

Efficacy of Hyaluronidase in Enhancing the Effect of Inferior Alveolar Nerve Block when Used in Conjugation with Lidocain

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Abstract: *Aim: Present study was conducted to assess the efficacy of hyaluronidase in enhancing the effect of inferior alveolar nerve block when used in conjugation with lidocain. Methods: Patients diagnosed with irreversible pulpitis in mandibular molars were selected for study. After noting the baseline stimulus on premolars by electronic pulp tester, inferior alveolar nerve block was injected. Thirty minutes after the onset of anesthesia placebo and hyaluronidase was injected during the control and test phase of the study respectively. Duration of the anesthesia was recorded with the help of electronic pulp tester on the premolar and by needle prick on the gingiva. Results: Significant increase in the pulpal and gingival anesthesia was observed by administering hyaluronidase after the lidocain injection. Conclusion: Hyaluronidase when used before the end of anesthetic effect of lidocain in inferior alveolar nerve blocks can increase the efficacy of anesthetic.*

Keywords: hyaluronidase, lidocain, inferior, alveolar, nerve, block

1. Introduction

The discovery in the late 1800s of a group of chemicals with ability to prevent pain without inducing loss of consciousness was one of the major steps in the advancements of the medical and dental professions. For the first time, medical and dental procedures, could be carried out easily and in the absence of pain, a feat that is virtually taken for granted by contemporary medical and dental professionals and their patients.²

Local anesthesia has been defined as loss of sensation in a circumscribed area of the body caused by depression of excitation of the conduction process in peripheral nerves.¹ The concept behind the local anaesthesia is simple: They prevent both the generation and conduction of nerve impulse. Therefore the absorbed impulse, prevented from reaching the brain, cannot be interpreted by the patient as pain.²

The options among long-term local anesthetics used in dentistry are very restricted, and currently there are no long-term local anesthetics available that can be safely used with medically compromised patients. Therefore, to increase the duration of action, Local anaesthetics with intermediate duration such as lidocaine, articaine, and prilocaine can be combined with the hyaluronidase enzyme.³

Therapeutically, this enzyme is used as a comedication with LAs and drugs with pain-reducing behavior. The term hyaluronidase was introduced by Meyer et al.⁴ The first therapeutic use of this enzyme was mentioned in 1928 as a so-called spreading factor, which facilitates the uptake of subcutaneously applied vaccines and toxins. Hyaluronidase is an enzyme derived from bovine testes, and it exhibits hydrolytic and transglycosidic effects via the splitting of the b-1, 4-glycosidic bond. Hyaluronidase enzymes are able to degrade hyaluronic acid, chondroitin-4- and -6 sulfate, and dermatan sulfate, which are the main components of the extracellular matrix.⁵

However hyaluronidase was not found to improve the success of lidocain anesthesia in a recent double-blind randomized clinical study.⁶ The present study aimed to assess the effect of hyaluronidase on the duration of lidocain anesthesia when used for inferior alveolar nerve block before the reversal of anesthesia.

2. Materials and Method

The present study was approved by the ethical committee of the Bhojia Dental College and Hospital, Baddi, Himachal Pradesh, India. Twenty patients aged from 19 to 53 years suffering from chronic irreversible pulpitis of mandibular molar having intact premolars adjacent to the affected tooth were included for the study. After explaining the procedure, informed consent was taken from the patients. Patch test was performed over the patients, both for the local anesthetic solution and hyaluronidase to rule out any kind of allergy for the drugs.

After the recording the baseline stimulus over the premolar tooth local anesthetic was administered (2ml of lidocain solution with 1:100000 adrenalin) to block the inferior alveolar nerve. Subsequent to the anesthetic injection, stimuli (by electronic pulp tester) were applied every 2 minutes until they reached a value of 80 which was considered to be the onset of profound anesthesia. Thirty minutes after the profound anesthesia a placebo (1ml of saline) was injected and the duration of anesthesia was noted by checking it with electric stimuli over the adjacent premolar tooth after every 10 minutes. Anesthesia was considered to be profound until the score remained 80.

The duration of the anesthetic effect on the soft tissue was evaluated using a nociceptive mechanical stimulus (pinprick) using a 25-G needle in the buccal gingiva around the first and second lower premolars. These stimuli were performed in the same intervals as the electrical stimuli. The duration of the anesthetic effect in the gingiva was considered to be the interval from the loss of sensation to the

mechanical stimulus until the return of the pinprick sensation.

In the next appointment same procedure was performed except that this time 30 minutes after the profound anesthesia, 1ml of 75IU of hyaluronidase was administered and the duration of anesthesia was recorded.

Statistical Analysis

Data analysis was performed using SPSS 16.0 software. Comparisons between the control and experimental phase were performed using the Student t test. P value <.05 was considered to be significant. (Table 1)

3. Results

Lidocaine with hyaluronidase significantly increased pulpal and gingival anesthesia.

4. Discussion

Following administration of a local anaesthetic into soft tissues near a nerve, molecules of the local anesthetic transverse the distance from one site to another according to their concentration gradient. During the induction phase of the anesthesia, the local anesthetic moves from extraneural site of deposition toward the nerve (as well as in all other possible directions). This process is called as diffusion. Penetration of an anatomic barrier occurs when a drug passes through a tissue that tends to restrict free molecular movement.²

The role of hyaluronidase here is that it increases the diffusability of the local anesthetic through tissues so as to reach it to nerve, therefore when it is used in conjugation with LA solution, it might fasten onset of anesthetic effect as observed in the previous studies.^{7,8} However, the present study aimed to increase the duration of the anesthesia as the hyaluronidase was not administered in conjugation with LA, rather it was injected thirty minutes after the onset of anesthesia.

When the local anesthetic is administered it diffuses in all the directions. A portion of the injected local anesthetic diffuses towards the nerve and into the nerve. However, a significant portion of the injected drug also diffuses away from the nerve into the tissue. This solution is present in the tissues until it is completely absorbed up in the blood.² Injection of hyaluronidase 30 minutes after the onset of anesthesia might have increased the diffusion of the LA present in the tissues and directed it towards the nerve.

Our findings show that hyaluronidase injected before the end of anesthesia significantly prolongs the duration of nerve blockade compared with the control group (LA without hyaluronidase) in both tissues. The duration of pulpal anesthesia was increased by 27.5 minutes in the experimental group. In the soft tissue, the hyaluronidase group also showed an increased duration of anesthesia compared with the placebo group (ie, an increase of 26.2 minutes)

The question whether the findings of the present study were because of the mere introduction of the liquid after the onset of the anesthesia which might have caused the movement of LA toward the nerve is also excluded as the control phase of the study did not show any increase in the duration of anesthesia.

The addition of hyaluronidase, which has a pH of 6.5 and an optimal pH (pKa) between 6.4 and 7.4, may decrease the pH of the tissue surrounding the nerve because the pH of normal tissue is approximately 7.4. Thus, increasing the amount of the ionized form (cation) and reducing the amount of the nonionized base form³ of the LA would make it difficult for the compound to cross the membrane. If the LA and hyaluronidase injections were concomitant, the onset of the block may occur later when the acidic pH of the tissue requires buffering. The onset of the effect will be directly related to the amount of LA that exists in the base form. However, in our study, at the time point at which the hyaluronidase was injected (ie, 30 minutes after inducing ongoing pulpal anesthesia), even the amount of nonionized LA would have been reduced by the acidic pH. Nevertheless, there was most likely a sufficient amount of LA available because the intensity or "depth" of anesthesia was not affected. In addition, the LA used was lidocaine, which has a low pKa (7.7) compared with those of other LAs. This pKa is close to the tissue pH of 7.4,² possibly allowing a sufficient proportion of nonionized LA to diffuse into the nerve even though the tissue pH level may have decreased after the injection of hyaluronidase.

In a previous similar study⁹ the subject chosen for control group and test group were different. In our study subjects were first subjected to control phase and then they were subjected to test phase of study. This prevented the inter-subject bias as different patients may have different pain perception physiology.

5. Conclusion

Under the limitation of present study it is concluded that the hyaluronidase administered before the end of anesthesia may enhance the duration of anesthesia.

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Table 1: The Duration of Pulpal and Gingival Anesthesia in the Control and Experimental Groups

| <i>Time</i> | <i>Groups</i> | <i>Control</i> | <i>Experimental Difference</i> | <i>P value</i> |
|---------------------------------|----------------|----------------|--------------------------------|----------------|
| Duration of anesthesia (min) | 50.45 +/- 2.69 | 85.70 +/- 5.78 | 37.25 | <.0001 |
| Duration of treatment | 70.04 +/- 6.32 | 77.65 +/- 4.65 | 2.01 | .22 |
| Duration of gingival anesthesia | 68.15 +/- 5.04 | 91.40 +/- 6.25 | 24.25 | <.0001 |

