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Effect of chlordiazepoxide and oxazepam on the success rate of mandibular nerve block anesthesia: A randomized double blind control trial

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ABSTRACT

Introduction: The success rate of inferior alveolar nerve block (IANB) has always been discussed. The present study was aimed to investigate the effect of chlordiazepoxide and oxazepam on the success rate of mandibular block anesthesia. Materials and Methods: In this randomized double blind clinical trial study, 75 healthy adults with no consumption of medications affecting pain perception were investigated. The participants were randomly assigned into three groups, 25 participants in each group. The patients in chlordiazepoxide and oxazepam groups received 10 mg chlordiazepoxide and 10 mg oxazepam orally two hours before the nerve block, respectively. The patients in control group received placebo. Then, the inferior alveolar nerve block was performed using a cartridge containing lidocaine 2% and epinephrine 1/80,000. The success rate of IANB in 5, 15 and 30-minute periods after performing the nerve block in the second premolar and first molar in reaction to the stimuli resulting from an electric pulp tester was considered as the block success, and the pain level during the needle insertion into the soft tissue was measured by a visual analoge scale (VAS). Data were analyzed by SPSS 16 software using ANOVA, chi-square and Fisher's exact tests. Results: The chlordiazepoxide and diazepam groups indicated a significantly higher success rate than the control group ($P<0.05$). However, there was no significant difference between chlordiazepoxide and diazepam groups in terms of the block success rate ($P>0.05$). The pain level during the needle insertion into the soft tissue was significantly lower in chlordiazepoxide and diazepam groups in comparison with control group ($P<0.05$). Moreover, no significant difference was observed between chlordiazepoxide and diazepam groups regarding the pain level during the needle insertion into the soft tissue ($P>0.05$). Conclusion: Oral administration of chlordiazepoxide and diazepam can significantly increase the success rate of inferior alveolar verve block for the first 15 minutes and can reduce the pain during needle insertion.

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INTRODUCTION

Pain relief and control is one of the essentials in dental treatments which are significant for both the dentist and the patient. It is an important factor that determines the attitude of the patient towards dental treatment. Appropriate application of local anesthesia and pain control is necessary for the success of the treatment [1]. The mandibular teeth are more prone to anesthetic failure than maxillary teeth due to difficulty in inferior alveolar nerve block and nerve sub-branches [2]. A failure rate of 4.8-20% has been reported for inferior alveolar nerve block [3,4].

Numerous studies have evaluated different techniques to enhance the success rate of mandibular block anesthesia [5-9]. Some alternative or auxiliary techniques such as infiltration anesthesia, intra-ligamentous anesthesia, intraosseous anesthesia, and mental nerve block have also been introduced [10-13]. Some other studies have investigated the administration of different analgesics such as non-streoid anti-inflammatory medications before nerve block injection in order to enhance the success of mandibular nerve block [14,15].

Benzodiazepines are drugs that are commonly used in dentistry prior to treatment aiming to produce sedative effects especially in children. The performance of benzodiazepines is dependent on their potential to inhibit nerve stimulators, which is applied through gamma-aminobutyric acid (GABA) receptors. GABA neurotransmitters are main intermediate inhibitors in brain; therefore, benzodiazepines indicate anxiolytic, anti-epileptic, sedative and hypnotic effects through contacting GABA receptors [16]. It has been shown in an

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animal model that an agonist of benzodiazepine receptors relieves neuropathic and inflammatory pain depending on the dose of the medication [17]. Benzodiazepines inhibit painful sensations in the central nervous system by increasing the threshold of painful stimuli [18].

Oral administration of benzodiazepines reduces the anxiety during dental treatments [19,20]. Several drugs belonging to benzodiazepines, in addition to producing sedative effects, reduce the caesarean-related pains [21]. Vuilleumier *et al* reported that benzodiazepines reduce the pain [22]. Also, Heckmann *et al* showed that clonazepam relieves the pain in the patients with burning mouth syndrome [23].

The present study was conducted to examine the effect of chlordiazepoxide and oxazepam on the pain and success rate of mandibular block anesthesia.

MATERIALS AND METHODS

In this double blind clinical trial study, the samples were selected from the patients referred to Oral and Maxillofacial Surgery Department at Kermanshah School of Dentistry. The present study was approved by the research ethics committee of Kermanshah University of Medical Sciences (Grant# 93065 and 93066). The patients were informed about the administration of the study and written consent forms were taken from them.

To calculate the study sample, a pilot study including 11 participants was conducted. According to the obtained data and using the formula of the relationship between groups, the sample size for each group was calculated 21 people with confidence level of 95% (α=0.5) and potency of 80% using the formula: P_2=30%, p_1=60%, ($Z_{1-a/2}$ =1.96), ($Z_{1-\beta}$ =0.84), (β = 20%). To compensate the possible loss of samples, 4 participants were added to each group; thus, a total of 25 participants were included in each group.

The research method was fully explained to the patients prior to initiation of the study, and they were told thay could leave the study in any stage of the study. All patients (18-45 years old) that required inferior alveolar nerve block for wisdom tooth removal were included in the study. The criteria for exclusion from the study included necrosis, pulpitis or tooth pain, mandibular orthodontic treatments, consumption of analgesics like Non-steroidal anti-inflammatory drug (NSAID) during the past two weeks, daily consumption of benzodiazepines during the past two weeks, pregnancy or breastfeeding, contraindications of chlordiazepoxide and oxazepam and consumption of drugs interfereing with chlordiazepoxide and oxazepam.

The patients were randomly divided into three groups including chlordiazepoxide, oxazepam and control groups. A chlordiazepoxide (10 mg Iran Hakim) or oxazepam (10 mg Iran Hakim) tabl*et al*ong with a glass of orange juice was given to the patient by the main researcher to take two hours before administration of the anesthetic and inferior alveolar nerve block. The patients in the control group received a capsule containing vitamin C with a glass of orange juice as placebo.

Two hours after drug administration, anesthetic injection (HN) and assessment of the success rate of anesthesia (MD) and pain level (AK) were performed. A cartridge syringe (Dena Instruments; Forgeman Instruments Co, Sialkot, Pakistan) was used to create the nerve block. The syringe was equipped with a blood aspiration device and a thumb ring. A 27g×38 mm dental needle (Carpule; Heraeus Kulzer Gmbh, Hanau, Germany) was placed on the syringe. Before injection, blood aspiration test was carried out. To this end, following the needle insertion according to the inferior alveolar nerve block technique when the needle tip reached the bone, the needle was pulled out for 1-2 mm and aspiration was performed. Having ensured the lack of blood aspiration, the anesthetic solution containing lidocaine 2% and epinephrine 1/80,000 (Darou-Pakhsh, Iran) was injected into the tissue during 1 minute. A 1.8 ml cartridge was used for every participant. The participants were evaluated in terms of soft tissue anesthesia. The patients were asked to determine their pain level during needle insertion into the soft tissue from 1-10. Accordingly, the pain severity was rated based on visual analog scale (VAS) as follows [24]: Needle insertion with no pain (0), with low pain [1-3], with moderate pain [4-6] and with severe pain [7-10].

If lip anesthesia was not induced, the nerve block was considered unsuccessful and the patient was excluded for the study. In the case of lower lip anesthesia, the degree of anesthesia was measured by an electric pulp tester (Parkell edgewood, USA) in the second premolars and first molars in the quadrant recipient of nerve block in 5, 15 and 30-minute periods after anesthetic injection. The success and failure rate of the mandibular block anesthesia was determined by the pulp tester [24]; success: 8, 9 and 10 and failure: 1-7.

The severity of pain reported by the participants for each tooth at different periods was recorded in a data collection form.

Data were analyzed by SPSS-16 software using one-way ANOVA, chi-square and Fisher's exact tests. $P<0.05$ was considered significant.

Results:

In the present study, 75 patients in three groups (n=25) including control (17 males and 8 females), chlordiazepoxide (17 males and 8 females) and oxazepam (13 males and 12 females) were investigated. The mean age for the control, chlordiazepoxide and oxazepam groups were 29.8±8.4, 26.2±7.8 and 29.9±9.4,

respectively. There was no statistically significant difference between groups in terms of gender distribution and mean age (P>0.05).

The success rate in chlordiazepoxide and oxazepam groups was significantly higher than control group in 5 and 15-minute periods, but there was no significant difference between groups in the 30-minute period. The maximum success rate was reported for oxazepam group (6.40) followed by chlordiazepoxide group (6.04); however, the minimum success rate was observed for placebo group (4.24). Chlordiazepoxide and oxazepam groups indicated higher success rate compared to control group (P<0.05). Moreover, no significant difference was reported between chlordiazepoxide and oxazepam groups in terms of block success rate (P>0.05) (Table 1).

The amount of pain during anesthetic injection in control group (3.72±1.79) was significantly higher than chlordiazepoxide (0.76±1.012) and oxazepam (0.6±0.191) groups (P<0.05). Further, there was no statistically significant difference between chlordiazepoxide and oxazepam groups (P>0.05).

Table 1: Comparison of the success rate of mandibular block anesthesia between study groups

Tooth type	Time (min)	Control	Chlordiazepoxide	Oxazepam
Second premolar	5	(%4) 1[a]	(%32)8[b]	(%44)11[b]
	15	(%32)8[a]	(%72)18[b]	(%80)20[b]
	30	(%52)13[a]	(%76)19[a]	(%80)20[a]
First molar	5	(%8)2[a]	(%64)16[b]	(%64)16[b]
	15	(%56)14[a]	(%88)22[b]	(%92)23[b]
	30	(%72)18[a]	(%88)22[a]	(%92)23[a]

The values indicated with different letters in each row represent statistically significant difference and similar letters show no statistically significant difference.

Discussion:

The results of this study revealed that administration of chlordiazepoxide and oxazepam significantly increased the success rate of inferior alveolar nerve block in the 15-minute period following anesthetic injection.

Previous research has shown that males and females have different treatment needs to use specific amount of benzodiazeoines [25]. It has also been shown that gender affects the performance of GABA receptors [26]. Moreover, the existing evidence is indicative of the changes of benzodiazepine receptors with age increase [27]. Since age and gender affect the performance of GABA receptors, the study groups were matched in terms of age and gender to prevent the effect of confounding factors on the results of the study. Accordingly, the mean age showed no significant difference between groups, and in terms of gender distribution, two groups were completely similar (each group consisting of 68% male and 32% female).

The success rate of the nerve block in 5 and 15-minute periods in the case group was higher than the control group, which is indicative of the effect of chlordiazepoxide and oxazepam on pain relief and anesthesia induction. Berthold *et al*. reported that sublingual administration of triazolam with higher effectiveness and oral administration with lower intensity reduced the pain and anxiety in dental patients [28].

Moreover, Shadangi *et al*. investigated the effects of single injection of bupivacaine or together with midazolam on the time of sensory nerve block, motor nerve block and pain relief and reported that adding midazolam to bupivacaine injection increased the time of anesthesia without affecting the motor block [29].

In addition, in the study carried out by Heckmann *et al*. on the patients with burning mouth syndrome, administration of clonazepam relieved the pain [23]. The results of the study by Vuilleumier *et al*. indicated pain-relieving properties for benzodiazepines [22]. Gupta *et al* found out that a combination of midazolam and ketamine prior to extraction of the third molars relaxed the patient during surgery and reduced postoperative face swelling and pain [30].

However, there is no precise information to explain the cause of pain relief by benzodiazepines reported in some studies. Although the mechanisms of pain relief by benzodiazepines are not fully recognized, a study carried out on laboratory animals has shown that a benzodiazeoine receptor agonist with drug-dependant effects caused a decrease in neuropathic and inflammatory pain [17]. It has also been reported that benzodiazepines affect the central nervous system and consequently enhance the threshold of pain stimulators, thereby inhibiting painful senses [18].

In contrast with these studies, however, Lindemann *et al* evaluated the effect of triazolam on the success rate of IANB in the patients with irreversible pulpitis and reported that the success rate of IANB in triazolam (a kind of benzodiazepine) group showed no statistically significant difference in comparison with the placebo group [31]. According to the results of Khademi *et al*., alprazolam did not significantly increase the success rate of IANB in the teeth with irreversible pulpitis (53%) compared with the placebo (40%) [32].

The results of the present study indicated that the success rate in chlordiazepoxide group in 5 and 15-minute periods was significantly higher than that of the control group, but 30 minutes after mandibular nerve block, no significant difference was observed between the case and control groups in terms of the success rate of block

anesthesia. The difference between the results of 5 and 15-minute periods and 30-minute period can be attributed to the pharmacokinetic properties of the drug.

Furthermore, the findings of the present study revealed that the block success rate of the first molar was higher in all groups in equal intervals compared with second premolar. This confirms the fact that molars are more quickly anesthetized than premolars in a jaw arch due to anatomically peripheral location of nerve fibers in molars than in premolars [33,34].

Conclusion:

Oral administration of chlordizepoxide (10 mg) and/or oxazepam (10 mg) two hours prior to the mandibular block anesthetic injection enhanced the success rate of anesthesia to reduce pain during anesthetic injection in patients undergoing dental treatments.

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