Phentolamine Mesylate in Reversal Local Anesthesia: A Review

MV Srikar¹, A Aravind², B N Niranjan³, Rakshit Vijay Sinai Khandeparker⁴, Sangeeta⁵, Shekhar Grover⁶

Contributors:
¹Professor and Head, Department of Oral and Maxillofacial Surgery, Daswani Dental College and Hospital, Kota, Rajasthan, India; ²Reader, Department of Oral and Maxillofacial Surgery, DA Pandu Memorial RV Dental College, Bengaluru, Karnataka, India; ³Professor and Head, Department of Dentistry, MVJ Medical College and Research Hospital, Hoskote, Bengaluru, Karnataka, India; ⁴Consultant and Private Practitioner, Department of Oral and Maxillofacial Surgery, Goa, India; ⁵Dental Surgeon Private Practitioner, Patna, Bihar, India; ⁶Senior Resident, Department of Preventive and community dentistry, MAIDS, New Delhi, India.

Correspondence:
Dr. Srikar MV. Department of Oral and Maxillofacial Surgery, Daswani Dental College and Hospital, Rajasthan State Industrial Development Area, Ranpur, Kota, Rajasthan, India.
Email: srikarshastry@gmail.com

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Abstract:
The most of the dental treatment procedures are not so traumatic in nature that they need a patient to discharge from dental clinic with residual numbness to their lips and tongue that usually persists for 3-5 h and causes hassle for the patients who want to continue with their routine work immediately after dental appointment. Commencing phentolamine mesylate injection as a reversal local anesthesia (LA) acts as a boon for this kind of patients who want to reinstate into their routine work immediately after dental procedure. Phentolamine has a chemical structure similar to epinephrine and acts as a competitive inhibitor to epinephrine and blocks its effect by blocking a-adrenergic receptors causing smooth muscle relaxation and increased blood flow leading to more prompt systemic absorption of the LA. The article aims to present information on the hastened reversal of the residual soft tissue numbness following dental procedures.

Key Words: Epinephrine, local anesthesia, phentolamine mesylate

Introduction
Local anesthesia (LA) is the most widely used drug and forms the backbone of dental management of the patient. It enables the dentist to provide pain-free comfortable dental treatment. The history of introduction of this amendable treatment environment backs to 1884 with the first LA injection of cocaine by William Stewart Halsted followed by introduction of other esters procaine, tetracaine, and chloroprocaine. The amides were introduced in 1932 with the commencement of dibucaine followed by lidocaine, mepivacaine, prilocaine, bupivacaine, etiodacaine, articaine, ropivacaine, and levobupivacaine.

Procaine under the trade name of Novocain was the most widely used LA in dental treatment before the introduction of lidocaine by Nils Lofgren of Astra Pharmaceuticals in 1948 which has now become a gold standard for dental management of patients. LA are categorized into three types on the basis of expected duration of pulpal anesthesia, i.e., short, intermediate and long-acting LA (Table 1). The purpose of utilizing the type of LA formulation is to provide a pain-free comfortable environment until the completion of dental treatment and an average turnaround time of dental appointment is around 44 min. The downside related with the nerve block is the continual presence of soft tissue numbness after dental treatment that generally lasts for 3-5 h and causes hassle for the patient who wants to continue with his routine work immediately after dental appointment. The commencement of use of phentolamine mesylate injection as a reversal LA acts as a boon for the patients who want to reinstate into their routine work after dental procedure.

Mechanism of Action
The addition of vasopressors such as epinephrine and norepinephrine accounts for longer duration of LA and provides prolonged period of pain control. Epinephrine is the most common used vasoconstrictor. The standard dose and concentration is 5 mcg/ml or 1:200:000. Epinephrine decreases vascular absorption and reduces blood concentration of LA, thus permitting more availability of LA molecules at the nerve membrane. Thus, the increased concentration of molecules at nerve membrane site results in an increase in the depth and duration of LA blockade. The addition of epinephrine for neuraxial blockade also activates endogenous analgesic mechanisms via a-adrenergic receptors that results in increased intensity of analgesic action. Phentolamine has a chemical structure similar to epinephrine, but the presence of bulky side chains prevent receptor activation and allow only receptor binding. It acts as a competitive inhibitor to epinephrine and blocks its effect by blocking a-adrenergic receptors resulting in smooth muscle relaxation. This relaxation resulted in the increased blood flow leading to more prompt systemic absorption of the local anesthesia. Its primary action is vasodilation due to a blockade. Hence, phentolamine mesylate is an antagonist of the epinephrine, which is added to lengthen the effect of the LA.

Potential benefits of phentolamine mesylate
The most of the dental treatments that include conservative dental restorations, periodontal procedures such as scaling...
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and root planning that they need a patient to discharge from
dental clinic with residual numbness to their lips and tongue
that usually persists for 3-5 h while gradually resolving.12 It is of
great use in patients with medical conditions such as diabetics
that require strict adherence to eating regimens.1 The other
candidates for reversal of residual numbness are pediatric
and geriatric patients that are at risk of self-inflicted injuries.10
Boytes et al.10 carried out a survey to identify complications
related with administration of LA and found that the most
encountered complication was self-inflicted soft tissue
injury. Yagieala14 carried out a clinical trial in which doses of
phentolamine was revealed by the age of patient and volume of
LA injected. It was administered in doses of 0.2-0.8 mg (0.5-2
cartridges) and found that there was a significant difference
in the loss of anesthesia in adults and children 6 years of age
and older as compared to control group. Median lip recovery
duration was reduced by 75-85 min. Functional insufficiency,
i.e., drooling and difficulty in smiling, talking or drinking
and subjects’ approach regarding alteration in function or
appearance were constantly resolved by the period sensation
to touch reverted to normal. Similarly, Tavarese et al.15 evaluated
efficacy and safety of formulation of phentolamine mesylate
as a reversal LA agent in 152 pediatric patients, injection was
administered in a 1:1 cartridge ratio at the same site were LA
with 2% lidocaine and 1:100,000 epinephrine was injected
before undergoing dental treatment. The median lip recovery
duration was 60 min against 135 min for the subjects in the
control group. The study concluded that of phentolamine
mesylate as a reversal LA agent was well tolerated, efficient and
safe in children 4-11 years age group. Elmore et al.16 carried
out a prospective study to assess the reversal of pulpal and
soft tissue anesthesia when phentolamine was administered
and found that phentolamine significantly reduced duration
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out a prospective study to assess the reversal of pulpal and
soft tissue anesthesia when phentolamine was administered
and found that phentolamine significantly reduced duration
at either 30 or 60 min after an inferior alveolar nerve block.

Phentolamine mesylate is an old drug and was approved in
1952 under the trade name of Regitine by the United States
Food and Drug Administration (FDA). It is used for the
diagnosis and treatment of severe hypertension in patients with
pheochromocytoma (a rare tumor of the adrenal medulla that
secretes excessive epinephrine and or norepinephrine) and for
prevention or therapy of dermal necrosis due to intravenous
administration or extravasation of norepinephrine.17 The other
indications are hypertensive emergencies, clonidine withdrawal
syndrome, vasospasm of Raynaud disease and frostbite, peripheral vascular disease and impotence.18

Formulations of phentolamine mesylate
Phentolamine mesylate under the trade name of OraVerse is the
first therapeutic agent approved and marketed for the soft-
tissue anesthesia reversal and the associated functional deficits
due to intraoral submucosal injection of an LA consisting of a
vasoconstrictor.

OraVerse is approved and sold only in the U.S.19 Dosage
form of OraVerse is 0.4 mg/1.7 ml solution per cartridge.20
The suggested dose of OraVerse is on the basis of the number
of cartridges of LA with vasoconstrictor administered. It
is administered in an equal volume, up to a maximum of
2 cartridges (Table 2). OraVerse is administered at the
same location and by the same technique(s) (nerve block
or infiltration) used previously for the LA administration.
The maximum dose of OraVerse recommended in pediatric
patients weighing 15-30 kg is 1/2 cartridge (0.2 mg). OraVerse
is contraindicated for use in children weighing less than 15 kg
(33 lbs) or less than 6 years of age.21

In India, phentolamine mesylate is available under the
trade name of fentanor, phentosol, and fentosol. It is
contraindicated in patients with fast heart rate, heart attack
and hypersensitivity to this drug. It is categorized by the FDA
as a pregnancy category C drug and as “Safety Unknown” for
nursing mothers.22 There are no adequate and well-controlled
studies in humans and animal reproduction studies have
shown an adverse effect on the fetus, but possible benefits
may permit use of the drug in pregnant women in spite of
potential risks.23

Conclusion
The numbness after administration of LA may prove to
to potentially injurious in children, geriatric and special needs
patients. Moreover in adults and young people causes
embarrassment due to difficulty in speaking, eating and
drinking. Patients become uncomfortable due to drooling of
saliva. The clinical trials reveal that phentolamine mesylate
as a reversal LA agent can help dentists to reduce the post-
treatment numbness of soft-tissues and can decrease the
post-treatment lip and tongue related self-inflicted injuries
in pediatric and geriatric patients.

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References