Original Article

The newer aspect of dexmedetomidine use in dentistry: As an additive to local anesthesia, initial experience, and review of literature

Department of Anaesthesiology and Critical Care, Pt. BD Sharma PGIMS, [1]Department of Oral and Maxillofacial Surgery, Post Graduate Institute of Dental Sciences, University of Health Sciences, Rohtak, Haryana, India

Prashant Kumar, Manju Thepra[1], Amrish Bhagol[1], Kannu Priya[1], Virendra Singh[1]

ABSTRACT

Introduction: Despite the availability of a wide variety of pharmacological agents in the field of anesthesia, there has always been a continuous search for newer local anesthetic agents with improved efficacy, potency, and better handling properties. Dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, is an emerging agent for provision of additive local anesthetic effect if used with conventional local anesthetics, which can be implicated in dentistry for performing many minor oral surgical procedures. The present paper reports a pilot study comparing clinical efficacy and potency of this newer emerging drug in combination with lignocaine. **Materials and Methods:** Ten patients undergoing orthodontic extraction for correction of malocclusion and other dentofacial deformities requiring orthodontic treatment were locally infiltrated with 2% lignocaine plus dexmedetomidine 1 μ/ml and 2% lignocaine plus adrenaline in 1:200,000 dilution at two different appointments. The onset of action, duration of action, and pain threshold were assessed. **Results:** Onset of action was found to be faster with longer duration of action with the newer drug dexmedetomidine and lignocaine combination when compared with combination of lignocaine and adrenaline. **Conclusion:** The study demonstrated that the combination of dexmedetomidine with lignocaine enhances the local anesthetic potency of lignocaine without significant systemic effects when locally injected into oral mucosa.

Address for correspondence:
Dr. Prashant Kumar,
17/8 FM, Medical Enclave,
Rohtak - 124 001, Haryana, India.
E-mail: pk.pgims@yahoo.com

Key words: Dexmedetomidine, lignocaine, local anesthetic adjuvants, orthodontic extraction

Introduction

Dexmedetomidine, a selective alpha-2 adrenoceptor agonist, is used intravenously as a sedative in intensive care unit and for procedural sedation. However, attention has recently been paid to dexmedetomidine as a possible additive for local anesthesia.[1,2] The addition of dexmedetomidine to local anesthetics has been carried out for spinal and nerve blocks, and the enhancing effect of dexmedetomidine on local anesthetic action has been demonstrated.[3-7] The effect of locally

Access this article online

Quick Response Code:

Website: www.njms.in

DOI: 10.4103/0975-5950.196137

How to cite this article: Kumar P, Thepra M, Bhagol A, Priya K, Singh V. The newer aspect of dexmedetomidine use in dentistry: As an additive to local anesthesia, initial experience, and review of literature. Natl J Maxillofac Surg 2016;7:76-9.

injected dexmedetomidine combined with lignocaine on local anesthesia has also been shown in the backs of guinea pigs.[8] However, the effect of locally injected dexmedetomidine on the anesthetic action in humans has not fully been clarified. Furthermore, because the intravenously administered dexmedetomidine induces sedation in patients and occasionally influences the cardiovascular system, such as causing hypotension and bradycardia, the use of dexmedetomidine as an adjunct to local anesthetic may exert its effect with minimized systemic effects.

This study was taken to evaluate the effect of dexmedetomidine injected into the oral mucosa in combination with lignocaine in patients undergoing exodontia in terms of onset and duration of action and adverse effect if any when compared with injection epinephrine with lignocaine.

Materials and Methods

The present, randomized, single-blinded pilot study was undertaken in the Department of Oral and Maxillofacial Surgery, at a Teaching Hospital of University of Health Sciences, after approval by the local Institutional Review Board. The procedure was performed in the operating clinic where all monitoring equipment as well as emergency equipment for resuscitation was readily available. Ten healthy volunteers, aged between 10 and 25 years belonging to ASA class I of either gender, planned to undergo orthodontic extraction of the right and left maxillary and mandibular first or second premolars were included in the study. Patients with a history of an allergy or hypersensitivity to lignocaine or dexmedetomidine, having uncontrolled hypertension, diabetes mellitus, hyperthyroidism, renal or hepatic disease, cardiovascular disease, on antipsychotic drugs for 3 months or β-blockers, dental phobia, and pregnant or lactating mothers were not included in the study.

After explaining the study protocol, consent was taken from the patient or attendant as appropriate. Visual analog scale (VAS) score was explained to the patient and recorded at baseline and during the procedure. Pulse rate (PR), noninvasive blood pressure, and peripheral saturation of oxygen (SpO_2) were monitored and recorded. Other parameters such as onset of action of drug and duration of action were evaluated. For the surgical procedure, patients received either injection lignocaine plus dexmedetomidine (2% lignocaine + dexmedetomidine 1 μ/ml) (study drug was prepared by addition of 30 μ of dexmedetomidine using appropriate dilution with insulin syringe to 30 ml vial of 2% lignocaine plain solution by an anesthesiologist) or injection lignocaine plus adrenaline (2% lignocaine in 1:200,000 adrenaline) for control group.

Subjects were studied on two separate days at least 4 days apart. On the 1st day, thorough history and examination of all patients were done. Local anesthesia with injection lignocaine 2% plus dexmedetomidine was administered in the respective maxillary or mandibular first premolar/second premolar of right side in the first appointment, and 2% injection lignocaine plus 1:200,000 adrenaline (3 ml approximately) was administered in the left maxillary and mandibular first premolar/second premolar in the second appointment. Nerve block used in the maxillary premolar extraction procedure was infraorbital through premolar approach and greater palatine nerve block for palatal anesthesia. Mandibular premolar extraction nerve block given was classical inferior alveolar nerve block through premolar approach and lingual nerve block of corresponding side. Onset of action was taken till patient felt no pain on probing, while in postoperative when VAS was ≥4, it was taken as duration of action. All patients received tablet ibuprofen with paracetamol twice a day for analgesia thereafter.

Results

All ten volunteers aged between 10 and 25 years, male: female - 2:8, in the present study were thoroughly investigated. Pain threshold was noticeably increased after the injection of lignocaine plus dexmedetomidine solution than those with lignocaine plus adrenaline. Onset of action was found to be shortened significantly ($P < 0.05$) for dexmedetomidine group with prolonged duration of action although not statistically significant [Table 1].

Furthermore, there were no significant changes in the systolic blood pressure, diastolic blood pressure, and heart rate from the baseline just before injection with either test solution, and no significant changes in these values were noted between the two groups.

Table 1: Effect of adjuvant on onset of action and duration of local anesthetic

Patient parameter	Lignocaine with dexmedetomidine	Lignocaine with epinephrine	*P*
Onset of action (min'-sec")	2'-35" (SD ± 46.2 s)	3'-27" (SD ± 40.5 min)	0.000268 ($P<0.05$, S)
Duration of action (h-min')	2-6' (SD ± 86.4 s)	1-43' (SD ± 81.7 min)	0.19424 ($P<0.05$, NS)

S: Significant, NS: Not significant, SD: Standard deviation

Discussion

The invention of local anesthesia has made oral minor surgical procedures to be accomplished successfully with no or little pain, but all surgical procedures whether minor or major are invariably associated with stress, anxiety, and pain.[2,3,8] There are some limiting factors for the use of local anesthetics. The most important is duration of action that is extended by addition of number of adjuvants. These adjuvants also help to reduce the dose of local anesthetic. Commonly used adjuvants include both nonopioids including epinephrine, alpha-2 agonist clonidine, nonsteroidal anti-inflammatory drugs, Mg^{2+}, and $NaHCO_3$ and opioids such as fentanyl, sufentanil, and morphine.[2]

All are invariably associated with some adverse effects. However, attention has recently been paid to dexmedetomidine as a possible additive for local anesthesia. Dexmedetomidine, a selective alpha-2 agonist, used intravenously as a sedative in intensive care unit and for procedural sedation, is associated with less respiratory depression and alteration of hemodynamics compared with other anesthetic agent.[8-12] Researchers added dexmedetomidine to intrathecal bupivacaine for spinal block and caudal block and to levobupivacaine for axillary brachial plexus block, showing longer block duration, shortening of the block onset time, and improving postoperative analgesia.[1-8] It has been demonstrated that locally injected dexmedetomidine has an anti-inflammatory effect and induces vasoconstriction at the injected site.[11,12] The findings suggest that dexmedetomidine can be an effective additive to local anesthetics. In the present study, we found that the addition of dexmedetomidine to lignocaine for the maxillary and mandibular nerve block significantly prolonged block duration and shortened onset of action, as well as postoperative analgesia in patients undergoing orthodontic extraction. Furthermore, the basic vital parameters remained within normal limits, except slight fall in pulse rate in some patients receiving dexmedetomidine plus lignocaine.

In our study, the enhancing effects on local anesthetic potency by adrenaline and dexmedetomidine have also been compared. Epinephrine has been used for over a century as an additive to local anesthetics.[9] In a typical dose range of 5–10 μ/ml, epinephrine is believed to prolong duration by its vasoconstrictive properties that prevent systemic reabsorption of local anesthetic. Epinephrine can be added to local anesthetics to detect intravascular injection, and its vasoconstrictive properties have the presumed added benefit of decreasing systemic toxicity, allowing for larger doses of local anesthetic to be given safely. Epinephrine has shown mixed efficacy as an adjuvant to prolong nerve blockade. Using lignocaine with high-dose epinephrine (200 μ/ml) for axillary block prolonged motor block and sensory block by approximately 25 and 40 min, respectively, however, was associated with tachycardia and hypertension. A lower dose of 25 μ/ml had minimal effect, prolonging motor block by 10 min and sensory block by 30 min.[10] Despite its long-term use as an adjuvant in local anesthetics, epinephrine has been shown to compromise endoneurial blood flow and increase neurotoxicity, particularly in the setting of diabetic animal models, arguing against its use in patients with diabetic peripheral neuropathy.[12-14]

Dexmedetomidine use as an additive can be traced to 2004 when used to supplement intravenous regional anesthesia.[15] Multiple randomized controlled trials have since been conducted, and recently, Abdallah and Brull published a meta-analysis that examined four studies of dexmedetomidine as an additive for brachial plexus blocks. They found that dexmedetomidine significantly prolonged mean motor block by 268 min and time to first analgesic by 345 min. However, the mean sensory block prolongation of 284 min was not statistically significant.[16]

A study looking at the addition of dexmedetomidine to mepivacaine for brachial plexus blocks showed a block prolongation of approximately 75 min; however, the duration was minimally increased when compared to 200 mcg epinephrine.[11] Volunteer studies have also demonstrated the efficacy of dexmedetomidine. In one volunteer study, dexmedetomidine was added to ropivacaine ulnar nerve blocks and resulted in a 200-min prolongation of analgesia.[17] In contrast, systemic dexmedetomidine increased the duration of analgesia by only 50 min. In another volunteer study, dexmedetomidine was added to ropivacaine for posterior tibial nerve blocks, resulting in a prolongation of analgesia by approximately 5 h.[18] A recent study found that the duration of sensory and motor block when dexmedetomidine was added to bupivacaine supraclavicular blocks was almost twice as long compared to the addition of clonidine.[19] The potential for dexmedetomidine to cause neurotoxicity in humans has not been extensively studied. However, in animal models of spinal anesthesia and sciatic nerve block, dexmedetomidine did not show toxicity and was potentially neuroprotective when combined with lignocaine and bupivacaine.[20,21] The published data support the efficacy of dexmedetomidine for peripheral nerve block prolongation of approximately 200 min at doses around 1 mcg/kg, and it appears to be a viable option as an additive to local anesthetics, especially where bradycardia and hypotension is an issue.

Dexmedetomidine has been known to have a central action, which inhibits substance *P* release in the nociceptive pathway at the level of the dorsal root

neuron through the activation of alpha-2 adrenoceptors in the locus coeruleus.[14] The mechanism by which alpha-2 adrenoceptor agonists enhance the local anesthetic potency has not been fully clarified. *In vitro* studies demonstrate that alpha-2 adrenoceptor agonists have a direct inhibitory effect on the C-fiber action potential and Na + channels in neurons.[22,23] One previous study demonstrated that dexmedetomidine enhances local anesthetic potency through peripheral alpha-2A adrenoceptor subtype.[8] However, recent investigations demonstrated that alpha-2 adrenoceptor agonists have an alpha-2 adrenoceptor-independent effect on nerve fiber action potentials without alpha-2 adrenoceptor activation.[15,16] Brummett *et al*. showed that the duration of analgesia is prolonged by blocking the hyperpolarization-activated cation current and not through alpha-2 adrenoceptors. These findings suggest that the mechanism of dexmedetomidine's peripheral action is complex and multifactorial.

Conclusion

The present study demonstrates noticeable enhancement of local anesthetic potency and duration of lignocaine without systemic effects when injected locally into the oral mucosa with dexmedetomidine. With the encouraging results of this pilot study, we continue this study with a larger group to evaluate clinical usefulness of this novel combination.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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