Comparative evaluation of the efficacy of lidocaine with adrenaline and lidocaine with clonidine in maxillary infiltration anesthesia.

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ABSTRACT: Aim- Comparative evaluation of the efficacy of lidocaine with adrenaline and lidocaine with clonidine in maxillary infiltration anaesthesia is the aim of study. Materials and method- study conducted in department of Oral and Maxillofacial surgery. 40 patients were selected and divided into two groups. Odd serial number patients in Group 1- 20 patients, received 2 mL of 2% lidocaine with epinephrine (1:80,000) and even number patients Group 2 - 20 patients, received 2 mL of 2% lidocaine with clonidine (150mg/mL). The systolic blood pressure (SBP), diastolic blood pressure, mean arterial pressure, heart rate (HR) was recorded before and during administration of local anesthesia, 5 minutes after administration of anesthesia, during extraction, 10 minutes after extraction, and 30 minutes after extraction. Results- The parameters of maxillary infiltration anesthesia produced were similar in both the groups, with the exception of a significant reduction in heart rate and systolic blood pressure in the lidocaine + clonidine group and significant increase in heart rate in the lidocaine + epinephrine group, 10 min after surgery. Conclusion – The results of this study indicate for the dental anesthesia, the lidocaine + clonidine combination could be a useful and safe alternative to lidocaine + epinephrine for intraoral infiltration anaesthesia.

KEYWORDS: Clonidine, Hypertension, Maxillary infiltration

I. INTRODUCTION

The development of safe and effective local anesthetic agents has been possibly the most important advancement in dental science to occur since the last century. The agents currently available in dentistry are extremely safe and fulfill most of the characteristics of an ideal local anesthetic. These local anesthetic agents can be administered with minimal tissue irritation and with little likelihood of inducing allergic reactions. A variety of agents are available that provide rapid onset and adequate duration of surgical anesthesia. The agents provide anesthesia that is completely reversible, and systemic toxicity is rarely reported. An ideal local anesthetic agent, one that would induce regional analgesia by selectively inhibiting pain pathways without interrupting transmission of other sensory modalities, has not yet been discovered.

When extraction is performed under local anesthesia, it is important to achieve adequate anesthesia. This is largely dependent on the presence and concentration of the added vasoconstrictor¹. The presence of vasoconstrictors in local anesthetic solutions is beneficial with regard to the onset, depth of anesthesia, blood loss and the reduction of systemic toxicity. Clinical efficacy of a local anesthetic is dependent on the action of the vasoconstrictor². Most local anesthetic solutions used today, contain epinephrine in different concentrations (from 1:50,000 to 1:200,000). Epinephrine enhances duration and intensity of anesthesia and provides a desirable hemostasis at the surgical site. Systemic toxicity of the local anesthetic agent is also reduced because absorption into the systemic circulation is slowed, and peak plasma concentration of the local anesthetic is lowered. GOLDSTEIN et al. have reported that intraoral block anesthesia with 2% lidocaine/epinephrine (1:100,000) in healthy patients, resulted in increased circulatory epinephrine levels associated with cardiovascular changes even with a relatively small dosage of epinephrine.

However, it is known that oral surgery procedures under local nerve block anesthesia achieved with an epinephrine-containing solution are associated with an increase in plasma epinephrine, with significant³ or non-
significant cardiovascular changes. A further study, with both healthy and hypertensive patients, has also recorded significant changes in blood pressure, heart rate during and after tooth extraction under local anesthesia using 2% lidocaine with 1:80,000 epinephrine. It is important to note that in patients having cardiovascular problems (poorly controlled ASA III and all ASA IV group), the recommendation is to limit or avoid exposure to vasoconstrictor epinephrine, if possible. Also, for patients who are suffering from cardiovascular problems (poorly controlled ASA III and all ASA IV group), the recommendation is to limit or avoid exposure to vasoconstrictor epinephrine, if possible.

Factor adding to the safety of epinephrine in dental practice is that for most dental procedures, adequate pain control and/or hemostasis usually requires far less local anesthetic and vasoconstrictor than used in the study by Hersh and colleagues.

Beta-adrenergic blocking agents are classified as either being nonselective, which means they block both b1 receptors on the heart and b2 receptors on the bronchial and the vasculature smooth muscle almost equally well; or they are cardio selective, that is they preferentially block b1 receptors. Both classes of beta-adrenergic blocking agents are commonly used in the treatment of hypertension, angina, and cardiac arrhythmias, although the cardio selective b-blockers have become more popular in these patient populations because b2 blockade produced by drugs such as propranolol can lead to bronchoconstriction in sensitive individuals, a potentially lethal event in asthmatic patients and in those with other bronchospastic disorders. A patient’s medical history that indicates significant cardiovascular impairment may indicate limited use of vasoconstrictors. A common recommendation, when a vasoconstrictor is required for a dental treatment and when there is a medical history that suggests a need for caution, is to limit the dose of epinephrine to 0.04 mg.

Clonidine is a selective alpha-2 adrenergic receptor agonist with both central and peripheral action. Through central activation of presynaptic alpha-2 adrenoceptors, clonidine decreases blood pressure and causes central analgesic activity as well as sedation. By activation of peripheral postsynaptic alpha-2 adrenoceptors, clonidine produces vasoconstriction of the peripheral blood vessels. Clonidine has been used as an alternative to epinephrine for different types of local anesthesia in major surgery as a safer vasoconstrictor, providing haemodynamic stability due to its central hypotensive action.

Clonidine, like epinephrine, is very useful in prolonging and increasing lidocaine produced regional anesthesia for peripheral nerve block or brachial plexus blocks. Using 1% lidocaine, with either clonidine (150 mg/40 ml) or epinephrine (200 mg/40 ml) as vasoconstrictor, for brachial plexus block in patients undergoing elective surgery of the hand or forearm, GAUMANN et al. obtained the same quality of sensory block, regardless of the vasoconstrictor used. Analyses of the mechanism of clonidine’s prolonged local anesthetic action, which were done in vitro, revealed that clonidine possesses a vasoconstricting effect on isolated animal and human brachial arteries.

Recently, it has been demonstrated that lidocaine (2%) + clonidine (15 mg/ml) was able to increase and prolong the duration of intraoral block anesthesia of the inferior alveolar nerve in similar manner to lidocaine (2%) + epinephrine (12.5 mg/ml) for lower third molar surgery. There is evidence that the site of drug deposition (mandible versus maxilla) as well as the type of injection administered (nerve block versus infiltration) has an influence on the characteristics of local anesthesia and side effects of vasoconstrictors.

In the present study, the characteristics of clonidine (15 mg/ml) as a vasoconstrictor in lidocaine (2%) solution were evaluated for maxillary infiltration anesthesia, postoperative analgesia and hemodynamic parameters during anesthesia in patients undergoing maxillary tooth extractions, in comparison with lidocaine (2%) + epinephrine (12.5 mg/ml). Since there is evidence of a direct vascular effect of clonidine on isolated human brachial arteries, a similar effect on isolated human infraorbital arteries in vitro was also studied, because the reactivity of arteries to the same vasoactive substance may be different. Clonidine, an alpha 2-adrenoceptor agonist, used as a central antihypertensive agent, has been shown to enhance local anesthesia and analgesia using a variety of routes of administration and clinical circumstances such as epidural anesthesia, brachial plexus anesthesia, and peripheral nerve block. Clinical studies have also suggested that clonidine might have hemodynamic advantages compared with epinephrine and other vasoconstrictors because of its central hypotensive effect.

II. SUBJECTS AND METHODS

All patients were provided with written informed consent. The patients were divided into 2 groups. Odd serial number patients were in group 1 and even number patients were in group 2. Split mouth design was used and the same patients were treated with another drug after a week of follow up.

Group 1: 20 patients received 2 mL of 2% lidocaine with epinephrine (1:80,000)(12.5 _g/mL, Xylocaine, AstraZenca,Karnataka, Bangalore India).
Group 2 - 20 patients received 2 mL of 2% lidocaine with clonidine (150mg/mL) which were prepared prior to the procedure before application of the anesthesia by slowly adding clonidine (Catapres 1 ampule 150 mg/mL,bZydus, Mumbai, India) to 2 mL of 2% lidocaine (Xylocaine, AstraZenca, Bangalore, India). The solutions were prepared for injection by an investigator only. Before the infiltration procedure, the patients were tested for normal sensory perception on the operative side of the jaw. All procedures began 10 minutes after the administration of the local anesthetic solution.

Maxillary infiltration anesthesia and exodontia (with similar level of difficulty) procedure were performed by the post graduate students of the department without premedication. Primary investigator and participants were blinded to the nature of the anesthetic administered. A dose of 2 ml of the tested solutions were injected supraperiosteally into the apical area of the upper tooth to be removed. Into the palatal mucosa, a solution of lidocaine + clonidine (0.5 ml) or lidocaine + epinephrine (0.5 ml) were injected.

Postoperatively, the patients were evaluated with the pinprick test to establish the duration of anesthesia, with the testing repeated every 30 minutes after surgery until the patients felt blunt sensation and then continued every 10 minutes until the patients had full recovery of sensation. The intensity of anesthesia during surgical removal of the tooth was determined by 2 scores after the completion of treatment: first using a 10-cm visual analog scale, unmarked except for 1 end with “no pain” and the opposite end marked the “worst imaginable pain”; and second, using a 6-point verbal rating scale to describe the patient’s comfort during surgery, with the patient pointing to no pain, just noticeable pain or weak, moderate, severe, or extreme pain.

The vasoconstrictor effects of clonidine were compared with epinephrine, using 2 factors: the weight of the blood-soaked gauze pieces (3*2 in.) used for tooth extraction in both groups, and the time taken to form a stable blood clot as visualized clinically, starting at 3 minutes after completion of the procedure and evaluated every 30 seconds thereafter until stable clot formation.

The hemodynamic parameters and possible cardiovascular side effects of clonidine and epinephrine during intraoral anesthesia were continuously monitored. The systolic blood pressure (SBP), diastolic blood pressure, mean arterial pressure, heart rate (HR) was recorded before and during administration of local anesthesia, 5 minutes after administration of anesthesia, during extraction, 10 minutes after extraction, and 30 minutes after extraction. The patients were discharged after a full return of sensation with no adverse reactions or any complaints due to the injection of the anesthetic solution or procedure performed. They were given both verbal and written postoperative instructions.

One day after surgery, the presence of postoperative pain and the total dose of analgesic medication taken during the 24-hour postoperative period were compared between the 2 groups.

The primary predictor variables in the present study were the 2 treatment groups. The primary outcome variable was the hemodynamic response. The secondary outcome variables were the onset of anesthesia, duration of anesthesia, intensity of anesthesia and the vasoconstrictor effects of the solution. The other outcome variables were related to the sample size (age, gender, weight) and postoperative.

III. RESULTS

HISTOGRAM NO. -1

<table>
<thead>
<tr>
<th>NUMBER OF PATIENTS</th>
<th>CLONIDINE</th>
<th>ADRENALINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-40</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>40-50</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>50-60</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>60-70</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

HISTOGRAM NO. -2
**Postoperative pain (VAS SCALE)**

- **Number of Patients**
  - Mild
  - Moderate
  - Severe

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**Histogram No. -3**

**CLONIDINE - SYSTOLIC BLOOD PRESSURE**

- **Systolic Blood Pressure in mm of Hg**
  - Before Procedure
  - After 15 Minutes

- **Patients:**
  - PATIENT 1
  - PATIENT 2
  - PATIENT 3
  - PATIENT 4
  - PATIENT 5
  - PATIENT 6
  - PATIENT 7
  - PATIENT 8
  - PATIENT 9
  - PATIENT 10
  - PATIENT 11
  - PATIENT 12
  - PATIENT 13
  - PATIENT 14
  - PATIENT 15
  - PATIENT 16
  - PATIENT 17
  - PATIENT 18
  - PATIENT 19
  - PATIENT 20

- **p-value:** 0.083 (not significant)

**Histogram No. -4**

**CLONIDINE - DIASTOLIC BLOOD PRESSURE**

- **Diastolic Blood Pressure in mm of Hg**
  - Before Procedure
  - After 15 Minutes

- **Patients:**
  - PATIENT 1
  - PATIENT 2
  - PATIENT 3
  - PATIENT 4
  - PATIENT 5
  - PATIENT 6
  - PATIENT 7
  - PATIENT 8
  - PATIENT 9
  - PATIENT 10
  - PATIENT 11
  - PATIENT 12
  - PATIENT 13
  - PATIENT 14
  - PATIENT 15
  - PATIENT 16
  - PATIENT 17
  - PATIENT 18
  - PATIENT 19
  - PATIENT 20

- **p-value:** 0.002 (significant)
HISTOGRAM NO. -5

**ADRENALINE - SYSTOLIC BLOOD PRESSURE**

- **p -value**: 0.035 (significant)

HISTOGRAM NO. -6

**ADRENALINE - DIASTOLIC BLOOD PRESSURE**

- **p -value**: 0.026 (significant)

HISTOGRAM NO. -7

**CLONIDINE - HEART RATE**

- **p -value**: 0.039 (significant)
IV. DISCUSSION

Several studies have been carried out using different concentrations of clonidine for the enhancement of epidural anaesthesia, brachial plexus anaesthesia and anaesthesia of peripheral nerves. These studies have shown that the effective concentrations of clonidine, without significant side effects, were 150 mg/ml, 90 mg/ml, 30 mg/ml, 10 mg/ml, 5 mg/ml. In the present study we investigated the effect of clonidine in concentration of 15 mg/ml on clinical parameters of intraoral infiltration anaesthesia performed by 2% lidocaine.

The results of the present study suggest that clonidine, like epinephrine, is able to increase and prolong the efficacy of lidocaine-induced maxillary infiltration anaesthesia by Brkovic B, Todorovic L, Stojic D. The similar effect of clonidine was also seen during lidocaine-induced anesthesia. The enhancement of local anaesthesia by clonidine may be the consequence of alpha-2 adrenergically mediated vasoconstriction. The in-vitro experiments showed that clonidine in concentrations ranging from 10^{-7} to 10^{-5} M significantly increases the basal arterial tone in isolated human infraorbital arteries with and without endothelium. This is the first report on the endothelium-independent vasoconstricting effect of clonidine on human orofacial arteries. This effect of clonidine on isolated human infraorbital arteries is probably the consequence of its agonistic action on postsynaptic alpha-2 adrenoceptors of the vascular smooth muscle, as was described earlier for other arteries.

Since the in-vitro concentration of clonidine (10^{-6} M) that in this study produced vasoconstriction is related to its concentration obtained after intraoral infiltration injection (15 mg/ml), it seems that the vasoconstricting effect of clonidine could be seen also under in-vivo conditions. Direct evidence that the vasoconstricting effect of clonidine is a result of its agonistic effect on alpha-2 adrenoceptors was documented in vivo by KIOWSKI et al. The authors showed that the decrease in forearm blood flow after intra-arterial (brachial artery) injection of clonidine in humans was also present after the administration of prazosin, a selective alpha-1 antagonist, but abolished after the administration of phentolamine, a non-selective alpha-1 and alpha-2 adrenoceptor antagonist. Conversely, the vasorelaxing effect of clonidine achieved at a high concentration (10^{-4} M) in the present experimental study could be underlined by its agonistic action on presynaptic alpha-2 adrenoceptors and by a consequent decrease of noradrenaline release from the vascular sympathetic neurons. The similar dual endothelium-independent effect of clonidine on isolated rabbit pulmonary arteries was observed by LEE & HOU.

GAUMANN et al. did not show any prolongation of plasma lidocaine concentration when lidocaine + clonidine was used for brachial plexus block, indicating the absence of a local vasoconstricting effect of clonidine. In another clinical study with blockade of the human dorsal cutaneous nerves, the tissue lidocaine concentration was increased when clonidine was added to lidocaine compared to lidocaine alone, suggesting that the prolongation of nerve block was at least partially pharmacokinetically mediated.
Beside its vasoconstricting effect, clonidine may also enhance the local anaesthetic effect by direct action on nerve tissue. GAUMANN et al.\textsuperscript{9} demonstrated that clonidine enhances lidocaine-induced inhibition of C-fibre action potentials in rabbit vagus nerve. KROIN et al\textsuperscript{10} in a rat model, indicated that prolongation of duration of in-vivo lidocaine nerve blockade by clonidine is not mediated by an alpha-adrenergic mechanism but likely involves the hyperpolarisation-activated cation current in nerves.

Recently, clonidine has also been shown to have a peripheral analgesic effect. When injected into the knee after arthroscopic surgery clonidine significantly prolongs the time to first analgesic requirements and reduces the number of pain medication doses taken.\textsuperscript{10} The present results have demonstrated the lack of such effects of a lidocaine + clonidine combination on postoperative analgesia in patients undergoing third molar surgery since the need for analgesic medication remained in the postoperative period. These results indicate that clonidine is not able to prolong sufficiently lidocaine-induced intraoral infiltration anaesthesia in terms of postoperative pain control and reduction of postoperative needs for analgesics. The patients in the clonidine-treated group, which was different in comparison to the epinephrine-treated group, where pain was present in 85% of the patients. Consequently, the total number of pain medication doses taken was significantly lower in the clonidine-treated patients, compared with those treated with epinephrine in the 24-h postoperative period.

In general, clonidine produces dose dependent central side effects including sedation, bradycardia and hypotension during brachial plexus block or epidural block. It is difficult to say if more toxic effects might be expected, bearing in mind that clonidine did not inhibit systemic uptake of local anaesthetic, implying a reduced margin of safety with regard to local anaesthetic toxicity.\textsuperscript{5}

Data on haemodynamic parameters are presented in and, as can be noticed, there was a significant decrease in SBP and MAP in both groups for about 35 min after the administration of anaesthesia compared with values before administration, while DBP was significantly lower only in the clonidine group. There were no significant statistical differences in SBP, DBP and MAP between L + Epi and L + Clo groups at any time. However, HR significantly increased in the epinephrine group 5 min after administration of anaesthesia and during surgery regardless whether we compared these results with values in clonidine group or with basal values before administration of anaesthesia. On the other hand, 15 min after the completion of surgery, there was a significant decrease in HR observed in both treatment groups when compared with values before administration of anaesthesia.

There is no data concerning the vasoconstricting effect of clonidine in oral tissues. The fact that there are no differences in the enhancement of duration and intensity of intraoral anaesthesia due to L + Epi and L + Clo points to the similar vasoconstricting potency of clonidine, used in the 15 mg/ml concentration, to that of epinephrine in the 12.5 mg/ml concentration in oral tissues. It is interesting to note that clonidine causes a reduction in pulp blood flow in dogs and decreases arteriolar and venular diameters and volumetric flow in rats activating alpha-2 adrenoceptors.\textsuperscript{10}

These findings may be relevant to dentists endeavoring to find a vasoconstrictor for local anaesthetic solution with minimal cardiovascular risk. From investigating the impact of clonidine on lidocaine-produced intraoral infiltration anaesthesia, in this randomized, blinded, controlled clinical trial, it can be concluded that cardiovascular parameters during anaesthesia with clonidine-containing local anaesthetic solution were more stable than those in the group receiving the epinephrine containing local anaesthetic solution, while parameters of local anaesthesia were similar in both groups in spite of age and gender consideration.

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