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Impact of SCN10A Gene Polymorphism on the Success of Inferior Alveolar Nerve Block in Mandibular Molars with Symptomatic Irreversible Pulpitis

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ABSTRACT

Background and Objective: The success rate of inferior alveolar nerve block (IANB) is lower in teeth with symptomatic irreversible pulpitis, and the reported failure rate is variable. Since SCN10A gene polymorphisms can alter the effect of anesthetics on sodium channels, the present study was conducted to investigate the impact of SCN10A gene polymorphisms (rs6801957 and rs6795970), which encode Nav1.8, on the success of inferior alveolar nerve block (IANB) in mandibular molars with symptomatic irreversible pulpitis.

Methods: This cross-sectional study was conducted on 194 patients who required root canal treatment of the first or second mandibular molars due to symptomatic irreversible pulpitis. Root canal treatment began 10 minutes after lip anesthesia, when no response to the cold test or electric pulp test was observed. Saliva samples were collected for DNA extraction, and the polymorphisms were identified using Tetra ARMS PCR. The success to failure ratio of IANB was evaluated for different SCN10A polymorphisms.

Findings: Of the 194 examined patients, 87 (44.8%) were male and 107 (55.2%) were female. The success rate of IANB was significantly higher in women (61.7% vs. 46%, p=0.022). Patient age had no statistically significant effect on the success or failure of IANB. In rs6801957 polymorphism, no significant difference was observed in the success to failure ratio of IANB between genotypes and alleles. However, in the rs6795970 polymorphism, the AA and GG genotypes had significantly higher success to failure ratios (OR=1.398 and 5.182, respectively, p=0.015). Men in both the rs6801957 and rs6795970 genotypes had a lower success rate compared to women (OR=0.66).

Conclusion: The results of the study demonstrated that the rs6795970 polymorphism of the SCN10A gene significantly affects the success of IANB in mandibular molars with symptomatic irreversible pulpitis, and that male patients as well as those with the AG genotype of the rs6795970 polymorphism are at a higher risk of IANB failure.

Keywords: *SCN10A, Polymorphism, Inferior Alveolar Nerve, Irreversible Pulpitis, Mandibular Molars.*

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Introduction

Achieving profound local anesthesia through inferior alveolar nerve block (IANB) is challenging for many dentists during root canal treatment of mandibular molars. Evidence suggests that the success rate of IANB decreases in teeth with symptomatic irreversible pulpitis, and the reported failure rate for IANB in clinical studies varies between 43% and 83% (1, 2). Several theories have been proposed to explain the reasons for this reduced success (3). The hyperalgesia caused by inflammation alters neural response, reduces prostaglandin levels, activates pain receptors, and prevents optimal diffusion of the anesthetic through the nerve sheath due to decreased pH. Additionally, tetrodotoxin-resistant (TTX-R) sodium ion channels have been identified in symptomatic pulpitis and trigeminal ganglion. Reinnervation and increased levels of neuropeptides such as calcitonin gene related peptide (CGRP) and substance P (SP) as a result of the expression of proinflammatory mediators are other proposed theories to explain anesthesia failure in teeth with acute symptomatic pulpitis. Peripheral neurons are the source of pain perception, which are also known as nociceptors (3, 4).

Another proposed mechanism for hyperalgesia is the modulation of neuronal excitability. Voltage-gated sodium channels (VGSCs) play a fundamental role in neuronal excitability (5). The effects of VGSCs on pain, increased excitability, and hyperalgesia have been the subject of extensive research over the past two decades. Altered activity of many ion channels has been demonstrated in various pain models, and existing evidence supports the theory that some of these channels may play a prominent role in pain perception via nociceptors (3). At least nine subtypes of VGSCs are available, which differ in their expression patterns, biophysical properties, and roles in peripheral pain. VGSCs can be divided into two groups: tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) sodium channels. VGSCs have two subunits, α and β. The α subunit is voltage-sensitive, activating the channels and allowing ion passage by detecting the electrical field. Most VGSC channels (e.g., Nav1.8 and Nav1.9) are resistant to local anesthesia, which explains the weaker efficacy of anesthetic agents in patients suffering from toothache (5). The Nav1.8 sodium channel subtype is encoded by the SCN10A gene, which is expressed in the dorsal root ganglion and trigeminal ganglion neurons, most of which are nociceptors. It is also expressed in peripheral axons and free nerve endings in the skin and cornea. The important role of Nav1.8 channels in peripheral nerves and their presence at free nerve endings may indicate that Nav1.8 channels can significantly affect and stimulate nociceptors, thereby playing a role in pain perception (4).

Advancements in genetic science and in the field of genomic technologies have led to the introduction of several novel systems for disease diagnosis and the evaluation of therapeutic efficacy. An emerging branch known as "personalized dental care" utilizes the human genetic architecture for the diagnosis, treatment, and prevention of oral diseases. Targeted, specialized therapy is among the advantages of this scientific discipline in dental treatment, which may result in saving time and a reduction in energy expenditure as well as cost (6). Genes play a prominent role in human growth, development, and physiology. Genetic mutations may cause illness. Single nucleotide polymorphisms (SNPs) are defined as alterations at single nucleotides that may modify gene expression patterns. The detection of SNPs via genetic testing may enable risk assessment and personalized therapeutic interventions. Several pathogenic mutations have been reported in the gene encoding the Nav1.8 sodium channel subtype (e.g., SCN10A), which may cause peripheral neuropathy (3). The identification of SNPs in the SCN10A gene across different populations has been the subject of numerous investigations (4).

Polymorphisms of the SCN10A gene can alter the effect of anesthetic agents on sodium channels. Theoretically, polymorphisms in the encoded gene may influence gene expression, sodium channel structure, channel abundance, and their resistance to anesthetic agents (5). López‐Valverde et al. (7) found no significant association between four types of polymorphisms and the success of anesthesia with articaine or its onset of action. However, Duan et al. (4, 5) demonstrated that SCN10A gene polymorphisms significantly affect sensitivity to mechanical pain in humans. Given the potential influence of SCN10A gene polymorphisms on the role of anesthetic agents on sodium channels, this study was conducted to investigate the effect of common genetic polymorphisms (rs6801957 and rs6795970) of the SCN10A gene, which encodes the Nav1.8 sodium channel, on the success of inferior alveolar nerve block (IANB) in mandibular molars with symptomatic irreversible pulpitis.

Methods

After approval by the Ethics Committee of Tabriz University of Medical Sciences (ethics code: IR.TBZMED.REC.1401.306) and obtaining informed consent, this cross-sectional study was conducted on 194 patients (107 females, 87 males) who referred to the Department of Endodontics, Faculty of Dentistry, Tabriz University of Medical Sciences, and required root canal treatment of the first or second mandibular molars with symptomatic irreversible pulpitis. Patients with symptomatic irreversible pulpitis (prolonged positive response to cold testing) and systemic health (ASA physical status classification system) who did not need modifications to the treatment plan (8–10) were included in the study. Patients were excluded from the study if they had with any of the following criteria: immunodeficiency, known hypersensitivity to local anesthetic agents, a history of alcohol consumption or analgesic use within 12 hours prior to treatment, unwillingness to IANB administered via the standard technique, use of antidepressant medications, neuropathy, pregnancy, complete prosthetic crowns on the mandibular molars, periapical pathology, calcified root canals, or infection and inflammation in the adjacent teeth.

The diagnosis of irreversible pulpitis was established using a cold test with a refrigerant spray (Diamant, Iran) and the Visual Analog Scale (VAS). Patients with moderate pain scores (4–6) and severe pain scores (7-10), as well as a prolonged and intense response to cold testing compared to the contralateral control teeth, were diagnosed with symptomatic irreversible pulpitis (11, 12). An electric pulp test (EPT; Parkell Edgewood, NY, USA) was also performed on the affected tooth and the control tooth. Patients who exhibited a positive response to the aforementioned tests were included in the study.

IANB was administered via injection of 2% lidocaine with 1:800,000 epinephrine using a 27-gauge needle (30 mm) (Persocaine-E/Lidocaine-Epinephrine; Darou Pakhsh, Iran). After 10 minutes, patients were questioned regarding lip numbness; those without lip numbness were excluded from the study and received supplemental anesthetic injections. In cases with lip paresthesia, the success to failure ratio of IANB was determined using cold testing and electric pulp testing. The criteria for IANB success included lack of response to cold testing, the highest reported EPT value (7) 10 minutes after injection, and the absence of perceived pain during access cavity preparation, pulpal roof removal, and initial root canal instrumentation according to the Visual Analog Scale (VAS). Two consecutive negative responses to maximal stimulation on EPT were required to confirm IANB success (13). Treatment was performed under rubber dam isolation (14). Patients were instructed to raise their hand if they experienced pain. In such cases, the procedure was interrupted, supplemental injections were administered, and treatment was subsequently resumed. The presence of pain was also recorded. Patients who did not raise their hand were questioned regarding their pain experience using the VAS after the treatment (15).

Saliva samples were collected from patients using the spitting method, stored in microtubes, and sent to a genetics laboratory for DNA extraction (16). DNA extraction was performed on the saliva samples using the Yektatajhiz/Tissue Genomic DNA Mini Extraction Kit, and sample quality and quantity were assessed using a NanoDrop spectrophotometer. The SNPs rs6795970 and rs6801957 were retrieved from the NCBI database.

Following primer design for the different SNPs, the tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR), a PCR-based technique, was employed to amplify the polymorphisms. In this technique, two pairs of primers (inner and outer) are used for the exclusive amplification of normal and mutant alleles of the relevant SNP within a single PCR reaction. After the reaction and electrophoresis of the PCR products, the formation of three bands on the gel indicated a heterozygous mutation, whereas the presence of two bands indicated a homozygous mutation for each allele (17). Table 1 presents the sequences of the primers used in this study.

Table 1. Primer sequences employed in this study

Polymorphism	Primer	Sequence
rs6801957	Forward-Outer	CTCTGGCAGCCTGTGATGTG
	Reverse-Outer	AGCACCTCCAACTCTTATTTGCTG
	Forward-Inner	GAAAGATGAGTCTGTTCCTCAGGT
	Reverse-Inner	GACATACCTACCTCAGCAGGAG
rs6795970	Forward-Outer	ATTCACCTCTGCCCAACGTG
	Reverse-Outer	GAGCATGAAGACTATAGCTAGATAGACC
	Forward-Inner	CCATATTTTACATGCCTTTGTCTAGGTA
	Reverse-Inner	AGAGTTCATGCTCTCTGCTGCC

Tetra ARMS PCR for the rs6795970 and rs6801957 single nucleotide polymorphisms (SNPs) of the gene encoding the Nav1.8 sodium channel was performed and consisted of an initial denaturation at 95°C for 5 minutes, denaturation at 95°C for 30 seconds, primer annealing to each template strand at 60°C for 30 seconds, extension at 72°C for 40 seconds, and a final extension at 72°C for 5 minutes. The reaction was repeated for 25 cycles.

Data were analyzed using SPSS 26 (SPSS Inc., IL, USA). Quantitative data were presented as mean ± standard deviation (SD), while qualitative data were presented as numbers and percentages. Comparisons between two groups for qualitative data were performed using the chi-square test. Comparisons between two groups for quantitative data were conducted using the independent t-test and the Mann-Whitney U test for parametric and nonparametric data, respectively. Logistic regression was employed to assess the correlation between SCN10A polymorphisms and IANB success, and a $p<0.05$ was considered statistically significant.

Results

Of the 194 patients examined, 87 (44.8%) were male and 107 (55.2%) were female. The success rate of IANB was significantly higher in women compared to men (61.7% vs. 46%, p=0.022). There was no significant difference in age between the two groups (Table 2).

The success rate of IANB did not differ significantly between different genotypes or alleles of the rs6801957 polymorphism. The success rate of IANB differed significantly between different genotypes of the rs6795970 polymorphism (p=0.015). Patients with the AA genotype had a higher IANB success rate

compared to those with the AG genotype, and patients with the AG genotype had a higher IANB success rate compared to those with the AA genotype (Table 3). The success rate of IANB did not differ significantly between different alleles of the rs6795970 polymorphism. No significant differences were observed between men and women regarding the frequency of different genotypes (p=0.029), TG genotype (p=0.042) of rs6801957 polymorphism, and different genotypes of the polymorphism (p=0.029). Furthermore, the frequency of the G allele in the rs6801957 polymorphism (p=0.028) did not differ significantly between males and females with successful or failed IANBs (Tables 4 and 5).

Table 2. Frequency of gender and age of patients with successful or failed IANB

Inferior Alveolar Nerve Block	Gender			Age			
	Female N(%)	Male N(%)	p-value	Number	Mean±SD	Median	p-value
Success	66(61.70)	40(46.00)	0.029	106	33.88±10.61	33	0.229
Failure	41(38.30)	47(54.00)	0.029	88	35.37±9.61	35	0.229

Table 3. Frequency of different genotypes and alleles of rs6801957 and rs6795970 polymorphisms

Parameter	Inferior Alveolar Nerve Block		Odds Ratio	p-value
	Success N(%)	Failure N(%)		
Genotype (rs6801957)				
TT	17(16.0)	10(11.4)	1.403	0.608
TG	49(46.2)	45(51.1)	0.904	
GG	40(37.7)	33(37.5)	1.005	
Allele				
T	83(39.15)	65(36.93)	1.060	0.654
G	129(60.84)	111(63.06)	0.964	
Genotype (rs6795970)				
AA	54(50.9)	32(36.4)	1.398	
AG	46(43.4)	55(62.5)	0.694	0.015
GG	6(5.7)	1(1.1)	5.182	
Allele				
A	154(72.64)	119(67.61)	1.074	0.280
G	58(27.35)	57(32.38)	0.845	

Table 4. Frequency of successful/failed IANB in different genotypes and alleles of the rs6801957 polymorphism in men and women

Genotype (rs6801957)	Inferior Alveolar Nerve Block		Odds Ratio	p-value
	Success N(%)	Failure N(%)		
TT				
Male	7(70)	3(30)	1.61	0.692
Female	10(59)	7(41)		
TG				
Male	13(38)	21(62)	0.41	0.420
Female	36(60)	24(40)		

GG				
Male	20(46)	23(54)	0.42	0.089
Female	20(67)	10(33)		
Total				
Male	40(46)	47(54)	0.66	0.029
Female	66(62)	41(38)		
T				
Male	20(45)	24(55)	0.547	0.128
Female	46(60)	31(40)		
G				
Male	33(43)	44(57)	0.72	0.012
Female	56(51)	34(49)		

Table 5. Frequency of successful/failed IANB in different genotypes and alleles of the rs6795970 polymorphism in men and women

Genotype (rs6795970)	Inferior Alveolar Nerve Block		Odds Ratio	p-value
	Success N(%)	Failure N(%)		
AA				
Male	21(57)	16(43)	0.65	0.314
Female	33(67)	16(33)		
AG				
Male	17(35)	31(65)	0.44	0.052
Female	29(55)	24(45)		
GG				
Male	2(100)	0(0)	-	1.000
Female	4(80)	1(20)		
Total				
Male	40(46)	47(54)	0.66	0.029
Female	66(62)	41(38)		
A				
Male	38(45)	47(55)	0.526	0.028
Female	62(61)	40(39)		
G				
Male	19(38)	31(72)	0.432	0.050
Female	33(57)	25(43)		

Discussion

The results of this study demonstrated that patients with the AG genotype had a significantly higher frequency of IANB failure compared to those with the AA genotype; those with the GG genotype experienced a lower frequency of failure. The frequency of IANB failure in men was 1.84 times higher than in women. Local anesthetic agents inhibit the influx of sodium ions through VGSCs and reduce the transmission of pain signals, thereby inducing analgesia (18). Other factors, such as the activation or inactivation of VGSCs and the processing of pain perception, also play a role in pain perception.

Consequently, a number of genes are involved in pain perception (19). Mutations in the SCN10A gene, which encodes the Nav1.8 sodium channel subtype, may cause impairment in pain perception. Therefore, genetic sequencing of these channels can provide valuable information in the clinical setting (20). In the present study, two SNPs (rs6801957 and rs6795970) of the SCN10A gene were evaluated for their role in IANB success/failure in patients with symptomatic irreversible pulpitis, given that a potential relationship between certain SNPs of the SCN10A gene and pain had been suggested (5, 21, 22). The present results demonstrated the effect of the rs6795970 polymorphism of the SCN10A gene in patients with symptomatic irreversible pulpitis, which was consistent with the findings of Karataş et al. (23).

Interindividual variability in pain perception can be explained by variations in specific genes (24). In the present study, the frequency of different genotypes of the rs6795970 polymorphism differed significantly between the IANB success and failure groups, and patients with the AG genotype were at a higher risk for IANB failure compared to those with the AA genotype, whereas individuals with the GG genotype were at a lower risk for IANB failure. This finding was consistent with the results of the study by Karataş et al. (23). Duan et al. (4) demonstrated that the rs6801957 polymorphism of the SCN10A gene in patients with T alleles was significantly associated with the frequency of anesthetic success. The results of Duan et al. regarding allele comparison by gender are consistent with the present study. The SCN10A gene, which encodes the Nav1.8 alpha subunit, is predominantly expressed in the trigeminal ganglion and the dorsal root ganglion. Nav1.8 significantly influences the excitability of nociceptors. However, there are not many studies available regarding the impact of IANB success and SNPs of the SCN10A gene with which to compare our results (25).

Duan et al. (4) reported that the rs6795970 allele and the rs6801957 T allele alter the activation of sodium channels and significantly reduce repetitive firing of dorsal root ganglion neurons, thereby affecting the pain perception threshold. Although they did not evaluate IANB success, their findings regarding the rs6795970 SNP were consistent with the present results. Karataş et al. (23) assessed the correlation between pain and the frequency of the rs6795970 A allele as well as the T alleles of the rs6801957 polymorphism, and reported a higher frequency of successful anesthesia in patients carrying these alleles. In the present study, comparison of alleles between genders demonstrated greater success for the T allele of the rs6801957 polymorphism and the A allele of the rs6795970 polymorphism. The rs6795970 polymorphism induces a nonsynonymous amino acid substitution within the intracellular loop of Nav1.8 (26). However, the rs6801957 SNP is located within an intronic region, and introns are not involved in the protein-coding sequence (except for alterations at splice sites) (27). Conversely, noncoding intronic sequences are gene regulatory regions that influence gene expression. A recent study confirmed that various intronic sequences can affect gene expression through alterations in splice sites or regulatory mechanisms, thereby playing a role in disease pathogenesis (28). One possible explanation for the present results is that certain genotypes of the rs6801957 and rs6795970 polymorphisms are likely involved in gene expression and alterations in pain perception (29). Evidence indicates that specific receptors at peripheral nerves are activated in response to noxious stimuli and electrical shock. Therefore, it may be hypothesized that differential gene expression profiles and amino acid alterations in peripheral nerve terminals contribute to interindividual variability in pain perception (30).

Among the limitations of this study were anatomical variations among patients, the subjective nature of pain, the limited sample size, and the evaluation of only two polymorphisms. Future studies investigating a larger number of SCN10A gene SNPs with a larger sample size are recommended. Furthermore, SNPs of other genes involved in pain perception should also be evaluated.

In conclusion, this study demonstrated that genetic polymorphisms in the SCN10A gene, particularly rs6795970, influence the success of inferior alveolar nerve block (IANB) in patients with symptomatic irreversible pulpitis. Patients with the AG and AA genotypes of the rs6795970 polymorphism are more likely to experience IANB failure, whereas those with the GG genotype have a lower risk of failure. Furthermore, men experience a higher rate of IANB failure compared to women. These findings highlight the role of genetic factors in pain perception and anesthetic efficacy, and indicate that further research investigating a broader range of single nucleotide polymorphisms (SNPs) and larger sample sizes is essential to better understand the genetic influences on anesthesia.

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