Effect of Nitrous Oxide on Pulpal Anesthesia: A Preliminary Study

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To compare the success of perceived pulpal anesthesia between groups using nitrous oxide/oxygen (N₂O/O₂) and oxygen (O₂) in children premedicated with ibuprofen with symptomatic irreversible pulpitis permanent teeth. Thirty-three children (mean age 10.4 ± 1.9 years) with 33 symptomatic irreversible pulpitis permanent teeth were included in this preliminary study. All children were premedicated with ibuprofen and randomly assigned to receive either N₂O/O₂ (17 participants) or O₂ (16 participants). Four percent articaine with epinephrine 1:100,000 was administered, and vital pulp therapy was performed. Children used the Wong-Baker FACES Pain Rating Scale (WBFPS) to report their pain at baseline as well as during carious dentin removal, pulpal exposure, and pulpal tissue removal steps. The success was determined when the reported WBFPS score was ≤ 4 . The chi-square test was used to compare the success between both groups. The success of pulpal anesthesia was 71% (12/17) and 19% (3/16) in the N₂O/O₂ and O₂ groups, respectively. The success in the N₂O/O₂ group was 52% higher than that in the O₂ group (confidence interval = 22.9% to 80.7%; significant difference $p = .003$). From the result of this preliminary study, N₂O/O₂ significantly increased the success of perceived pulpal anesthesia in children premedicated with ibuprofen with symptomatic irreversible pulpitis permanent teeth. However, further study with a larger sample is required to confirm this result.

Key Words: Pulpal anesthesia; Symptomatic irreversible pulpitis; Nitrous oxide; Ibuprofen.

Achieving profound pulpal anesthesia in permanent teeth diagnosed with irreversible pulpitis has always been problematic, with the limited success ranging between 60 and 80% with maxillary infiltration^{1,2} to between 13 and 65% with inferior alveolar nerve block.^{3–6} Researchers have been continuously searching for adjunctive therapies, such as supplementary injection, preemptive analgesia, and sedation, to improve the success of perceived pulpal anesthesia in these teeth. Ibuprofen, a nonsteroidal anti-inflammatory drug, has previously been shown to provide a success rate of pulpal anesthesia from 27 to 78%.^{5–13} Nitrous oxide/oxygen (N₂O/O₂) inhalation sedation, in one

study, significantly enhanced the success of perceived pulpal anesthesia in teeth with symptomatic irreversible pulpitis up to 50%.¹⁴ However, these studies have clearly shown that the use of either ibuprofen or N₂O/O₂ alone was insufficient to provide complete pulpal anesthesia in teeth with symptomatic irreversible pulpitis. Moreover, all previous studies have evaluated pulpal anesthesia only in patients who were at least 18 years of age,^{5–14} and there are limited studies on pulpal anesthesia in younger patients.

In pediatric patients, preventing pain by administering preemptive analgesia and/or sedation should be greatly beneficial because inadequate pain control, especially in this group of patients, could lead to a failure in behavior management, a negative experience for the patient, and a poor treatment outcome. Moreover, fear and anxiety may also be major factors that cause the failure of pulpal anesthesia in this group of patients. In addition, young permanent teeth have a larger pulp that possesses a more extensive blood and nerve supply than do older teeth^{15,16}; these specific

Received April 17, 2017; accepted for publication August 13, 2017.

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Anesth Prog 65:156–161 2018 | DOI 10.2344/anpr-65-02-08
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characteristics of the young pulp may, consequently, lead to more response to noxious stimuli. To achieve the greatest possible success of pulpal anesthesia in pediatric patients, the combination of methods previously reported in adults is therefore worth investigating. Ibuprofen is one of the most common drugs used to reduce pain and inflammation in pediatric patients with minimal side effects. N₂O/O₂ has also been commonly used in children with mild to moderate anxiety levels. Besides its anxiolytic properties, N₂O also has an analgesic effect and has been recommended for patients in whom profound local anesthesia cannot be obtained.¹⁷

At present, there is no clinical study on the combination of preemptive ibuprofen and N₂O/O₂ inhalation sedation in pediatric patients with symptomatic irreversible pulpitis permanent teeth. Therefore, the aim of this preliminary study was to compare the success rates of pulpal anesthesia between using N₂O/O₂ and O₂ in patients younger than 18 years who had symptomatic irreversible pulpitis permanent teeth and were premedicated with ibuprofen.

METHODS

This single-blind randomized clinical trial was approved by the Human Experimentation Committee of the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand. Children and their legal guardians were informed about the study procedure. The legal guardians were asked to sign the informed consent on behalf of the eligible participants if both agreed to participate in the study.

Study Population

The participants were recruited from pediatric patients attending the Pediatric Dentistry Clinic, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand, during September 2014 to June 2015. The inclusion criteria included American Society of Anesthesiologists class I and II patients aged 6 to 18 years for whom there was no contraindication to ibuprofen or N₂O/O₂ sedation. Patients had a deep carious lesion in a permanent molar with a diagnosis of symptomatic irreversible pulpitis, judged by the patient's having pain on the day of treatment and prolonged pain response to cold test with Green Endo-Ice (Coltene Whaledent, Cuyahoga Falls, Ohio) even after the cold stimulus had been removed. The periapical radiographs showed extension of the dental caries having penetrated three-fourths or more of the entire dentin thickness without

any prominent periapical pathosis. Condensing osteitis and/or widened periodontal ligament space was not considered as an excluding criterion in this study. If the patient had more than 1 tooth that met the inclusion criteria, only the first treated tooth as requested by the patient was included in the study. Other teeth also received the treatment but were not included in the study.

Sample Size Calculation

Sample size was calculated for a superiority trial. In a previous study, the success of pulpal anesthesia with ibuprofen was 27%.⁸ In this trial, in view of the findings of Stanley et al,¹⁴ we expected 22% greater success in the N₂O/O₂ group than in the O₂ group. To detect a significant difference of success between both groups, 73 participants in each group would be required for a trial with a 5% type I error and 90% precision. However, we were able to include only 16 and 17 samples for each group; therefore, we intended to primarily report a preliminary result of this study.

Study Procedure

One unblinded postgraduate student in pediatric dentistry performed all procedures. The initial preoperative subjective pain was evaluated using the Wong-Baker FACES Pain Rating Scale (WBFPS). The WBFPS is a 6-face pictures scale with fixed scores from 0 to 10, ranging from *does not hurt* to *hurts the worst*.¹⁸ This scale is preferred by both children and health care providers because it is quick and easy to use.^{19,20} Then, all patients received 10 mg/kg (maximum of 600 mg per dose) of ibuprofen syrup (Bunofen; The Government Pharmaceutical Organization, Bangkok, Thailand) immediately after a meal, 1 hour before a treatment procedure. Immediately before the beginning of the procedure, the operator evaluated the preoperative fear and anxiety level of the participants using the Facial Image Scale (FIS). The FIS consists of pictures of 5 different facial expressions ranging from very happy to very unhappy. This scale is easy for children to understand and rate their anxiety level through pictures with fixed numbers, and it takes only a short time interval for assessment.²¹ Then, all patients were divided into 4 strata by a combination of FIS (1–3 in one group and 4–5 in a second group) and tooth type (maxillary or mandibular) and then further randomly assigned into 2 treatment groups (N₂O/O₂ or O₂) using a block randomization. A computing program²² was used to

generate the randomized table with a block size of 4. Both groups of patients were blinded to the treatment they received. Vital signs, including pulse rate and oxygen saturation, were recorded before and during the procedure. A properly sized nasal hood was placed over each patient's nose at an appropriate flow rate of 100% oxygen for 5 minutes.

For the N₂O/O₂ group, the range of N₂O concentration administered was between 30 and 50%. Patients received N₂O via nasal hood by the slow titration or rapid induction method, as appropriate for each patient, until the patient reached a good stage of sedation, defined as feeling comfortable and relaxed as assessed by the operator with eyes becoming less active and having a glazed-like appearance. After 5 minutes, the operator began the treatment, and the concentration of N₂O/O₂ was maintained throughout the procedure.

For the O₂ group, the operator pretended to adjust the N₂O machine, but the patient received 100% oxygen. Similar to the N₂O/O₂ group, the operator began the treatment after 5 minutes, and 100% oxygen concentration was maintained throughout the procedure.

All patients then received an inferior alveolar nerve block with long buccal nerve block for a permanent mandibular molar or a buccal and palatal infiltration for a permanent maxillary molar, using a gauge-27 13/16-in.-long needle (Terumo Dental Needle, Terumo Corporation, Tokyo, Japan). One cartridge of 1.7 mL of 4% articaine with 1:100,000 epinephrine (Septanest SP, Septodont, Saint-Maur-des-Fasses, France) was administered. The operator tested soft-tissue numbness by asking the patient about the numbness of surrounding tissue or by probing with an explorer at the surrounding gingiva for a permanent maxillary molar or the ipsilateral cheek and lip for a permanent mandibular molar. Tissue numbness was evaluated every 5 minutes after injection. If a patient did not experience soft-tissue numbness within 5 minutes in maxillary molars and 15 minutes in mandibular molars, the patient was then excluded from the study. After soft-tissue numbness was confirmed, treatment was then started, and patients were instructed to indicate their pain level using the WBFPS during the steps of carious dentin removal, pulpal exposure, and pulpal tissue removal. Pulpal anesthesia was considered as a success if the WBFPS score was less than or equal to 4 in all steps of treatment. Pulpal anesthesia was considered as a failure if the WBFPS score was more than 4 in any step of treatment. In cases of failure, supplementary injections, such as intraligamentary and/or intrapulpal injection, were added before continuing on with treatment.

The baseline variables were compared using the chi-square test, Fisher exact test, or the 2-sample *t* test. The

data obtained were analyzed using the chi-square test with 95% confidence level to compare the success rates between both groups. The software used for these analyses was SPSS 17.0 (SPSS Science, Chicago, IL).

RESULTS

Thirty-three children with 33 teeth were included and randomly assigned to the N₂O/O₂ (17 children) and the O₂ (16 children) groups, respectively. All children reported soft-tissue anesthesia after primary injection with inferior alveolar nerve block or infiltration, resulting in no exclusion from this study. The participants consisted of 22 girls and 11 boys, aged between 8 and 16.8 years, with a mean age of 10.4 ± 1.9 years. Forty-nine percent of participants rated the initial WBFPS at 6 and 70% of participants rated the FIS scores of 1 to 3. The mandibular first permanent molar was the most studied tooth (70%), followed by the maxillary first permanent molar (30%). The baseline variables, including gender, age, initial WBFPS, FIS, and tooth type, are shown in Table 1. Baseline variables between the N₂O/O₂ and O₂ groups were not significantly different. The mean concentration of N₂O administered was $40.0 \pm 7.1\%$.

The success rates of pulpal anesthesia are shown in Table 2. The success rate was 71% in the N₂O/O₂ and 19% in the O₂ groups, respectively. The success rate in the N₂O/O₂ group was 52% higher than that in the O₂ group, with statistical significance (Confidence interval 22.9% to 80.7%; $p = .003$).

DISCUSSION

In this study, all patients were premedicated with ibuprofen; the success rate of pulpal anesthesia in the O₂ group was significantly lower than that in the N₂O/O₂ group (19% vs 71%; $p = 0.003$). Moreover, it was also much lower than that in previous studies with ibuprofen alone (27-78%).⁵⁻¹³ The reason for this lower success rate may be the younger group of patients in this study. Young patients may have more fear and anxiety that consequently decreases their pain threshold.^{23,24} However, most patients (70%) in this study reported FIS scores of 1 to 3, which indicated mild to moderate anxiety. Moreover, when compared with older pulp, young pulp is larger and has more blood supply and more innervation.^{15,16} These factors may lead to a higher degree of difficulty in achieving pulpal anesthesia. Consequently, only 1 intervention, such as premedication with ibuprofen alone, may become inadequate in managing pulpal anesthesia in this group of patients.

Table 1. Baseline Variables of the N₂O/O₂ and O₂ Groups

	Total	N ₂ O/O ₂ Group	O ₂ Group	<i>p</i> Value*
No. of patients	33	17	16	
Gender				
Female, <i>n/N</i> (%)	22/33 (67)	13/17 (76)	9/16 (56)	.218†
Male, <i>n/N</i> (%)	11/33 (33)	4/17 (24)	7/16 (44)	
Age				
Range, y	8.0–16.8	8.0–14.5	8.3–16.8	—
Mean ± SD, y	10.4 ± 1.9	10.5 ± 1.9	10.4 ± 2.0	.915‡
Initial Wong-Baker FACES				
Pain Rating Scale, <i>n/N</i> (%)				
4	9/33 (27)	3/17 (18)	6/16 (38)	.277§
6	16/33 (49)	9/17 (53)	7/16 (44)	
8	7/33 (21)	5/17 (29)	2/16 (12)	
10	1/33 (3)	0/17 (0)	1/16 (6)	
Facial Image Scale, <i>n/N</i> (%)				
1–3	23/33 (70)	12/17 (71)	11/16 (69)	1.000§
4–5	10/33 (30%)	5/17 (29)	5/16 (31)	
Tooth type, <i>n/N</i> (%)				
Maxillary first molar	10/33 (30)	4/17 (24)	6/16 (38)	.465§
Mandibular first molar	23/33 (70)	13/17 (76)	10/16 (62)	

* Significant level $p < .05$.† Values analyzed by χ^2 test.‡ Values analyzed by *t* test.

§ Values analyzed by Fisher exact test.

Ibuprofen is a nonspecific cyclooxygenase enzyme inhibitor. Cyclooxygenase-1 and cyclooxygenase-2 enzymes are important enzymes involved in the synthesis of prostaglandin, a mediator of inflammation, fever, gastroprotection, and pain. Theoretically, reducing the inflammatory mediator prostaglandin E₂ (PGE₂) in pulp would be advantageous in both decreasing pulpal nociceptor sensitization and elimination of prostanoid-induced stimulation of tetrodotoxin-resistant sodium channel activity.²⁵ However, this study and previous studies^{5–13} similarly reported insufficient pulpal anesthesia of preemptive ibuprofen. Thus, the search for other approaches for adequate pulpal anesthesia is highly recommended.

Since the mechanisms of ibuprofen and N₂O work through different targets and pathways, the authors hypothesized that the combination of both would increase the success rate of pulpal anesthesia in teeth of young patients with symptomatic irreversible pulpitis. The success of pulpal anesthesia in the N₂O/O₂ group (71%) in this study was higher than that in the previous study by Stanley et al,¹⁴ who reported a 50% success

rate of pulpal anesthesia when only N₂O/O₂ was used, without any preemptive drugs. In this study, after premedication with ibuprofen, N₂O/O₂ could provide an additional success of 52% (95% confidence interval 22.9 to 80.7%). At subanesthetic concentration, N₂O has anxiolytic and analgesic properties, both of which are highly desirable for young, anxious patients with symptomatic irreversible pulpitis teeth. The anxiolytic effect of N₂O likely involves interactions with the gamma-amino-butyric acid (GABA) receptor.²⁶ The analgesic effect of N₂O seems to involve primarily N-methyl-D-aspartate glutamate receptor antagonism.²⁷ Although the combination of ibuprofen and N₂O has shown a promising result, approximately one-third of the patients (29%) still experienced pulpal anesthetic failures during the procedure, making supplementary injections unavoidable. Therefore, other combinations should be further investigated to increase the success of pulpal anesthesia.

In this single-blind randomized clinical trial, efforts were made to meet the requirements of the CONSORT 2010 statement.²⁸ All patients were randomly allocated, which resulted in baseline variables that were equally distributed in both groups. The limitation, however, was that the operator could not be blinded to the procedure performed; nevertheless, all the patients were blinded to the treatment received, and the pain was self-reported by the patients themselves, using the WBFPS. The WBFPS can be used effectively in children, by themselves, as young as 3 years old¹⁸ and has been found to be more

Table 2. Success Rates of Pulpal Anesthesia of Each Group*

N ₂ O/O ₂ Group	O ₂ Group	RD	95% CI	<i>p</i> Value
71% (12/17)	19% (3/16)	52%	22.9% to 80.7%	.003†

* RD indicates risk difference; CI, confident interval. Significant level $p < .05$.† Values analyzed by χ^2 test.

sensitive than a visual analogue scale.²⁹ At the beginning of this study, the most rated WBFPS was 6 (*hurts even more*; 49%), and all patients rated initial WBFPS between 4 (*hurts a little more*) and 10 (*hurts the worst*), which corresponded with the diagnosis of symptomatic irreversible pulpitis. Another limitation of this study lies in its sample size. We were able to include a lower number of patients than the number we estimated. For this reason, we reported our results as a preliminary study. However, in this study, we observed 52% of difference of the additional effect. With 16 and 17 samples in each group, this study seems to have adequate power to detect the difference of success of at least 35% or more. However, a larger sample size should be considered in further studies.

CONCLUSIONS

Based on the findings of this preliminary study, the following conclusions can be made:

1. The success rate of pulpal anesthesia after inferior alveolar nerve block as a primary injection is quite low in permanent teeth with symptomatic irreversible pulpitis of pediatric patients premedicated with ibuprofen.
2. N₂O/O₂ inhalation sedation can increase the success rate of pulpal anesthesia in permanent teeth with symptomatic irreversible pulpitis of pediatric patients premedicated with ibuprofen. However, a further study with a larger sample is required.

ACKNOWLEDGMENTS

This research was supported by the Research Fund for Postgraduate Student from the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand. The authors also wish to thank Dr M. Kevin O. Carroll, Professor Emeritus of the School of Dentistry, University of Mississippi, Jackson, and faculty consultant with the Faculty of Dentistry, Chiang Mai University, for his assistance in the preparation of the article.

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