Review Article

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Role of Epinephrine in Local Anesthesia and its Systemic Effects: A Review

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ABSTRACT

Background: Since Heinrich Braun in 1904 conceived the use of epinephrine to enhance local anaesthesia, its use has dominated the surgery. Even though in subsequent years, nordefrin, phenylephrine, norepinephrine, and levonordefrin were developed as adrenergic vasoconstrictors, none of these agents has proved superior or perhaps even equal to epinephrine. By opposing the vasodilating action of the local anesthetic, epinephrine retards its absorption from the injection site, thereby extending duration of action. Addition of a vasoconstrictor to a local anesthetic may have several beneficial effects: a decrease in the peak plasma concentration of the local anesthetic agent, increase in the duration and the quality of anesthesia, reduction of the minimum concentration of anesthetic needed for nerve block, and decrease of blood loss during surgical procedures. Local anaesthetics containing epinephrine have been considered relatively safe pharmacological agents and have been used in dental practice for over fifty years. However, like all pharmacological agents epinephrine added to the local anaesthetics can also exert its own action on the recipient site and its absorption into the circulation has a potential to causes systemic effects. The discussion regarding the safety of epinephrine in local anaesthetics, its effect on the body and its physiology has been a topic of debate and contention for a very long time. There have been a range of issues about the effects of epinephrine like, its effects on central nervous system, use in cardiac patients, effects on endocrine system, use in extremities and possible drug interactions with inhalational anesthetics, tricyclic antidepressants, beta blockers and, possibly, phenothiazines. This concern can be well founded and is because the amounts of epinephrine used in dentistry can result in significant elevations in circulating levels of epinephrine and concomitant physiologic changes. So, it can be contended that addition of a vasoconstrictor to a local anesthetic does have a potential to also have some detrimental effects. Review of the current available literature suggests that eliciting a thorough medical history of the patient, use of minimum required concentrations of epinephrine in local anaesthetics, avoiding an intravascular injection as some of the ways to avoid any untoward systemic effects.

Keywords: Local anesthesia, epinephrine, systemic effects, dogmas and facts.

INTRODUCTION

Pain is an unpleasant sensory and emotional experience[1], and can be thought of as one of the oldest of all dental problems. In fact, the control of pain during routine dental procedures is an important part of dental care delivery. Local anaesthesia serves as one of the means to achieve a

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painless situation and has become an integral part of every practicing dentist's daily work as it helps in performing the majority of surgical and restorative dental procedures. It is a universal method of pain control, and its popularity is a testament to efficacy and safety.[2] The first local anesthetic, cocaine, was isolated from coca leaves by Albert Niemann and Francesco Di Stefano in Germany in the 1860s. It was first used as a local anesthetic on September 15th of 1884 by Karl Koller[3], who demonstrated its use during painless ophthalmological surgery. Local anesthesia has been defined as *loss of sensation in a circumscribed area of the body caused by depression of excitation in nerve endings or inhibition of the conduction process in peripheral nerves.* [4]

Local anesthetic agents possess a degree of vasoactivity, most producing dilation of vascular bed into which they are deposited, with the exception of cocaine which is the only local anesthetic agent that consistently produces vasoconstriction.[4]

Clinical effects of such vasodilating property of local anesthetic agents are:[4]

1) Increased rate of absorption of the drug into the blood,
2) Decreased quality and duration of pain control,
3) Increased plasma concentration of the drug,
4) Increased potential for overdose (toxic reaction) and
5) Increased bleeding at the site of treatment as a result of increased perfusion.

Once the local anesthetic agent is absorbed into the systemic circulation, it gets distributed throughout the body to all tissues. Highly perfused organs such as the brain, head, liver, kidneys, lungs, and spleen achieve higher anesthetic blood levels than less highly perfused organs. This elevated plasma concentration of the drug will have significant bearing in certain target organs like the central nervous system (CNS) where it can lead to generalized tonic clonic seizures, cardiovascular system (CVS) where it can have an inhibitory effect on the rate of conduction and force of contraction of the myocardium, respiratory system, where it can produce respiratory arrest as a result of generalized CNS depression at overdose.

If the purpose of the local anesthetic injection is to allow a soft tissue or osseous surgical procedure to be performed in a painless manner, increased local blood flow may result in increased intraoperative bleeding and complicate the performance of the surgical procedure.

Addition of a vasoconstrictor to the local anesthetic solution has potential beneficial effects. It may

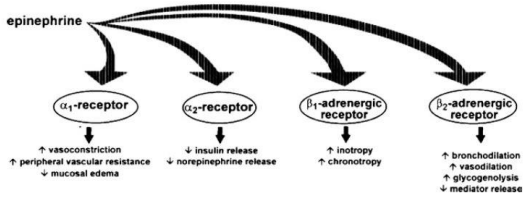
1) Decrease the peak plasma concentration of the local anesthetic agent,
2) Increase the duration of anesthesia and improve its quality,
3) Decrease the minimum concentration of local anesthetic agent needed for nerve block,
4) Reduce blood loss during surgical procedures and also improves the vision of surgical field.[4]

Vasoconstrictor agents available are adrenaline (epinephrine), noradrenaline (norepinephrine), phenylephrine, levonordefrin, felypressin, among which adrenaline (epinephrine) is the most common vasoconstrictor that is added to local anesthetic solution.[4] One hundred and twenty years ago, the English physician George Oliver reported that extracts of the adrenal gland exerted powerful effects on the heart and blood vessels. Several years later, the American pharmacologist John Abel isolated the active principal, naming it epinephrine. In 1900 a Japanese industrial chemist, Jokichi Takamine, discovered how to obtain epinephrine in pure form and arranged for the drug to be marketed by Park, Davis, and Company of the United States under the trade name of "Adrenaline," which subsequently became the official name of the hormone in most other countries. The use of epinephrine to enhance local anesthesia was conceived by Heinreich Braun, a noted German authority on nerve blockade. In 1904, Braun combined epinephrine with procaine.[5] Today, epinephrine combined with lidocaine is the local anesthetic combination generally judged as giving a clinically optimal effect with respect to anesthesia and hemostasis in oral surgical procedures.

Pharmacology of epinephrine:

Epinephrine produces its vasoconstrictor effects by binding to and stimulating both α_1 and α_2 adrenergic receptors located in walls of arterioles. Epinephrine also has β_2 adrenergic activity and may

cause vasodilation in tissues, such as skeletal muscle, which have a predominance of β_2 adrenergic receptors. (Fig 1)[6] In tissues that have approximately equal numbers of α and β receptors, the β effects of epinephrine will normally predominate due to greater sensitivity of the β receptors to epinephrine. At the low systemic concentrations normally associated with dental anesthesia, epinephrine can increase heart rate (a β_1 adrenergic effect), cardiac output, and peripheral vasodilation. Local anesthetics with epinephrine marketed for dental use contain either 1: 50,000 (0.02 mg/mL), 1: 80,000 (0.0125 mg/mL), 1: 100,000 (0.01 mg/mL), or 1: 200,000 (0.005 mg/mL) concentrations of the vasoconstrictor.[4]



Apart from the desired local effects, epinephrine added to the local anesthetic solution also produces systemic effects as it gets absorbed into the systemic circulation and interacts with different receptors in respective organs. In this paper we will review various systemic effects produced by epinephrine added to the local anesthetic solution, with emphasis on effects related to the cardiovascular system and blood glucose levels.

Effects on Cardiovascular system (CVS):

The effects of local anesthesia with adrenaline on cardiovascular system includes changes in heart rate (HR) and blood pressure,[7,8] changes in cardiac rhythm and electrocardiographic ST-segment wave,[9,10] endogenous catecholamine release,[11] endocrine response to surgery,[12] and hypokalemic response to local analgesia.[13] These changes are regulated by the net balance between sympathetic and parasympathetic activity, and in addition to modification, there is evidence that the autonomic response is further influenced by both stress and pain.[14] Epinephrine promotes platelet aggregation through α2 receptor-mediated mechanisms. It produces dilation of the coronary arteries, increasing coronary artery blood flow. It stimulates β1 receptors of the myocardium leading to a positive inotropic (force of contraction) and a positive chronotropic (rate of contraction) effect. Both cardiac output and heart rate are increased. Systolic blood pressure is increased whereas diastolic pressure is decreased when small doses are administered because of the greater sensitivity to epinephrine of β2 receptors compared with α receptors in vessels supplying the skeletal muscles. Diastolic pressure is increased with larger epinephrine doses because of constriction of blood vessels supplying the skeletal muscles caused by α receptor stimulation. The primary action of epinephrine is on smaller arterioles and precapillary sphincters. Blood vessels supplying the skin, mucous membranes, and kidneys primarily contain α receptors. Epinephrine produces constriction in these vessels. All these events imply a certain morbidity, which has in the past been frequently extrapolated to the more susceptible population by means of citing the dangers inherent in the combination of dental stress, local anesthesia, and exogenous and endogenous catecholamines.[4,8] However, these reservations have often been poorly voiced and may in general apply to a medically compromised population or, in particular, to the use of catecholamine vasoconstrictors.[15] However, the combination of a catecholamine and a posterior pituitary analog should act synergistically on both arterial and venous aspects of the capillary bed.[16] This synergy might permit an effective reduction to the concentration of one or both agents without compromise to vasoconstrictor potency and a consequent improvement to the management of cardiovascular risk.

In 1955 the New York Heart Association recommended a maximal dose of 0.2 mg of epinephrine (≤11 cartridges of 1:1,00,000 epinephrine) when used with LA in patients with CVD[17]. This recommendation however, was not specific to dentistry, and was formed based on extrapolations from results of epinephrine in healthy patients. In 1964, a Working Conference of the American Dental Association and the American Heart Association stated that the concentrations of vasoconstrictors used in LA are not contraindicated in patients with CVD[18]. More recently, Malamed[19] and Bennett[20] have recommended a maximal dose

of vasoconstrictor for patients with CVD to be no more than 0.04 mg of epinephrine at one appointment. Furthermore, Kaneko[21] recommended even lower levels (0.02 mg) for severe cases of CVD.

Despite the general acceptance of these recommendations by clinicians, these guidelines may not be fully supported by current scientific evidence. The reason being is that most studies to date have been conducted on young and healthy subjects[22-24], and the current recommendations were made based on the results from this population group that were then extrapolated to patients with CVD. These results do not apply to CVD patients since hemodynamic responses to epinephrine in healthy patients differ from that of cardiovascular disease patients. Furthermore, hemodynamic changes in CVD patients may appear exaggerated when directly compared to the changes in healthy patients. These factors may lead to an underestimation of the amount of epinephrine required.

Nevertheless, recent studies have attempted to include more relevant patient populations. A recent systematic review by Bader *et al,*[25] examined the effects of LA with epinephrine on hypertensive patients. When comparing hypertensive patients with healthy patients they found only small, nonsignificant increases in systolic and diastolic blood pressure with no adverse outcomes. Studies have shown that when compared to a healthy patient, a cardiovascular compromised patient showed little or no significant cardiovascular effects when subjected to comparable levels of epinephrine in local anesthetic solution[25]. The pathophysiology of cardiac compromised patients differs drastically from that of healthy patients. Consequently, tissue response to epinephrine, effective dose, and drug interactions may differ drastically as well. Administration of exogenous epinephrine in LA does not appear to cause significant hemodynamic changes in patients with CVD. Any transient increases in heart rate, blood pressure or arrhythmias were likely due to the release of endogenous catecholamines as a result of emotional stress or pain rather than the pharmacological effect of exogenous epinephrine. This is because peak exogenous epinephrine has been shown to occur five to eight minutes after injection[26], whereas the hemodynamic changes were observed during or immediately after injection. Furthermore, the transient arrhythmias and ST-segment depressions that were observed occurred two hours post injection.

Limiting anxiety and pain during dental procedures may be of greater importance when managing CVD patients, since both anxiety and pain result in a significantly increased release of endogenous catecholamines that can potentially lead to adverse cardiac effects.[27,28] The release of catecholamines due to ineffective pain control during dental treatment have been noted to exceed that of exogenous administration from the use of LA with vasoconstrictors[24,25,29,30]. Thus to gain effective pain control, administering adequate amounts of LA with vasoconstrictors in order to prolong the duration of anesthesia may in fact work in favor to the CVD patient.

Change in blood glucose levels:

Few studies have shown that plasma levels of glucose were affected following administration of dental local anesthetic 2% Xylocaine containing adrenaline (1:80,000), The changes in blood sugar levels following administration of local anesthesia containing epinephrine have been observed as a subject of controversy in some studies.[31,32,33,34]Meechan and Rawlins[35] concluded in their study that the levels of blood glucose and plasma potassium have been shown to change after administering clinical doses of dental local anesthetics containing epinephrine. In spite of many studies conducted in this regard no conclusive evidence was found. There was no significant difference before and following tooth extraction in healthy and diabetic patients with medication, whereas significant change was found in diabetic patients without medication. Tily and Thomas[36] emphasized that dental local anesthesia containing adrenaline can be safely used in healthy and diabetic patients as no significant ($p > 0.05$) result was seen pre and post-extraction levels of blood glucose.

Meechan[37] concluded that there was a significant increase in blood glucose levels following the injection of a solution containing epinephrine at 10 and 20 min when compared to the baseline and to the injection of epinephrine- free solution. The study did not mention the medical status of

patients. Therefore, this study showed a significant rise of the blood glucose level ($p< 0.05$) in diabetic patients who had not taken their hypoglycemic medication, this showed that the hypoglycemic medication taken by the patient masks the actual effect of adrenaline in the local anesthesia solution on the blood glucose level. This transient rise in blood glucose level might have a major effect on gastrointestinal motor activity[38].

Christensen[39] observed that an increase in blood glucose levels due to vasoconstrictors used with local anesthetics may be insignificant in normal patients, but can be relevant in diabetic patients. The metabolic changes also observed in untreated diabetics are, in many aspects, similar to those produced by an infusion of catecholamine. It has been proved, theoretically, that there was an increase in blood sugar levels in diabetic patients after using local anesthesia containing adrenaline[40] and on the other hand, epinephrine released through endogenous and exogenous sources leads to suppression of insulin secretion,[41,42] stimulates both glycogenolysis and gluconeogenesis[43] to produce hyperglycemia. Therefore, the adrenaline (1: 80,000) we are using in local anesthesia is present in very small quantities compared to its release from the body. It might be the effect of time period needed to be absorbed in the body and to change the blood sugar level.

Tily and Thomas[36] in their study emphasized the correlation between the number of anesthesia cartridges injected and the blood glucose level, the change post operatively was found to be not significant up to a limit of six cartridges ($p> 0.05$). However, many other factors have to be considered which can change the blood glucose level, either to increase or decrease it, therefore consideration of this study as a pilot study extends further to analyze the relation of age, gender, psychological factors, measurement of time interval (after injection and tooth extraction), type of hypoglycemic medicine, and nature/extent of surgery to blood glucose level of patients.

In a study conducted by Kalra P et al[44] the mean blood glucose concentration increased from the base line level of 84.81 to 85.09 mg/dl in healthy patients and from 206.82 to 207.09 mg/dl in diabetic patients 10 min following the injection of 2% plain lignocaine. This increase in blood glucose concentration following the administration of plain lignocaine was statistically not significant ($P<0.05$). There was statistically significant ($P>0.05$) increase in the blood glucose concentration from 88.81 to 105.55 mg/dl in healthy, and 208.77 to 242.46 mg/dl in diabetic patients 20 min following the injection of lignocaine with adrenaline.

While assessing the generalized effects of local anaesthetic solutions, metabolic as well as haemodynamic responses should be investigated. Adrenaline containing LA should be used with caution in Type 2 diabetics as adrenaline causes suppression of insulin release. Adrenaline increases blood glucose levels probably due to the following reasons:

1. Reduction in insulin secretion by the action of α2 adrenergic receptors causing inhibition of β cells of the islets of Langerhans in the pancreas.[45]

2. Stimulation of glycogenolysis via adrenergic stimulation of β receptors resulting in cyclic AMP-dependent activation of phosphorylation.

3. Decrease in glucose utilization both directly by affecting peripheral tissue glucose uptake and indirectly by decreasing insulin release.[45]

4. β-Adrenergic mediated increase in glucagon concentration. Glucagon increases glucose production by stimulating glycogenolysis and gluconeogenesis and inhibiting hepatic glycolysis.[46]

5. β-Adrenergic stimulation causes skeletal muscles glycogenolysis thereby increasing the lactate concentration, which thus become available for hepatic gluconeogenesis.

Action on extremities:

Because of the vasodilatory effect of this anaesthetic, Braun proposed the addition of adrenaline (epinephrine), to obtain vasoconstriction, resulting in a better hemostatic effect. Adrenaline induces this hemostatic effect, by binding to the α-1 and α-2 receptors. This causes a vasoconstrictive effect, by activating the phosphatidylinositol system and adenylate cyclase pathways. The classical dogma not to use adrenaline

seems to be based on a limited number of cases using cocaine and procaine as anaesthetic, published before 1950,[47] and it is an interesting phenomenon why this dogma has been maintained for such a long time despite the available contradicting evidence. Although the available randomised controlled trials comparing lidocaine with lidocaine supplemented with adrenaline are performed in small groups of patients,[48,49] their outcome is similar and consistent. Also in the cohort studies investigating more than 3000 patients,[50,51] no complications were found in patients in whom adrenaline was used. Studies investigating the blood flow after adrenaline injection did not found important problems or complications.[52,53] Of note is that in most studies, patients suffering from vascular diseases were excluded.[50,51,52,53]. Therefore, formally it cannot be concluded that the use of adrenaline in these patients is safe. However, as no cases involving ischemic complications after administration of local anaesthesia with epinephrine have been reported in the last 60 years, the risk in these patients, if present, seems to be rather small.

There were no reported vascular or ischemic incidents involving the use of adrenaline supplemented lidocaine. The use of adrenaline reduced the total amount of lidocaine used, and resulted in a reduced number of bleeding incidents.[54]

Reduction in Neuronal blood flow:

Vasoconstrictors affect the blood supply to the nerves in the area of injection, in addition to their effects on non-nervous tissues in the area. Myers and Heckman[55] found that the blood supply to rat sciatic nerve was reduced 78% when 2% lidocaine with 1: 100,000 was applied to tissues surrounding the nerve. Application of 1% lidocaine without vasoconstrictor reduced blood flow to the nerve by 19%. Myers and Heckman believed that epinephrine may have a pathogenic role in those relatively rare reports of neurologic deficit following local anesthetic procedures. Partridge[56] in a study of the effects of lidocaine and epinephrine on rat sciatic blood flow, demonstrated similar reductions in nerve blood flow to those reported by Myers and Heckman. Partridge also reported a synergistic reduction in blood flow when lidocaine and epinephrine were combined. Two percent lidocaine alone decreased nerve blood flow by 18%; application of 5-4µg/mL epinephrine alone decreased blood flow by 20%. The combination of lidocaine and epinephrine reduced nerve blood flow by 60%. Bupivacaine, which is a more potent vasodilator than lidocaine, also reduced nerve blood flow. A 0.25% bupivacaine solution decreased nerve blood flow by 35%, 0.5% bupivacaine by 25%, and 0.75% bupivacaine by 15%.

Adverse reactions:

Although systemic responses to vasoconstrictors in local anesthetic solutions are generally mild, adverse reactions may occur in certain situations. Patients with heart disease are the largest group at risk and will serve as the focus for the remainder of this presentation. Specific dangers to cardiac patients include myocardial ischemia and dysrhythmia. Measures of cardiac performance, such as cardiac output, left ventricular ejection fraction, and myocardial contractility index, are less influenced by epinephrine in patients with coronary artery disease than in normal subjects. This insensitivity may reflect reduced cardiac reserve or a down regulation of cardiac, β receptors. Nevertheless, myocardial oxygen consumption, which goes up in response to the increased cardiac work, begins to outpace oxygen delivery in patients with coronary artery disease as the epinephrine infusion rate approaches 0.06µg/kg/min. In one study, clinically evident myocardial ischemia occurred in sensitive patients when the epinephrine concentration exceeded 650 pg/mL.[57] Signs and symptoms of ischemia included chest pain, ST segment depression, and ventricular dysrhythmias.

Drug interactions:

The most important of these relate to possible enhanced cardiovascular stimulation. Vasopressors found in local anesthetic formations have cardiotonic effects, and this may become more significant when patients are medicated with any drug having similar influences. These include tricyclic and monoamine oxidase inhibitor antidepressants, digoxin, thyroid hormone, or any of the sympathomimetics used for weight control or attention deficit disorders. Vasopressors are not contraindicated in these patients, but they should be administered with caution. For patients

suspected of stimulant drug abuse, eg, cocaine, it may be wise to avoid vasopressors altogether. Cautious use of vasopressors is also advised for patients medicated with nonselective beta blockers. Unlike selective agents that only block beta-1 receptors on the heart, nonselective agents also block vascular beta-2 receptors. In this case the alpha agonist action of vasopressors becomes more pronounced and both diastolic and mean arterial pressures can become dangerously elevated. This is generally accompanied by a sudden reflex slowing of heart rate. Significant consequences of this interaction are well documented.[59-61] The interaction with beta blockers follows a time course identical to that observed for normal cardiovascular responses to epinephrine. It commences following absorption from the injection site, which generally peaks within 5 minutes and declines over the subsequent 10-15 minutes. Vasopressors are not contraindicated in patients taking nonselective beta blockers, but doses should be conservative and blood pressure monitored periodically during administration. Gingival retraction cords impregnated with racemic epinephrine should be avoided. These products contain epinephrine in amounts far exceeding those contained in local anesthetic formulations.

CONCLUSION

Some of the conclusions that can be drawn from this review are

a) Use of epinephrine containing local anesthesia causes a significant increase in the blood glucose level in diabetic patients who did not take their medications and it is safe to use in healthy and diabetic patients with hypoglycemic medications.

b) Adrenaline can be safely applied in local anaesthesia of distal extremities with lidocaine, and does not result in ischemic injury when a normal functioning vasculature is present. The ancient textbook dogma not to use adrenaline should be revisited.

c) Recommendation by American Heart Association in 1986[58] is as good as any summary pronouncement on the subject of maximum dosage of epinephrine that can be used in a cardiovascular disease: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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