Original Article

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Assessment of the effect of premedication on the success of inferior alveolar nerve block in tobacco chewing patients with symptomatic irreversible pulpitis: a randomized control trial

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Background: This study aimed to evaluate and compare the efficacy of oral premedication with ibuprofen on the anesthetic efficacy of inferior alveolar nerve block (IANB) using 2% lignocaine and 1:100000 epinephrine in tobacco-chewing (TC) and non-tobacco-chewing (NTC) patients with symptomatic irreversible pulpitis (SIP) during nonsurgical endodontic intervention (NEI).

Methods: This multicenter, prospective, double-blind, two-arm parallel-group randomized controlled trial involving 160 patients was conducted for a period of 9 months. The patients were classified into the study (TC patients) and control (NTC patients) groups, which were subdivided into two subgroups 1 hour before the procedure based on oral premedication with tab ibuprofen 600 mg. Nicotine dependence was assessed using the Modified Fagerstrom Tolerance Nicotine Scale. Patients were administered an IANB injection of 2% lignocaine containing epinephrine 1:100000 after premedication. Pulpal anesthesia before NEI was confirmed using electric pulp testing and cold spraying. Patients rated their pain on the 10-point visual analog scale (VAS) during NEI thrice at the dentin, pulp, and instrumentation levels. No pain at each level indicated the success of anesthesia.

Results: The success and failure rates did not differ between the premedication and non-premedication subgroups in the TC or NTC groups ($P > 0.05$). However, the success rate was higher in the premedication subgroup of the NTC group (52.5%) than in the TC group (45%). Most patients with premedication experienced failure at the instrumentation level, whereas patients in the non-premedication group experienced pain at the dentin level. Failure rates of IANB did not differ significantly at different levels between the groups ($P > 0.05$). The mean VAS scores differed significantly at the dentin level in both groups, with lower values in the premedication group ($P < 0.05$).

Conclusions: The efficacy of ibuprofen premedication with IANB during NEI did not differ significantly between the TC and NTC patients with SIP. The effect of premedication was more significant in the NTC group than in the TC group. A causal relationship between nicotine consumption and the success of premedication could not be established, and further studies are required to validate the results of the present study.

Keywords: Anesthetic Efficacy; Inferior Alveolar Nerve; Irreversible Pulpitis; Nerve Block; Pain; Root Canal Therapy.

INTRODUCTION

Painless endodontic therapy is the primary objective of endodontists and general dental practitioners [1]. However, achieving adequate anesthesia for the mandibular molars with symptomatic irreversible pulpitis (SIP) is challenging [2]. Although inferior alveolar nerve block

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(IANB) is the most common local anesthetic (LA) technique used to anesthetize mandibular molars that require endodontic treatment, it has a higher failure rate of 40–80% in SIP [2-4]. Numerous factors can be attributed to the frequent failure of IANB in SIP. However, the most compelling reason could be the sensitization of nociceptors by inflammatory mediators, such as prostaglandin (PGE2). PGE2 molecules, formed during the arachidonic acid metabolism, are abundant in the inflamed pulp and are implicated as a primary source of pain [5].

Premedication with nonsteroidal anti-inflammatory drugs (NSAIDs) is used to enhance the success rate of IANB in SIP [6,7]. Ibuprofen, a nonselective/selective cyclooxygenase (COX) pathway inhibitor with immense analgesic and anti-inflammatory activities, inhibits the COX enzyme and prevents the breakdown of arachidonic acid to inflammatory mediators such as PGE2. Various randomized controlled trials have shown that premedication with ibuprofen can significantly increase the success rates of IANB in SIP [6,8,9].

Previous studies have primarily focused on evaluating the efficacy of IANB with premedicated ibuprofen in the general population, with little focus on patient demographic variations and altered habit histories, such as nicotine dependence. Currently, 28.6% of the population aged ≥ 15 years in India uses tobacco in any form, of which 21.4% and 10.7% individuals use smokeless and smokable tobacco, respectively [10]. The mechanism of action of LA and nicotine is paradoxical. Notably, lidocaine closes the sodium channels and prevents their entry, whereas nicotine opens the sodium channels [3,11]. Recent studies have strongly highlighted the upregulation of the COX 2 enzyme and the associated increase in PGE2 production using nicotine [12,13].

Al-Noori et al. [14] conducted a case-control study and reported that simple tooth extraction in smokers required more LA. Notably, studies on the effect of nicotine on the effectiveness of IANB in SIP remain limited. Therefore, this study aimed to evaluate and compare the efficacy of oral premedication with ibuprofen on the anesthetic efficacy of IANB with 2% lignocaine with 1:100000 epinephrine in tobacco-chewing (TC) and non-tobacco-chewing (NTC) patients with SIP during nonsurgical endodontic intervention (NEI) at the dentin, pulp, and instrumentation levels. The null hypothesis was tested to determine whether premedication had a similar effect on the success of IANB in the TC and NTC groups.

METHODS

1. Study design and ethical considerations

This multicenter, prospective, double-blind, two-arm parallel-group randomized controlled trial was conducted for a period of 9 months from August 2023 to March 2024 at the Department of Dentistry in two government medical colleges in Uttar Pradesh, India. A consecutive sampling technique was used to recruit participants. The participants were allocated to two groups in a 1:1 ratio based on a computer-generated block randomization. The allocations were concealed using sequentially numbered, opaque, sealed envelopes. One investigator generated the allocation sequence for the enrolled participants and assigned the intervention. All study procedures were performed by trained and calibrated investigators.

In total, 160 patients were enrolled in this study. The findings of a previous study were used to estimate the sample size [7], in which the success rates in the ibuprofen and placebo groups were 72% and 36%, respectively. A sample size of 40 per group was estimated considering an alpha error of 5% and power of 90%.

Ethical clearance was obtained from the institutional ethics committees of both institutions. The trial was registered with the Clinical Trial Registry of India (REF/2023/05/068043). The participants were provided complete information about the study, and a patient information sheet in English and Hindi was provided. Written informed consent was obtained from all participants. This trial was conducted in accordance with the ethics code of the World Medical Association (Declaration of Helsinki).

2. Data collection

A structured and pre-validated questionnaire was used to collect data on sociodemographic characteristics (age and sex), oral hygiene practices, relevant medical and dental history, and tobacco use patterns. The Modified Fagerstrom Tolerance Nicotine Scale (FTNDS-smokeless), with a rating of 1 to 10, was used to assess tobacco dependence, wherein a score exceeding 3 or 4 indicates a low to moderate degree of dependence on tobacco [15]. A 10-point visual analog scale (VAS) was used to ascertain pain level, wherein 0 indicates no pain, 0–3 indicates mild pain, 4–6 indicates moderate pain, 7–9 indicates severe pain, and 10 indicates the most imaginable pain [16]. Participants indicated the level at which they believed their pain was most accurately represented on the scale. Success was defined as no pain or weak/mild pain during endodontic access preparation/instrumentation, whereas moderate or severe pain was defined as failure.

3. Study participants

ASA class 1 patients aged 18–69 years with moderate-to-severe symptoms of SIP in the mandibular first molar were selected for this trial. After discontinuing thes endo-ice-cold spray stimuli, all selected patients showed prolonged responses to cold tests. Radiographically, the roots without periapical radiolucency or periodontal ligament space alterations were included. Patients on bet a-blockers, opioids, or any NSAIDs preoperatively; pregnant or nursing mothers; and those with known allergies to LA or any of its constituents were excluded from the trial.

4. Intervention groups

Group I: TC patients with SIP

- Subgroup IA: Oral premedication (tab ibuprofen 600 mg) 1 h before IANB
- Sub-group IB: Without oral premedication before IANB

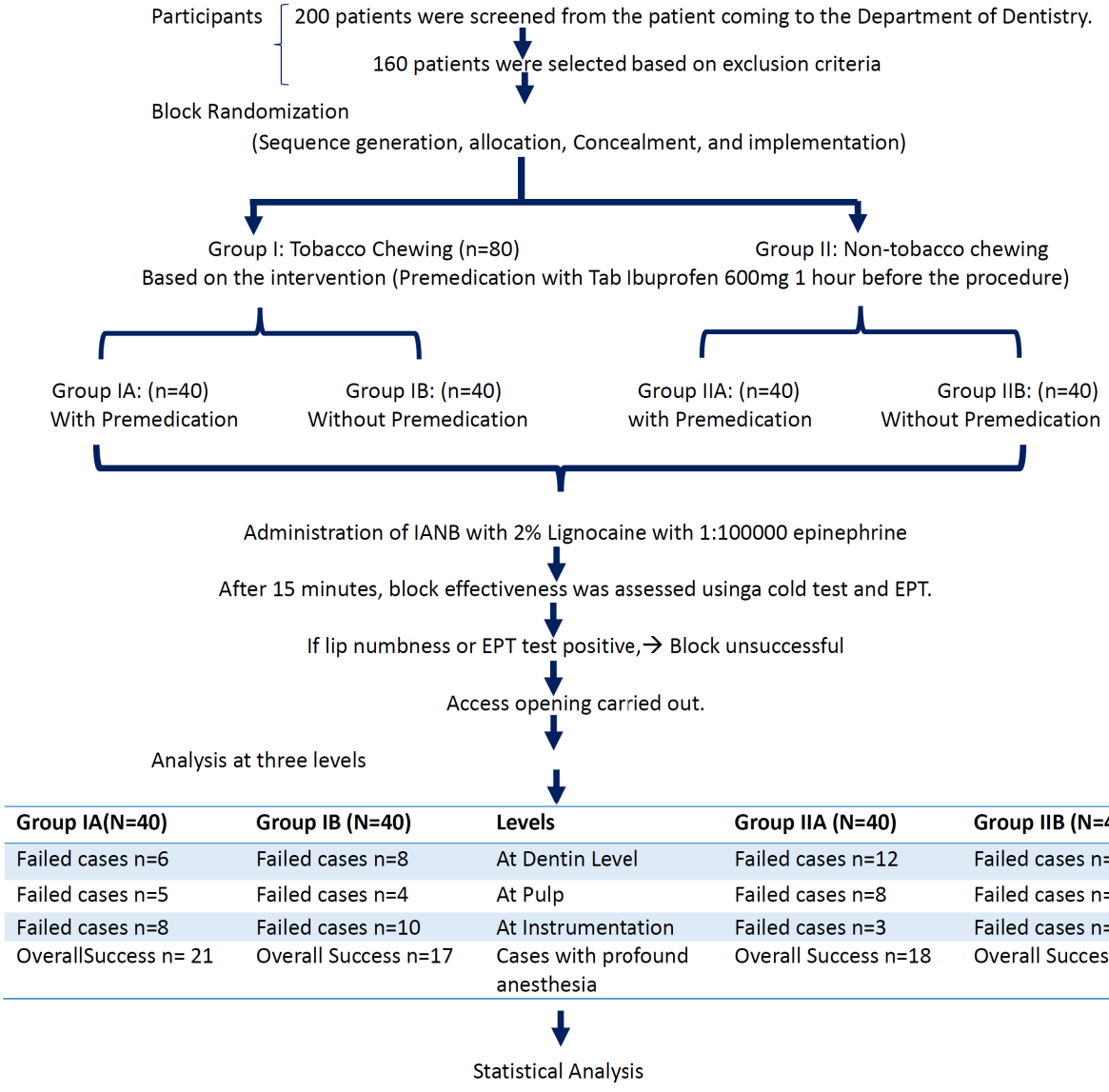
Group II: NTC patients with SIP

- Subgroup IIA: Oral premedication (tab ibuprofen 600 mg) 1 h before IANB
- Sub-group IIB: Without oral premedication before IANB

5. Treatment protocol

Preoperative radiographs of the involved teeth were recorded, and the pain level was ascertained using a 10-point VAS scale. In the subgroups IA and IIA, the patients were administered an oral dose of tab ibuprofen 600 mg 1 hour before starting the treatment. Subsequently, all patients received an IANB injection of 2% lignocaine containing epinephrine 1:100000 via the conventional IANB technique. The solution was deposited using a self-aspirating syringe. The participants were asked to report the onset of lip numbness after 15 min. Electric pulp testing (EPT Digitest, Parkell Inc., NY, USA) and cold spraying were performed on teeth that required endodontic treatment. The test was recorded as a failure in cases of a positive response to cold-spraying. Two consecutive negative EPT readings were taken to confirm pulpal anesthesia. Any IANB without the onset of lip numbness after 15 min was considered an anesthesia failure, and the participant was excluded from the trial.

Rubber dam isolation was performed in patients with successful anesthesia, and primary investigators prepared an access cavity using a 014 round carbide and Endo Z burs (Dentsply Sirona International, York, PA). The investigators, who were blinded to the premedication, performed IANB and evaluated the treatment success. Patients were asked to rate their pain on a 10-point VAS scale during NEI three times at the dentin, pulp, and instrumentation levels. Patients who reported more than mild pain on the VAS scale were excluded from further analysis, recording it as failure at a particular level. However, these patients were managed using intra-ligamentary and intrapulpal anesthesia as supplementary techniques before continuing treatment at our institution. The detailed methodology is presented in Fig. 1.



Group IA(N=40)	Group IB (N=40)	Levels	Group IIA (N=40)	Group IIB (N=40)
Failed cases n=6	Failed cases n=8	At Dentin Level	Failed cases n=12	Failed cases n=15
Failed cases n=5	Failed cases n=4	At Pulp	Failed cases n=8	Failed cases n=7
Failed cases n=8	Failed cases n=10	At Instrumentation	Failed cases n=3	Failed cases n=5
OverallSuccess n= 21	Overall Success n=17	Cases with profound anesthesia	Overall Success n=18	Overall Success n=13

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram for the study

6. Outcome measures

Successful anesthesia was clinically confirmed and defined as the absence of pain/mild pain during endodontic access or instrumentation.

7. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0. (IBM Corp., Armonk, NY, USA). Values obtained from the clinical evaluation were tabulated and subjected to statistical analyses. Results of the continuous measurement were presented as the mean ± SD and categorical measurements as frequencies and percentages. Mann–Whitney U test was employed for intragroup and intergroup comparisons for constant variables, and chi-square or Fisher's exact test was employed for categorical variables. Statistical significance was set at a two-tailed $P < 0.05$.

RESULTS

In total, 160 patients were enrolled in this study. No

Table 1. Baseline characteristics of the participants

IANB	Tobacco users		P value	Non-tobacco users		P value
	With premedication	Without premedication		With premedication	Without premedication	
Age (mean ± SD)	30.20 ± 5.69	31.23 ± 4.79	0.387	30.60 ± 5.26	32.43 ± 5.06	0.118
Gender M/F N(%)	20(50)/20(50)	20(50)/20(50)	1.00	20(50)/20(50)	20(50)/20(50)	1.00
Pre-operative VAS score (mean ± SD)	7.87 ± 1.22	8.37 ± 1.10	0.060	8.27 ± 1.06	8.30 ± 1.16	0.763
Modified fagerstorm score (mean ± SD)	8.50 ± 1.06	8.10 ± 1.12	0.107	-	-	-

F, female; IANB, inferior alveolar nerve block; M, male; N, number; SD, standard deviation; VAS, visual analogue scale.

Table 2. Comparison of IANB success or failure rate and VAS scores among the tobacco and non-tobacco users

IANB	Non-Tobacco users		P value	Tobacco users		P value
	With premedication N(%)	Without premedication N(%)		With premedication N(%)	Without premedication N(%)	
Success	21 (52.5)	17 (42.5)	0.370	18 (45)	13 (32.5)	0.251
Failure	19 (47.5)	23 (57.5)		22 (55)	27 (67.5)	
At dentin	6 (15)	12 (30)	0.098	8 (20)	15 (37.5)	0.125
At pulp	5 (12.5)	8 (20)		4 (10)	7 (17.5)	
At instrumentation	8 (20)	3 (7.5)		10 (25)	5 (12.5)	
VAS score (mean ± SD)						
At dentin	2.05 ± 1.28	2.92 ± 1.34	0.006*	1.75 ± 1.58	2.75 ± 1.56	0.005*
At pulp	2.52 ± 1.11	3.11 ± 1.37	0.092	2.15 ± 1.37	3.16 ± 2.07	0.057
At instrumentation	3.14 ± 1.27	3.25 ± 1.06	0.723	2.93 ± 1.19	3.38 ± 1.61	0.581

*statistically significant ($P < 0.05$)
IANB, inferior alveolar nerve block; N, number; SD, standard deviation; VAS, visual analogue scale.

Table 3. Comparison of IANB success or failure rate and VAS scores within the premedication and non-premedication groups

The failure rate of IANB	With premedication		P value	Without premedication		P value
	Non-Tobacco users N(%)	Tobacco users N(%)		Non-Tobacco users N(%)	Tobacco users N(%)	
Success	21 (52.5)	18 (45)	0.502	17 (42.5)	13 (32.5)	0.356
Failure	19 (47.5)	22 (55)		23 (57.5)	27 (67.5)	
At dentin	6 (15)	8 (20)	0.817	12 (30)	15 (37.5)	0.748
At pulp	5 (12.5)	4 (10)		8 (20)	7 (17.5)	
At instrumentation	8 (20)	10 (25)		3 (7.5)	5 (12.5)	
VAS score (mean ± SD)						
At dentin	2.05 ± 1.28	1.75 ± 1.58	0.214	2.92 ± 1.34	2.75 ± 1.56	0.749
At pulp	2.52 ± 1.11	2.15 ± 1.37	0.209	3.11 ± 1.37	3.16 ± 2.07	0.904
At instrumentation	3.14 ± 1.27	2.93 ± 1.19	0.724	3.25 ± 1.06	3.38 ± 1.61	0.925

IANB, inferior alveolar nerve block; N, number; SD, standard deviation; VAS, visual analogue scale.

significant differences were observed for the age, sex, or preoperative VAS scores between and within the groups. The modified Fagerstorm scores were high and homogeneous among tobacco users in both subgroups (Table 1).

The success and failure rates did not differ between the TC and NTC groups ($P > 0.05$). However, the success rate was higher in the NTC (52.5%) and TC (45%) premedication subgroups. Most patients in the premedication subgroup experienced failure at the instrumentation level, whereas those without premedication experienced pain at the dentin level only. Comparison of the failure rates of IANB at different levels did not differ between intragroup and intergroup ($P > 0.05$). The mean VAS scores differed significantly only at the dentin level in both groups, with lower values in the premedication subgroup (Table 2).

Table 3 presents the comparison between the IANB success or failure rates and VAS scores between the premedication and non-premedication groups. No significant differences were observed in the overall

success or failure rates of IANB at different levels or VAS scores ($P > 0.05$).

DISCUSSION

Successful pain management of SIP-affected molars requires a comprehensive approach considering the unique challenges posed by inflamed pulp tissues [17-19]. Tailoring treatment strategies based on individual patient factors and employing advanced techniques can significantly improve outcomes and patient comfort [1,4,20]. In TC patients, the nicotine in tobacco selectively binds to ‘‘nicotinic cholinergic receptors, facilitating the entry of cations such as sodium and calcium, which may interrupt the activity of sodium channels [3]. Therefore, the success rate can be increased using various supplemental techniques, such as oral premedication with NSAIDs. Notably, the multicenter approach used in this study increases the generalizability of the findings, and conducting a double-blind, randomized controlled trial helps minimize bias and improves the reliability of the results. Moreover, analyzing two parallel groups allowed a direct comparison between the premedication and control groups, providing a clearer understanding of the effect of NSAID premedication on the success of IANB.

Premedication with ibuprofen did not significantly increase the success rate of IANB in either TC or NTC groups. However, a general trend of increased success rates with premedication in both groups was observed, although the difference was not significant ($P < 0.001$). Additionally, baseline characteristics such as age, sex, and preoperative VAS scores did not differ significantly between the groups, suggesting that these factors did not affect the outcomes. Moreover, the mean preoperative pain assessed using the VAS score indicated severe pain associated with irreversible pulpitis in both groups.

A recent umbrella review stated that premedication with NSAIDs acts through COX pathways and blocks the synthesis of specific prostaglandins (PG) that complicate the mechanism of action of anesthesia, improving its success rate [21]. Notably, administering ibuprofen, if not contraindicated, at a dose of >400 mg 1 h before LA injection is an effective method for achieving deep anesthesia in teeth with SIP [8,22]. Similarly, Nagendrababu et al. [6] suggested that a single dose of ibuprofen (> 400 mg) increases the success rate of IANB. In recent randomized controlled trials, Elnaghy et al. [23] and Bidar et al. [24] reported that the success rate of IANB increases with ibuprofen premedication and the success rates were 58% and 3.1% in SIP in these studies, respectively. Notably, 65.21% of the success rate has also been reported using a combination of ibuprofen with 0.5 mg of dexamethasone or ketorolac [25].

In this study, the success rates of IANB in the NTC group with or without premedication were 52.5% and 42.5%, respectively (Table 3), which is concordant with those reported by Oleson et al. [26] and Aggarwal et al. [27], who also reported an improvement in the success rate with a statistically non-significant difference. Moreover, Parirokh et al. [9] reported that premedication with ibuprofen significantly increased the success rate to 78% compared to that with placebo, and similar findings were also reported by Modaresi et al. [8]. The differences in the results in the previous studies may be attributed to the different evaluation methods of the success rate based on the EPT 15 min after IANB. Notably, some studies included patients with prolonged pain responses in cold pulp tests [7-9].

In the present study, 45% and 32.5% success rates were observed in the TC group with and without premedication, respectively, which were lower than those in the NTC groups with and without premedication (Table 3). This could be attributed to the nicotine found in tobacco, which alters the function of voltage-gated channels and promotes nerve depolarization [3,11,28]. In recent studies by Ho et al. [12] and Zhou et al. [13], the upregulation of the COX 2 enzyme and increased production of PG were strongly associated with nicotine [12,13]. In contrast, NSAIDs inhibit the COX pathway, thereby reducing the breakdown of arachidonic acid and the subsequent release

of PGs. NSAIDs alleviate inflammation and reduce sensitization to nociceptors by inhibiting PG production, ultimately decreasing pain perception [26,29]. This approach targets both the inflammatory components of pulpitis and the potential effects of nicotine on nerve function, thereby offering a comprehensive strategy for pain management in these patients.

In the present study, the intragroup comparison between the TC and NTC groups did not exhibit statistically significant differences in the premedication and non-premedication subgroups. However, a general trend of higher failure in both subgroups of the TC group was observed. This finding was consistent with the findings of a case-control study on chronic smokers by Al-Noori et al. [14]. Notably, a higher volume of LA is required to achieve anesthesia in patients using tobacco [14].

In the present study, an intergroup comparison between two groups revealed a statistically significant failure only at the dentin level. With premedication, a general trend of less pain and a lower VAS score was observed in the NTC group than in the TC group, which is consistent with the findings of Miller et al. [30], who reported decreased tolerance to pain among the chronic nicotine users. However, they evaluated the effect of nicotine on the pharmacokinetics of the anesthetic in smokeless tobacco users.

A few meta-analyses have assessed the effect of NSAID premedication on the anesthetic success of IANB [31-35]. Notably, previous studies have indicated multiple mechanisms through which LA action is decreased in acute inflammatory conditions. Moreover, nicotine can further interrupt LA activity in tobacco users. Hence, evaluating the effect of premedication on the TC population with SIP is crucial.

To the best of our knowledge, few studies have examined the effects of tobacco or nicotine on the effectiveness of IANB in SIP. Therefore, this study holds significant value for filling this gap. Although not statistically significant, the findings of this study provide valuable insights into the potential effects of NSAID premedication on the success of IANB in TC patients with SIP. Our findings may help improve pain management strategies for this patient population.

The effectiveness of ibuprofen premedication with IANB did not differ significantly between the two groups. However, its effect was more pronounced in the NTC group than in the TC group. Notably, nicotine dependence may diminish the efficacy of premedication or IANB. However, a causal relationship could not be established in this study, and further studies are required to confirm the findings of the present study.

Further research involving biochemical analyses is needed to explore any potential association between nicotine and local anesthesia. Additionally, more extensive randomized clinical trials with larger sample sizes are necessary to confirm the aforementioned findings, establishing the potential benefits of the findings of this study in dental practice.

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