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Original Article

Effect of topical application of amitriptyline and nortriptyline on irreversible pulpitis pain in teeth with failed pulpal anesthesia after a successful inferior alveolar nerve block: A randomized clinical trial

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ABSTRACT

Background: No consensus has been reached on the effect of topical application of amitriptyline and nortriptyline on irreversible pulpitis pain in teeth with failed pulpal anesthesia after a successful inferior alveolar nerve (IAN) block. This study aimed to assess the effect of topical application of amitriptyline and nortriptyline on irreversible pulpitis pain in teeth with failed pulpal anesthesia after a successful IAN block.

Materials and Methods: This double-blind randomized controlled clinical trial was conducted on 45 patients with irreversible pulpitis. The patients were randomly assigned to three groups (n = 15) for topical application of 10 mg amitriptyline, 10 mg nortriptyline, and starch (placebo). An IAN block was primarily administered by injection of lidocaine with 1:80,000 epinephrine. Next, the abovementioned medications were topically applied in each group. The pain level of patients was quantified by the McGill Visual Analog Scale (VAS) and the Wong–Baker Faces Pain Rating Scale (FPRS) before the intervention, immediately after injection, and after topical application of materials and compared. Data were analyzed by SPSS version 21 using the Chi-square test, likelihood ratio, one-way ANOVA, repeated-measures ANOVA, and the Kruskal–Wallis test. $P < 0.05$ was considered statistically significant.

Results: All three interventions significantly decreased pain ($P < 0.05$). Although nortriptyline caused a greater pain relief, the difference among the three groups was not significant regarding the VAS or Wong–Baker FPRS scores ($P > 0.05$).

Conclusion: Although nortriptyline caused a greater reduction in irreversible pulpitis pain than amitriptyline, the difference between the two medications was not significant. Future studies without a placebo group are recommended.

Key Words: Amitriptyline, anesthesia, antidepressive agents, local, nortriptyline, pain, pulpitis

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INTRODUCTION

Pulpitis is defined as inflammation of the pulp tissue for any reason. In pulpitis, the pulp tissue is still viable, and complete necrosis has not yet occurred; thus, the injured tissue gives a prolonged response to stimuli such as heat. Such teeth require

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root canal therapy or extraction.[1] The term "hot tooth" refers to a tooth with irreversible pulpitis and spontaneous moderate-to-severe pain.[2] Inferior alveolar nerve (IAN) block is the most commonly adopted technique for local anesthesia of mandibular posterior teeth with irreversible pulpitis.[3,4] Clinical studies have reported a 44% to 81% failure rate for IAN block anesthesia for mandibular posterior teeth with irreversible pulpitis.[5,6] Several reasons have been proposed for such a high rate of failure in achieving optimal local anesthesia, such as changed resting potential, reduction of excitability threshold of the inflamed nerves, resistance of sodium channels to anesthetic agents, overexpression of sodium channels in irreversibly inflamed pulps, and low pain tolerance threshold of patients.[7,8]

Researchers have tried several combination treatments, supplemental anesthesia techniques, and different medications to increase the success rate of IAN block. Many medications have been used in combination with anesthetic agents for this purpose, such as dexamethasone, ketorolac,[9] sodium bicarbonate,[10] ketamine,[11] articaine,[12,13] and bupivacaine, among others.[14] Nonetheless, none of these complementary interventions have been 100% successful in achieving a complete pulpal anesthesia in all cases.

Tricyclic antidepressants (TCAs) are among the medications with analgesic effects, irrespective of their antidepressant effect,[15] that are extensively used to relieve neuropathic pains such as postherpetic neuralgia,[16,17] diabetic neuropathy,[18-20] and trigeminal neuralgia.[21] Evidence shows that the analgesic effects of such drugs occur irrespective of their antidepressant effect.[22] Amitriptyline (a tertiary amine) and nortriptyline (a secondary amine) are among TCAs.[23,24] Amitriptyline inhibits the presynaptic reuptake of serotonin and norepinephrine and resultantly increases the concentration of these neurotransmitters at the synaptic gap. Amitriptyline can activate the signaling of fibroblast growth factor receptor in glial cells, which is partly responsible for its antidepressant effect.[25] In addition to the antidepressant effect of amitriptyline, it has other pharmacological effects such as anti-inflammatory[26] and analgesic[27] effects, and it can alleviate pain due to dentin exposure in teeth with irreversible pulpitis[28] and also pain due to oral mucositis.[29]

The analgesic effects of antidepressants are due to their attachment to noradrenaline and serotonin, and subsequent inhibition of the reuptake of these neurotransmitters, resulting in increased levels of noradrenalin and serotonin in the synaptic gap.[30,31] Secondary amines such as nortriptyline are relatively selective for the reuptake of noradrenalin, whereas tertiary amines such as amitriptyline inhibit the reuptake of noradrenalin and also serotonin.[30] Nortriptyline is the active metabolite of amitriptyline.[22] In chronic neuropathic pain, secondary amines such as nortriptyline are often preferred to tertiary amines such as amitriptyline due to fewer side effects such as dizziness, restlessness, and drop in blood pressure.[30] Amitriptyline and nortriptyline have also been used for myofascial pains of the masticatory muscles, and it has been reported that nortriptyline is more effective than amitriptyline and is better tolerated.[22]

Aminsobhani *et al*.[28] and Moghadamnia *et al*.[32] used TCAs for anesthesia induction following an IAN block. However, only the efficacy of amitriptyline was evaluated in their studies, and no comparison was made with any other medication. Insignificant side effects of nortriptyline make it a suitable alternative to amitriptyline in patients with irreversible pulpitis for whom amitriptyline cannot be used due to its side effects. Moreover, the effects of nortriptyline on irreversibly inflamed pulps have not been previously investigated. Thus, this study aimed to assess the effects of topical application of amitriptyline and nortriptyline on irreversible pulpitis pain in teeth with failed pulpal anesthesia after a successful IAN block. The null hypothesis was that the topical application of amitriptyline and nortriptyline would have no significant effect on irreversible pulpitis pain in teeth with failed pulpal anesthesia after a successful IAN block.

MATERIALS AND METHODS

This double-blind randomized controlled clinical trial was conducted at the Endodontics Department of School of Dentistry, Isfahan University of Medical Sciences, from July 2019 to December 2019. The study protocol was approved by the Ethics Committee of the university (IR.MUI.RESEARCH.REC.1398.204) and registered in the Iranian Registry of Clinical Trials (IRCT20230313057710N1).

Trial design

In this randomized double-blind clinical trial, the two experimental groups received amitriptyline and nortriptyline, and the control group received starch

powder as the placebo. In the present study, the intervention was topical application of amitriptyline and nortriptyline, and the outcome was irreversible pulpitis pain in teeth with failed pulpal anesthesia after a successful IAN block.

Participants, eligibility criteria, and settings

The sample size was calculated to be 15 (a total of 45) in each group assuming $\alpha = 0.05$, $Z_{1-\frac{\alpha}{2}} = 1.96$, study power $(1 - \beta)$ of 0.80, $Z_{1-\beta} = 0.84$, $\delta_1 = \delta_2 = 1.67$ and $d = 1.7$. Accordingly, with 15 patients in each group, it would be possible to find a minimum significant difference of 1.7 units in the mean Visual Analog Scale (VAS) pain score at 0.05 level of significance in each method.

The inclusion criteria consisted of participants, aged between 10 to 68 years requiring endodontic treatment of mandibular first molars indicating signs and symptoms of irreversible pulpitis whom had successful IAN block. The exclusion criteria were allergy to lidocaine or TCAs, systemic diseases, history of hypersensitivity to TCAs, lidocaine or epinephrine, pregnancy and nursing, patients who took systemic analgesics within 4–6 h before their dental visit, and patients with complete anesthesia and no pain.

The sample consisted of 45 patients (between 10 and 68 years) with irreversible pulpitis presenting to the Endodontics Department of Isfahan University of Medical Sciences. The participants were selected by convenience sampling, and then, each patient was allocated a code and the patients were assigned to three groups of 15 using a table of random numbers. For this purpose, each patient in the first intervention group received a two-digit code from 1 to 15, each patient in the second intervention group received a two-digit code from 16 to 30, and each patient in the control group received a two-digit code from 31 to 45. One number was randomly selected from a table of random numbers by random finger placement, and the next numbers were consecutively selected in pairs. Numbers larger than 45 were excluded. Patients were assigned to their respective groups based on their allocated two-digit code.

Interventions

After obtaining written informed consent from the patients, the diagnosis of irreversible pulpitis was confirmed by the heat and cold tests and the presence of signs and symptoms of irreversible pulpitis such as severe prolonged pain response to cold test and pain during access cavity preparation (before pulp exposure). Patients showed signs of successful anesthetic injection 15 min[33] after the IAN block injection of 2% lidocaine and 1:80,000 epinephrine (Persocaine, Darupakhsh, Iran). The patients were randomly assigned to three groups ($n = 15$) of 10 mg amitriptyline (Darupakhsh, Tehran, Iran), 10 mg nortriptyline (Sobhan Pharmaceuticals, Tehran, Iran), and 10 mg starch (as placebo). The colored coating of the tablets was removed and each tablet was powdered and mixed with 2 cc saline in an Eppendorf tube until a homogeneous solution was obtained. Thus, each Eppendorf tube contained 10 mg amitriptyline, 10 mg nortriptyline, or 10 mg starch. The tubes were coded such that the dentist was blinded to the contents of each tube. The tubes were randomly assigned to patients by someone not involved in the study. After measuring the pain score of patients during access cavity preparation and before pulp exposure, one Eppendorf tube was randomly assigned to each patient while the dentist was unaware of its content.

The tube content was applied on exposed dentin by a microbrush, and a cotton pellet was placed over it, followed by a cotton roll, and then the patient was requested to bite on it for 3 min.[28,32] The tooth was not isolated with rubber dam, but the cotton pellet was not in contact with the saliva since the tooth was isolated with two cotton rolls, and a saliva ejector was also used. After this time period, the dentist continued the process of access cavity preparation and the pain score was measured again. Before the onset of treatment, the patients were ensured that in case of continuation of pain, supplemental injections would be performed to alleviate pain. The patients' age, gender, level of education, marital status, cigarette smoking, tobacco use, history of recent hospitalization, and pain score were collected in a datasheet. Pain was measured three times before the treatment onset, after the injection of anesthetic agent and initiation of access cavity preparation as the patient felt pain for the first time, and also after the application of medication using the VAS and Wong–Baker Faces Pain Rating Scale (Wong–Baker FPRS).[32] The VAS comprised a 10-cm line, with 0 indicating no pain at the left end and 10 indicating maximum imaginable pain in the right end. All treatments were performed by an endodontist.

Interim analyses and stopping guidelines

No interim analyses were performed, and no stopping guidelines were established.

Ethical considerations

The present study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (IR.SUMS.REC.1394.141). Written informed consent was obtained from the participants. The principles of voluntariness and confidentiality were also emphasized. The Helsinki Ethical Considerations Guide 1975, as revised in 2008, was also taken into consideration.

Blinding

Both patients and the operator were blinded to the tube contents (double-blind design). Each Eppendorf tube was coded such that the dentist was not aware of its content. A coded Eppendorf tube was assigned to each patient by someone not involved in the study. After measuring the level of pain of the patient during access cavity preparation and before pulp exposure, one Eppendorf tube was randomly assigned to each patient while the dentist was not aware of its content.

Statistical analysis

Data were analyzed by IBM SPSS statistics version 21 using the Chi-square test, likelihood ratio, one-way ANOVA, repeated-measures ANOVA, and the Kruskal–Wallis test. $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of patients was 34.1 ± 13.6 years (range: 10–57 years) in the amitriptyline group, 37.7 ± 15.5 years (range: 14–63 years) in the nortriptyline group, and 28.9 ± 14.7 years (range: 13–68 years) in the placebo group. One-way ANOVA revealed no significant difference among the three groups in the mean age ($P = 0.650$). The three groups had no significant difference regarding gender ($P = 0.913$), marital status ($P = 0.334$), or level of education ($P = 0.452$) [Table 1]. Furthermore, the three groups had no significant difference regarding current medication intake, affliction with a systemic disease, history of hospitalization, cigarette smoking, and substance abuse [$P > 0.05$, Table 1]. Figure 1 shows the CONSORT flow diagram of the study.

Repeated-measures ANOVA showed a significant effect of time on VAS pain score ($P < 0.001$). The mean VAS pain score significantly decreased with time. However, the effect of group ($P = 0.566$) and the interaction effect of group and time ($P = 0.556$) were not significant. In other words, the reduction in VAS pain score was not significantly different among the three groups [Table 2].

Repeated-measures ANOVA showed that the effect of time on Wong–Baker FPRS score was significant ($P < 0.001$) such that the mean Wong–Baker FPRS score significantly decreased with time ($P < 0.001$). However, the effect of group ($P = 0.437$) and the interaction effect of group and time ($P = 0.325$) were not significant. In other words, the reduction in Wong–Baker FPRS pain score was not significantly different among the three groups [Table 3].

DISCUSSION

This study assessed the effect of topical application of amitriptyline and nortriptyline on irreversible pulpitis pain in teeth with failed pulpal anesthesia after a successful IAN block. To the best of the authors' knowledge, this study is the first to assess and compare the efficacy of amitriptyline and nortriptyline for this purpose.

The three groups in the present study had no significant difference in demographics, underlying conditions, and tobacco use. The results showed a significant reduction in pain in all three groups. Although nortriptyline caused slightly greater pain reduction than amitriptyline and the control group, this difference was not statistically significant according to the VAS and Wong–Baker FPRS scores. Furthermore, the amitriptyline and nortriptyline groups showed higher analgesic efficacy than the placebo, but the difference did not reach statistical significance. AminSobhani *et al*.[28] evaluated 33 patients with irreversible pulpitis and showed that 10 mg amitriptyline significantly decreased pain in patients with irreversible pulpitis. Their result was in line with the present findings. However, lack of a significant difference among the three groups in the present study, compared with their study, may be due to smaller sample size of the present study. Moghadamnia *et al*.[32] evaluated 56 patients with irreversible pulpitis and reported pain reduction following topical application of 2% amitriptyline gel after two injections of lidocaine. They used a VAS and reported pain reduction after the use of amitriptyline. Difference between their results and the present findings can be due to different sample sizes and forms of medication (gel in their study) in the two studies.

Table 1: Frequency distribution of demographic variables in the three groups

Variable	Category	Amitriptyline		Nortriptyline		Placebo		*P*
		Number	Percentage	Number	Percentage	Number	Percentage	
Gender	Male	8	53.3	9	60	9	60	0.913*
	Female	7	46.7	6	40	6	40	
Marital status	Married	9	60	7	46.7	9	60	0.334**
	Widowed	0	0	2	13.3	3	20	
	Divorced	1	6.7	1	6.7	0	0	
	Single	5	33.3	5	33.3	3	20	
Level of education	Below high-school diploma	1	6.7	1	6.7	2	13.3	0.452***
	High-school diploma	6	40	7	46.7	0	33.3	
	Bachelor's degree	4	26.7	6	40	5	33.3	
	Higher than Bachelor's degree	4	26.7	1	6.7	3	20	
Current medication use		6	40	4	26.7	4	26.7	0.666*
Current systemic disease		6	40	3	20	3	20	0.372*
History of hospitalization		6	40	4	26.7	4	26.7	0.666*
History of cigarette smoking		3	20	5	33.3	4	26.7	0.709*
Current cigarette smoking		3	20	5	33.3	4	26.7	0.709*
History of substance abuse		0	0	0	0	1	6.7	0.326*
Current substance abuse		0	0	0	0	1	6.7	0.333*

*Chi-square, **Likelihood ratio Chi-square, ***Kruskal–Wallis

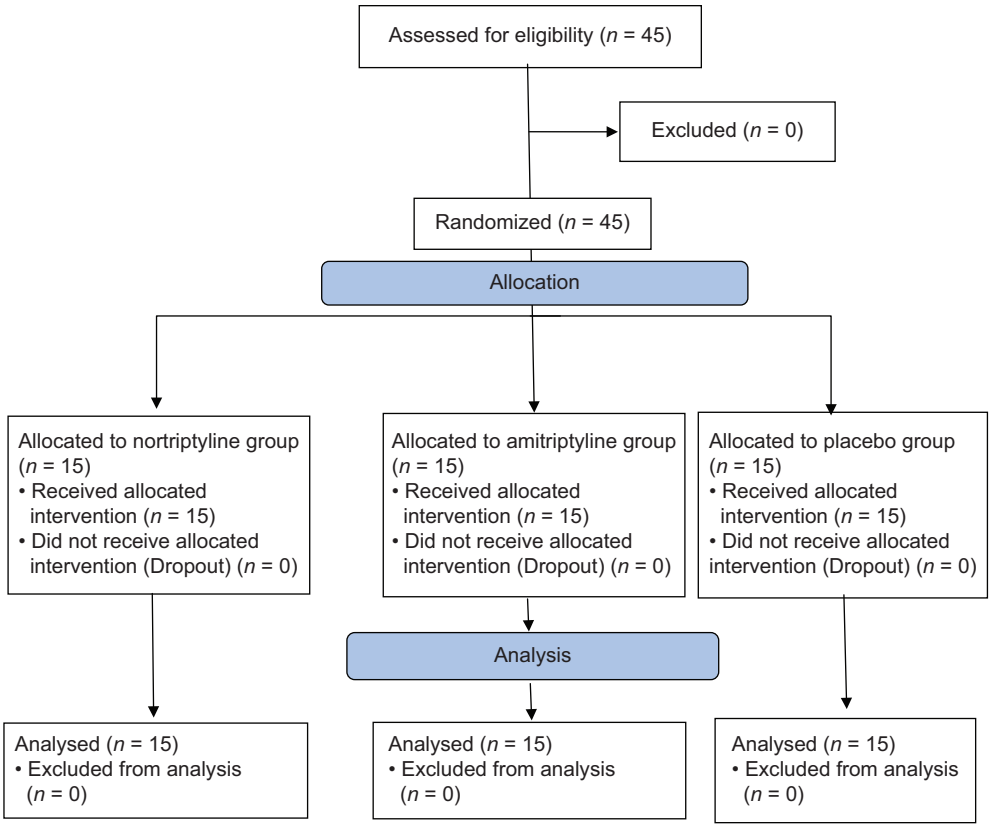

Figure 1: Flow diagram of patient selection.

Amitriptyline has a significant inhibitory effect on voltage-gated sodium channels (VGSCs) and causes a reduction in neural conductance of sensory neurons and pain receptors. Evidence shows that amitriptyline can attach to areas close to the local receptor responsible for inactivation of VGSCs and inhibit the activity of these receptors.[33] Moreover, Liang *et al*. (2013) showed that this medication

Table 2: Mean Visual Analog Scale pain score in the three groups at different time points

Time	Mean±SD			*P**	*P***	*P****
	Amitriptyline	Nortriptyline	Placebo			
Before the treatment onset	6.7±2.01	6.6±1.3	7.1±2.3	<0.001	0.566	0.556
After injection	6.3±3.1	5.5±2.3	5.5±2.4			
Immediately after the application of medication	4.6±1.9	3.4±1.4	4±2.4			

*Time, *Group, ***Time group. SD: Standard deviation

Table 3: Mean Wong–Baker face pain rating scale score in the three groups at different time points

Time	Mean±SD			*P**	*P***	*P****
	Amitriptyline	Nortriptyline	Placebo			
Before the treatment onset	3.3±1.4	3.1±0.6	3.5±1.3	<0.001	0.437	0.325
After injection	3.2±1.6	2.5±1.2	2.6±1.2			
Immediately after the application of medication	2.1±1.1	1.6±0.8	1.9±1.2			

*Time, *Group, ***Time group. SD: Standard deviation

can block different types of sodium channels resistant to tetrodotoxin such as Nav 1.8 and Nav 1.9.[34] It has been reported that amitriptyline has higher inhibitory effects on voltage-dependent sodium channels than bupivacaine.[35] However, Aminsobhani *et al*.[28] revealed significantly higher efficacy of amitriptyline than imipramine while both products had higher analgesic efficacy than the placebo.

Evidence shows that TCAs relieve neuropathic pain. This effect is due to the direct effect of drug on the nerve and stimulation of sodium-dependent channels.[36] Type and composition of drug, its distribution, level of gene expression, and activity of VGSCs all change following pulpal damage. Furthermore, evidence shows that the activity of tetrodotoxin-resistant sodium channels is doubled under inflammatory conditions.[37] The significance of these channels is better revealed knowing that these channels per SE attenuate the response to lidocaine by four times. It appears that overexpression of these channels in irreversible pulpitis is responsible for anesthesia failure and unsuccessful analgesia.[38] Although TCAs have not been comprehensively and systematically used for dental neuropathic pain relief due to the existing concerns regarding their side effects, some hypotheses have been proposed regarding their synergistic effects with the conventionally used agents for pulpal anesthesia. Considering the main mechanism of action of routine dental anesthetic agents such as articaine, lidocaine, and bupivacaine, which is through the stimulation of sodium channels, it may be postulated that TCAs may reinforce the analgesic efficacy of routine anesthetic agents.[32]

The present results revealed that nortriptyline decreased pain due to irreversible pulpitis more than amitriptyline and the placebo, and the efficacy of amitriptyline was also higher than the placebo; however, none of the differences reached statistical significance, which may be due to the placebo effect. The placebo effect is a cognitive-somatic phenomenon that leads to resolution of symptoms, and is attributed to psychosocial factors such as positive expectations from an intervention; the perceived effect is therefore not related to the drug used.[39] The placebo effect reportedly occurs in at least half of the participants, and this effect is often stronger in studies on pain and in the intervention group than the healthy control group. It is also greater in clinical trials than the experimental studies. One explanation for the placebo effect in the present study is that the placebo, at least partly, mimics the selective inhibitory mediation of serotonin reuptake, which results in positive effect of placebo and lack of a significant difference between the placebo and intervention groups even if a higher number of patients in the intervention group are satisfied with the treatment outcome.[40] In the present study, although there was no difference in analgesic efficacy of amitriptyline and nortriptyline, the placebo effect might have been responsible for lack of a significant difference between the two intervention groups and the placebo group. Although the differences were not significant, they were clinically important. It also appears that nortriptyline may have higher efficacy due to its smaller molecular structure. Thus, topical application of TCAs in combination with the commonly administered anesthetic agents may be helpful for pain management in patients with pulpitis, although further investigations are warranted on this topic.

Small sample size (due to difficulty in finding eligible patients) and the possibility of erroneous quantification of pain by patients due to its subjective nature were among the limitations of the present study. Moreover, administration of placebo can cause the placebo effect, and may compromise the accuracy of the results.

CONCLUSION

According to the present results, topical application of TCAs including amitriptyline and nortriptyline successfully decreased pain due to irreversible pulpitis in patients with a successful IAN block, and this reduction was greater in the nortriptyline group. However, the difference among the three groups was not significant, which may be due to the placebo effect. Further studies with a larger sample size are required on different doses of drugs and also with a control group without a placebo.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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