

## Phentolamine Mesylate in Reversal Local Anesthesia: A Review

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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  $\alpha$ -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.<sup>1</sup> It enables the dentist to provide pain-free comfortable dental treatment. The history of introduction of this amenable treatment environment backs to 1884 with the first LA injection of cocaine William Stewart Halsted followed by introduction of other esters procaine, tetracaine, and chlorprocaine. The amides was introduced in 1932 with the commencement of dibucaine followed by lidocaine, mepivacaine, prilocaine, bupivacaine, etiodacaine, articaine, ropivacaine, and levobupivacaine.<sup>2</sup>

Procaine under the trade name of Novocain<sup>®</sup> 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.<sup>3</sup> 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.<sup>4,5</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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  $\alpha$ -adrenergic receptors that results in increased intensity of analgesic action.<sup>8</sup> Phentolamine has a chemical structure similar to epinephrine, but the presence of bulky side chains prevent receptor activation and allow only receptor binding.<sup>9</sup> It acts as a competitive inhibitor to epinephrine and blocks its effect by blocking  $\alpha$ -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.<sup>10</sup> Its primary action is vasodilation due to  $\alpha_1$  blockade.<sup>11</sup> Hence, phentolamine mesylate is an antagonist of the epinephrine, which is added to lengthen the effect of the LA.<sup>10</sup>

### Potential benefits of phentolamine mesylate

The most of the dental treatments that include conservative dental restorations, periodontal procedures such as scaling

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.<sup>12</sup> It is of great use in patients with medical conditions such as diabetics that require strict adherence to eating regimens.<sup>1</sup> The other candidates for reversal of residual numbness are pediatric and geriatric patients that are at risk of self-inflicted injuries.<sup>10</sup> Boynes *et al.*<sup>13</sup> 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. Yagieala<sup>14</sup> 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, Tavares *et al.*<sup>15</sup> 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.*<sup>16</sup> 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 of both pulpal and soft tissue anesthesia when administered 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.<sup>17</sup> The other indications are hypertensive emergencies, clonidine withdrawal syndrome, vasospasm of Raynaud disease and frostbite, peripheral vascular disease and impotence.<sup>18</sup>

**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.<sup>19</sup> Dosage form of OraVerse is 0.4 mg/1.7 ml solution per cartridge.<sup>20</sup> 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.<sup>21</sup>

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.<sup>22</sup> 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.<sup>23</sup>

**Conclusion**

The numbness after administration of LA may prove 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.

**Table 1: Duration and formulation of local anesthesia.**

Duration	Anesthetic formulation
Short	Mepivacaine HCl injection plain 3% Prilocaine HCl injection USP, plain 4%
Intermediate	Articaine HCl with epinephrine USP, 4% 1:100,000 Articaine HCl with epinephrine USP, 4% 1:200,000 Lidocaine with epinephrine USP, 2% 1:100,000 Lidocaine with epinephrine USP, 2% 1:50,000 Mepivacaine HCl levonordefrin Injection USP, 2% 1:20,000 Prilocaine with epinephrine injection USP, 4% 1:200,000
Long	Bupivacaine with epinephrine injection USP, 0.5% 1:200,000

**Table 2: Dosage and administration.**

Volume (cartridge) of local anesthesia administered	Recommended (administration of number of cartridge of phentolamine)	Dose of phentolamine in cartridges in mg
1/2	1/2	0.2
1	1	0.4
2	2	0.8

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