 1, the children received LA. Then a visual barrier was placed over the patients' eyes. The body of PM (Oraverse, Novalar pharmaceuticals, San Diego) cartridges were covered with a custom made plastic cover and coded. The PM cartridges had different color, too. Then PM injection was performed by a dentist blind to the study 30 minutes after the LA injection with the same manner at the same side.

Patients with weight of 15-30 kg received one-half of the PM cartridge equals to (0.2 mg) and patients with weight greater than 30 kilograms, received one cartridge of PM (0.4 mg). The patients were evaluated and observed for the safety and efficacy and incidence of soft-tissue trauma including abrasions, lacerations and avulsive wounds by a dental hygienist blinded to the study for a period 3-5 hours every 15 minutes. The patient's vital sign were recorded 30 minutes after LA injection and then every 1 hour.

At the second visit, in the same patient, the contralateral side of the mouth received LA without a PM injection to serve as control. Then the dental procedures was done and a control injection (sham injection in which a needle does not penetrate the tissue) was simulated with the use of a covered needle and a shield over the child's eyes with the same manner. Then a cotton role was placed at the corner of the mouth and the parents were alerted about the subsequent possible soft-tissue trauma.



The CONSORT diagram of the clinical trial

Then the patient was observed for a period of 3 hours to assess the duration of STA and possible soft-tissue trauma. In group 2, at the first visit patients received control injection 30 minutes after LA injection and at the second visit received PM injection 30 minutes after LA injection. Then the reversal time for normal sensation of soft tissue, the vital signs, and incidence of soft-tissue trauma in a period of 3-5 hours after injection were evaluated. Patients were followed for at least 48 hours. Patients who stated soft-tissue trauma were called for repeated examinations. Data were analyzed by SPSS software version 11.5 by use of T test and McNemar. For all tests P value < 0.05 was considered as significant level.

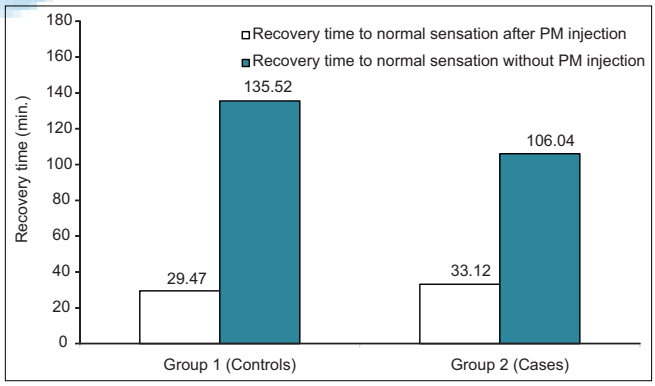


Figure 1: Recovery time to normal sensation in the two groups

RESULTS

This study included 54 patients (31 girls and 23 boys) in which 11 of them were excluded due to dissatisfaction of the parents or absence of the patients at the second visit or medical problems. Although a total of 43 patients (23 girls and 20 boys) completed this study, 34 subjects were 6-11-year old and 9 of them were 4-6-year old. Average recovery time of normal sensation of soft tissue with PM injection in group 1 was 29.47 min., and in group 2 was 33.12 min. The average recovery time of normal sensation without PM injection in group 1 was 135.52 and in group 2 was 106.04 [Figure 1]. There was a statistically significant difference (P < 0.001) in recovery time of normal lip sensation between case and control groups. T test showed a statistically significant difference was observed in reversal time of normal lip sensation with PM injection between two groups (P < 0.003).

Incidence of soft-tissue trauma in patients who received PM injection compared to those who did not received PM injection in both groups showed a statistically significant difference by *t* test ($P < 0.039$). Eight patients (19%) traumatized their lips a few hours after treatment without PM injection and only one patient (2%) traumatized his lip after PM injection. No trauma to tongue and cheek was found in participants. No significant difference was observed in blood pressure and pulse rate before and after PM injection in both groups. There were no deaths or other serious adverse effects, but one subject suffered nausea after PM injection and another experienced increased body temperature.

In this study 93% of the parents were satisfied of fast return of child's lip normal sensation which was assayed by questionnaire. 90.7% of the patient's were satisfied of PM injection which was evaluated with visual analogue scale (VAS). 48.8% of the children were agitated and crying after reversal of normal soft-tissue sensation with PM injection.

DISCUSSION

Our findings demonstrated that PM injection reduces the reversal time of normal soft-tissue sensation to approximately 70% which is in agreement with the findings of Tavares, *et al*. Study indicating 55.6% reduction in the reversal time of normal lip sensation and 60% reduction in the reversal time of normal tongue sensation.[15] Also the study of Laviola, *et al*., showed one hour reduction in reversal time of normal lip sensation but this reduction had no significant relationship with the age or sex of the patient, and also the type of treatment.[16] Moore, *et al*., also found similar results in their research.[17] Hersh, *et al*., represented a clinically and statistically significant ($P < 0.0001$) decrease in the duration of STA.[18] PM as a vasodilator increases the mucosal blood flow and accelerates the clearance of LA into blood stream which is approved by increased plasma concentration of PM after administration.[8,15,19] Other studies have demonstrated that while PM is injected after LA, the maximum plasma concentration of lidocaine increases which is consistent with the proposed mechanism.[16]

In the present study,19% of patient traumatized their lips after treatment without PM injection that similar to the results of a prospective study of 320 children showed that 16% of 4-7-year-olds and 13% of 8-to 11-year-olds reported having postoperative soft-tissue trauma after mandibular anesthetic blocks.[7] Trauma is reduced after PM injection. Hypotension and tachycardia are among expected side effects of PM injection which were not observed within the participants of this study.[11]

None of the participants showed arrhythmia or changes in blood pressure or pulse rate that may be attributed to lower concentration of PM used in dentistry compared to doses prescribed for medical purposes [1 mg intravenously (IV) or 1-3 mg intramuscularly (IM)].[8] In this study pediatrics received 1/15th to 1/5th of doses applied for IV or IM injection. No serious adverse effects were observed in this study which is in agreement with the study of Laviola, *et al*., who reported no adverse effects.[20] However, it should be noted that 48% of the children had pain and were agitated in the treatment side after recovery of normal soft-tissue sensation following PM injection. The origin of this pain may be attributed to dental treatments such as pulpotomy of the deciduous teeth or the pressure of the border of Stainless steel crown on the marginal gingival or probably the intrinsic effects of PM. Though, the authors suggest further investigations to evaluate the effect of analgesic drugs before treatment appointment or invention of a new drug with the ability to reduce the reversal time of normal soft-tissue sensation in addition to pain relieving effects and use of PM for dental procedures which has not pain after treatment such as pulpotomy, restorative and periodontal procedures

Faster recovery of normal lip and tongue sensation is highly desirable. The potential for PM to return patients' soft-tissues sensation with minimal risk in approximately half of the time would be highly beneficial for many pediatric patients and their parents or guardians.

Within the limitations of this study can be mentioned that the effectiveness of PM for children younger than 4 years, children required additional sedation or preoperative drugs and children required administration of more than 1 cartridge of lidocaine or LA without vasoconstrictor was not evaluated. A situation which does not usually represent indications for reversal of STA includes postsurgical patients, where prolonged STA is welcomed as a means of preventing breakthrough pain.

Our findings demonstrate that PM maybe considered as a safe and effective drug for reduction of STA after dental procedures, and PM may act as a new choice, for patients specially children requiring dental treatment. Further studies are needed with larger sample size to evaluate the possible side effects in pediatric patients.

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AUTHORS' CONTRIBUTION

All authors contributed in the concept of research question, data gathering, data analysis, manuscript preparation and read it before submission.

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