Effectiveness and Safety of Nitrous Oxide as a Sedative Agent at 60% and 70% Compared to 50% Concentration in Pediatric Dentistry Setting

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***Objective**: Sedation using 50% nitrous oxide (N_2O) concentration is common in pediatric dentistry.*

The aim to assess sedation and cooperation levels following sedation with 60% and 70% N_2O concentrations in children whose dental treatment failed using 50% N_2O concentration.

***Study design**: Children (n=51) aged 5-10 years were included. Sedation started with N_2O concentration of 50%; when appropriate cooperation and sedation were not achieved, N_2O concentration was increased to 60%, and subsequently to 70% during the same session. Sedation and cooperation levels were the primary outcomes. Adverse events were defined as secondary outcomes.*

***Results:** At 50% N_2O concentration, five children reached adequate sedation and cooperation and completed their dental treatment, where 32 children completed the treatment at 60% N_2O concentration. Fourteen children required a concentration of 70% to complete treatment. For ten of the latter, treatment was successfully completed, while for four, treatment failed, despite the achievement of adequate sedation. Adverse events were observed in 9%, 22%, of the children who received 60%, 70% N_2O concentrations, respectively. **Conclusions:** When sedation with 50% N_2O concentration does not achieve satisfactory cooperation to complete pediatric dental treatment, 60% N_2O concentration appears to be more effective than 50% and safer than 70%.*

***Keywords**: Cooperation, nitrous oxide, pediatric dentistry, sedative agent*

INTRODUCTION

The nitrous oxide/oxygen (N_2O) inhalation sedative agent is considered a safe and effective approach reducing anxiety providing analgesia, and enhancing effective communication between a patient and healthcare provider.[1] When using this agent, the drug administrator is able to rapidly increase or decrease the depth of sedation. Such control is an important feature of effectiveness and safety.[1,2] The use of N_2O at 50% concentration is very common in pediatric dentistry, it is not very potent and is generally used when the anxiety state is mild or moderate.[3] The level of cooperation achieved may be inadequate to complete the planned dental treatment. In such cases, moderate sedation with pharmacologic drugs or general anesthesia are alternatives to N_2O; however, these techniques entail certain dilemmas. While N_2O at concentrations higher than 50% may pose increased risk of adverse events, this matter is not conclusive.[4] In a cohort study of children in emergency department, Babl *et al* showed that 70% N_2O provides similar sedation depth to 50% N_2O, with no increase in adverse events.[5] Another study showed that N_2O can be safely administered up to 70% concentration by a nasal mask for short procedural sedation.[6] Few

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studies were conducted to compare the safety and efficacy of N_2O at concentrations higher than 50% in the pediatric dental setting.

Our hypothesis is that N_2O at 60% and 70% concentrations may provide better outcomes in dental setting, while maintaining the safety, under surveillance of pediatric anesthesiologist. The main aim of this study was to compare outcomes of 60% and 70% N_2O concentrations on sedation and cooperation levels in children who failed to cooperate when treated with 50% N_2O in previous session.

MATERIALS AND METHOD

Approval of the local ethical committee was attained Bnai Zion Medical Center (0092-16-BNZ).

Study was registered in the NIH clinical trials site (https://clinicaltrials.gov/) NCT02886351. Verbal and written explanations of the study were given to the children, and to their parents; and informed consent was obtained from all parents. Parents received a health questionnaire assessment to fill. Parents were instructed not to give their children anything to eat or drink during the 6 hours previously to the procedure, except for water, which was allowed up to 2 hours before the scheduled session.

Fifty-one children, with ASA I or II, aged 5-10 years who had experienced a previous unsuccessful dental session, where N_2O at 50% concentration was not sufficient to achieve cooperation dental treatment failed, were recruited. Dental treatments, included restorations that could be conducted solely with local anesthesia. Procedures that were scheduled for up to 45 minutes with at least one restoration was planned excluding extractions. The same former pediatric dentist, who carried out the previous treatments performed all sessions in the study.

Excluding criteria were children with a high potential risk for sedation; snoring, stridor, sleep apnea, maxillofacial malformation, history of airway difficulty, gastroesophageal reflux, reactive airway disease or acute runny nose, cardiac disease, altered mental status, inadequate fasting time or non-cooperative parents.

Study session, was initialized with N_2O administration at 50% for 10 minutes. If yet, cooperation was not sufficient to complete treatment concentration was increased to 60%, under the surveillance of a pediatric anesthesiologist. If, after 10 additional minutes, cooperation would still be insufficient, concentration was increased to 70%. (Fig.1.) Parents received explanation that midazolam sedation and general anesthesia are alternative approaches to achieve completion the dental treatment.

The dental clinic was equipped, with the Drager Fabius Plus XL, Anaesthesia Workstations, (Dräger Medical GmbH Moislinger Lübeck, Germany) and with standard monitoring and with defibrillator and a cardiopulmonary resuscitation chart.

Quantiflex MDM (Matrx, Orchard Park, NY, USA) machine, which delivers N_2O from 0% to 70% and includes a scavenging system to decrease environmental contamination. Monitor detecting heart rate, oxygen saturation, respiratory rate and a pre-tracheal stethoscope.

Main study outcome

Wisconsin Sedation Scale was assessed by a pediatric anesthesiologist.[7] The 6 grades of the scale were: 1= inadequate: patient is anxious, agitated, or in pain; 2= minimal: patient spontaneously awakens without stimulus; 3= moderate: patient is in a drowsy state, with eyes open or closed, but easily returns to consciousness with a verbal stimulus; 4= moderate deep: patient returns to consciousness with a moderate tactile or loud verbal stimulus; 5= deep: patient slowly returns to consciousness with a sustained painful stimulus; 6= anesthesia: patient is unresponsive to painful stimulus.

All children were evaluated by the same senior pediatric dentist, who also performed, and continuously assessed the children's cooperation using the Houpt Behavior rating scale[8]: 1= aborted: no treatment rendered; 2= poor: treatment interrupted, only partial treatment was completed, 3 = fair: treatment was interrupted but eventually completed, 4= good: difficult but all treatment was performed, 5= very good: some limited crying or movement, 6= excellent: no crying or movement.

Cooperation and sedation scores of 3 and higher, were considered positive and less considered failures. The correlation between cooperation and sedation was evaluated. Parents were present during the treatment and throughout the entire procedure.

Adverse events that were defined a priori: less than 93% oxygen saturation for less than 30 sec, the need for more oxygen concentration, oral airway insertion, bag mask ventilation, endotracheal tube and bag ventilation, as well as laryngospasm, aspiration, drowsiness, agitation, nausea and vomiting, All adverse events were recorded.

At the end of the dental treatment, the child received 100% oxygen for at least 5 minutes. Children were monitored and evaluated for discharge according to Steward Criteria for discharge. Which is based on 3 parameters: Each parameter (consciousness, airway and movement parameters) was rated from 0-2, and when a score of 6 was achieved the child was discharge home form recovery unit.[9]

Statistical evaluation

The primary outcome was defined as successful cooperation. Sample size was calculated to detect difference of 30% or more, as statistically significant in the cooperation score, level of 0.05 (power of 0.8, sample size, considering 10% unexpected exclusion or lost to follow. Fifty one children were recruited. The power analysis was performed using the G*Power version 3.0.10 freeware (Franz Faul, University of Kiel, Germany).

For the continuous demographic variables; gender, age and weight, were calculated and presented as medians- ranges, means-standard deviations.

For sedation and cooperation scores 1-5, numbers and percentages are presented of children who received 50, 60 and 70% concentrations of N_2O at 10, 20, 30 and 40 minutes. The success of the sedation was defined as a score of 3, 4 or 5 (a score of 1 or 2 was defined as a failure). Success of the cooperation was defined as a cooperation score of 3, 4 or 5 (a score of 1 or 2 was defined as a failure). Frequencies of categorical sedation and cooperation were analyzed by the Fisher-Irwin exact test (a non-parametric test for small numbers). The correlation between sedation score and cooperation score was analyzed by the Spearman's rank correlation and test. Frequencies of adverse events were compared between N_2O concentrations, using the Fisher-Irwin exact test. P value < 0.05 was considered statistical significance Data analysis was processed with SPSS software, version 14 (SPSS Inc. Chicago, IL, USA).

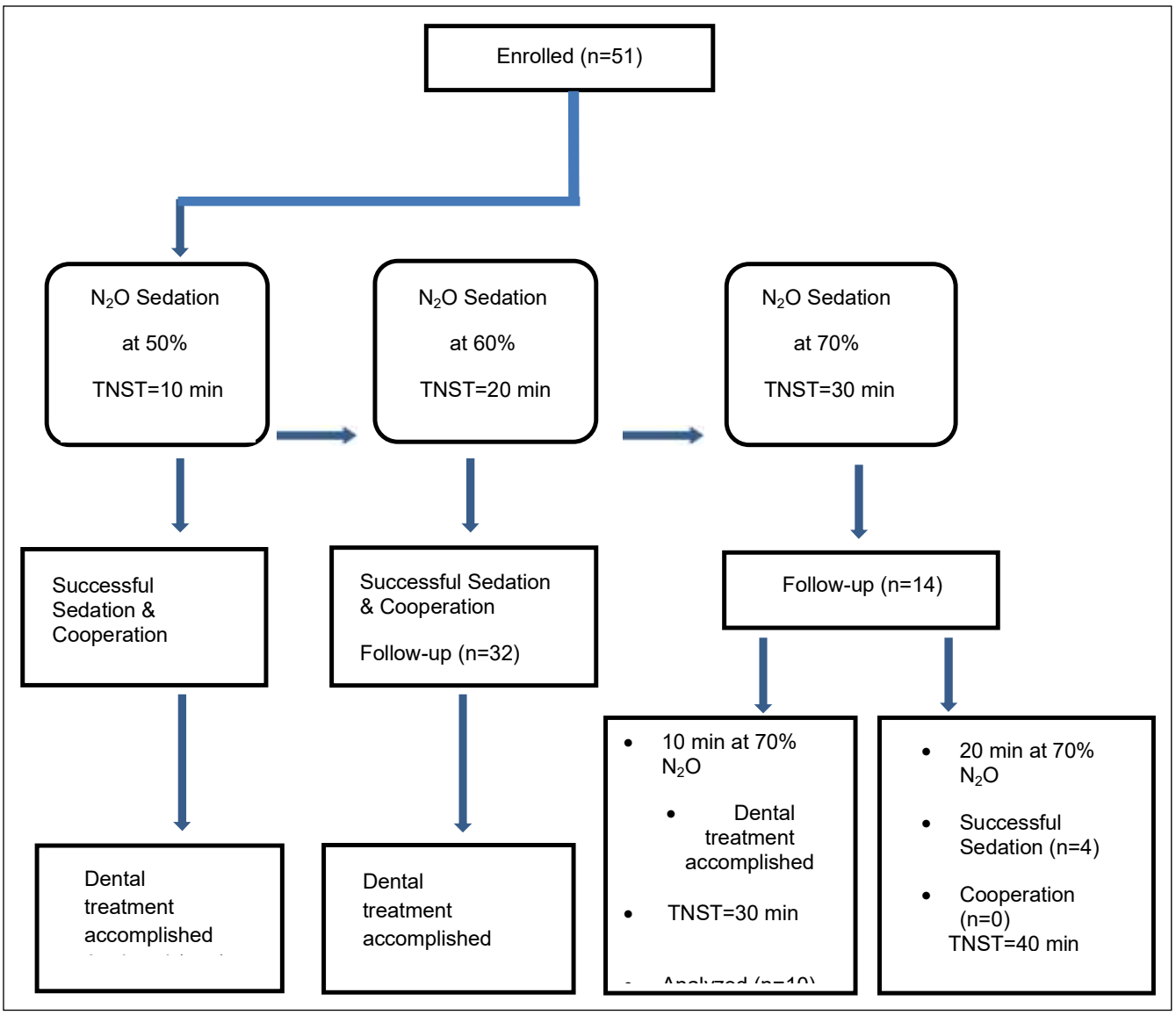

Figure 1. Study Flow Chart

RESULTS

Demographic parameters analysis, mean age was 6.7±1.7 years, mean body weight was 21.8±3.8 kg; 28 (55%) were boys.

Only 5 (10%) children reached a sedation score of 3 or 4 following administration of 50% concentration of N_2O for 10 minutes. For the remaining 46 children, the N_2O concentration was raised to 60% for an additional 10 minutes. Sedation score of 3 or 4 was achieved in 32 (70%) of these children. None of them reached deep sedation (score of 5). For the 14 children who still had sedation scores of only 1 or 2, the N_2O concentration was raised to 70% for additional 10 minutes (30 minutes total sedation time). A sedation score of 3-5 was achieved in 10 (71%) of these children. For the remaining 4 children, sedation at 70% concentration was continued for another 10 minutes (total of 40 minutes sedation time). The sedation score increased to 4. Eight of the 14 (57%) children who received N_2O up to 70% reached deep sedation (score of 5).

Sedation Score Analysis (Table 1)

Table 1. Sedation scores (failures/successes) by duration and concentration of nitrous oxide administration

Duration	10 min	20 min	30 min	40 min
N_2O Concentration %	50%	60%	70%	70%
Sedation score *				
(% successes/ % failures)	(9.8/90.2)	(69.6/30.4)	(71.4/28.6)	(100/0)

Nitrous oxide =N_2O
*Sedation score: successes =(3-5 score) failures =(1-2score)
P values by Fisher exact test< 0.001 statistically significant= §
50% vs 60% vs 70% (30min) vs 70% (40min) =0.0001; §
50% vs 60% =0.0001; §
50% vs 70% (30min) =0.0001; §
50% vs 70% (40min) =0.0001; §
60% vs 70% (30min) =1.0000;
60% vs 70% (40min) =0.0260;
70% (30min) vs 70% (40min) =0.0980

The success of sedation was significantly higher at 60% and 70% N_2O concentrations than for the 50% concentration: 70%, 71% and 10%, respectively (p=0.0001). No statistically significant difference was observed between the 60% and 70% concentrations in regard of the success of the sedation.

Cooperation Score Analysis (Table 2)

Table 2. Cooperation scores (failures/successes) by duration and concentration of nitrous oxide treatment

Duration	10 min	20 min	30 min	40 min
N2O Concentration %	50%	60%	70%	70%
*Cooperation score (% successes / % failures)	(9.8/90.2)	(71.7/28.3)	(71.4/28.6)	(71.4/28.6)

Nitrous oxide =N_2O
*Cooperation score: successes =(3-5 score) failures =(1-2score)
P values by Fisher exact test< 0.001 statistically significant= §
50% vs 60% vs 70% (30min) vs 70% (40min) =0.0001; §
50% vs 60% = 0.0001; §
50% vs 70% (30min) = 0.0001; §
50% vs 70% (40min) = 0.0001; §
60% vs 70% (30min) = 1.0000;
60% vs 70% (40min) = 1.0000;
70% (30min) vs 70% (40min) = 1.0000

Successful sedation was achieved in 5 (10%) children at 50% N_2O concentration with successful cooperation scores and completed dental treatment. The 32 children with successful sedation at 60% N_2O concentration, had successful cooperation scores and completed their dental treatment. From the 14 remaining children with successful sedation after 10 minutes with 70% N_2O concentration, 10 children achieved adequate cooperation and completed their dental treatment.

Although the 4 remaining children of the latter, who did not achieve successful cooperation following 10 additional minutes of N_2O at 70% concentration (a total of 40 minutes sedation). However, none of them was cooperative enough to complete the dental treatment and considered a failure.

Cooperation was significantly better at 60% and 70%) N_2O concentrations than at 50% concentration (p=0.0001). No statistically significant difference was observed between the 60% and 70% concentrations in regard to achieving adequate cooperation to complete the dental treatment

Correlation of Sedation and Cooperation Scores

Sedation and cooperation scores correlated at 10, 20 and 30 minutes of N_20 administration (r=0.40, p=0.0041; r=0.70, p=0.0001; r=0.46, p=0.0006, respectively), but not at 40 minutes (r-0.03, p=0.8605).

Adverse events (Table 3)

Table 3. Side effects correlated to the nitrous oxide concentration at 40 minutes

N_2O Concentration % at 40 minutes group size		50% n=5	60% n=32	70% n=14	
Adverse events					p value
Nausea	Yes (%)	0	4 (13)	2 (14)	a: 1.0000
Agitation	Yes (%)	0	0	2 (14)	a: 0.1340 c:1.0000 d: 0.0880
Drowsiness	Yes (%)	0	2 (6)	3 (21)	a: 0.2640 b: 1.0000 c: 0.5300 d: 0.1570
Desaturation<93%	Yes (%)	0	1 (3)	2 (14)	a: 0.4280 b: 1.0000 c: 1.0000 d: 0.2160
Total number of patients with an adverse event (%)		0	7 (22)	9 (64)	a:0.0070§ b: 0.5600 c: 0.0330 d: 0.0080§

Nitrous oxide =N_2O
p values are calculated by Fisher exact test, statistically significant =§
a: 50% vs 60% vs70%; b: 50% vs 60%; c: 50% vs 70%; d: 60% vs 70%;

Among the 5 children who had received only a 50% N_2O concentration, there were no adverse events. Among the 32 children who received a 60% N_2O concentration at 40 minutes, 7 (22%) had an adverse event (each had only one event). Only one of these children had desaturation <93% for less than 30 seconds; this was resolved spontaneously. Among the 14 children who received a 70% concentration of N_2O, 9 (64%) had an adverse event (each had only one event). Of them, 2 (14%) had desaturation <93% for less than 30 seconds. These desaturation episodes were resolved spontaneously. In addition, 8 of the 14 children who received N_2O at 70% concentration reached a state of deep sedation; The difference in adverse events between the 60% and 70% concentration groups was statistically significant (p=0.008). (Fig. 1.)

DISCUSSION

The present study showed that the N_2O inhalator sedative agent at concentrations of 60% and 70% achieved successful levels of sedation and adequate cooperation to enable the completion of planned dental treatment. More adverse events, including desaturation <93% for less than 30 seconds, as well as reaching a state of deep sedation, were observed at 70% more than at 60% N_2O concentration. Thus, 60% appears as the optimal concentration for effectiveness and safety of N_2O sedation use in the pediatric setting, when 50% concentration is insufficient.

Success in completing dental treatment was achieved in 70% (n=32) of children treated with 60% N_2O concentration and in 71% (n=10) of those who received 70% N_2O. In both 60% and 70% concentrations of N_2O, 91% (n=42) reached sufficient sedation and cooperation to complete successfully their dental treatment. This

finding demonstrates that even with 70% concentration, N_2O is not always sufficient to achieve children's cooperation, and that paradoxical agitation is an undesired side effect of this concentration.

Sedation scores

In this study, 83% of the children who received N_2O via a nasal mask, at high concentrations, remained in a minimally or moderately sedated state. However, only 8 (57%) of the children who received N_2O at 70% concentration went into deep sedation. Sedation is a process on a continuum; mild may shift to moderate, and may progress to deep sedation. Thus, the provider must be aware of these changes and be prepared to deal with the conditions that arise, using suitable equipment. Consequently, a senior pediatric anesthesiologist was present in all the procedures.

In contradiction with our study, in a prospective study of more than 700 children who underwent various procedures in a single pediatric emergency department, the use of 70% N_2O concentration (administered to 72% of the patients) achieved similar sedation depth as in 50% N_2O, with no increase in adverse events.[5] Also Zier *et al* reported that a considerable number of children remained minimally sedated while receiving N_2O at concentrations above 50%; N_2O was administered via a nasal hood by which the concentration was titrated from 0% to 70%.[6]

In the field of dental practice, the literature is sparse regarding the sedation level achieved when N_2O concentrations above 50% are used. Wilson et al. found that 89% of pediatric dentists used N_2O but only 2% reported using higher concentration than 50%.[10] Not all the N_2O that emerges from the delivery system reaches the lungs. Reasons for this are equipment leakage, dead space, mouth breathing, and the breathing status of the patient. Thus, when the N_2O concentration of the system is 50%, a substantially lower concentration is actually resulted; and when the concentration is set at 70%, the concentration of N_2O that actually reaches the alveoli is unlikely to exceed 30%-50%.[11] Nevertheless, 8 children in the current study achieved deep sedation at 70% N_2O concentration . This may be explained, at least in part, by the subtle differences in the definition of both moderate and deep sedation.

Cooperation scores

Cooperation was considered adequate when the child reached a Houpt[8] score of 3-5 and the dental treatment plan was accomplished. Only in 4 of 51 children the dental treatment was not completed even at a concentration of 70% N_2O after at 40 minutes of administration of the sedative agent. This was because these four children were very agitated, despite a sedation score of more than 2. Since the effectiveness of N_2O is largely dependent on psychological reassurance, the psychological status of the child at the beginning of the treatment is very important. This may explain the success with 50% N_2O among children who we failed to terminate the treatments in the previous session. Therefore, it is recommended always starting with 50% N_2O concentration, and only if, cooperation is not adequate for psychological reassurance, to consider increasing to 60% and later to 70% concentrations.[12]

In a large survey, in which the use of N_2O for pediatric dental treatment did not exceed 50%, 86% of the treatments were completed.[13] The success rate in that study is comparable to the results in our study; however, there, the proportion of dental restorations was fewer and the duration of the procedures shorter.[13]

Adverse events

No adverse effects occurred at 50% N_2O concentration, at 60% N_2O concentration, in 22% of the children, occurred mild adverse events (nausea, drowsiness) and only in one child desaturation, which was resolved spontaneously. There were no other respiratory adverse effects.

Of the 14 children who received a 70% concentration of N_2O, 9 (64%) had an adverse event. Two children (14%) had desaturation that was resolved after lowering the N_2O concentration by 10%. Importantly, 8 (57%) of these children went into deep sedation; this state increases the risk of respiratory adverse events.

The most common side effect of N_2O is vomiting and nausea. In this study vomiting appeared in six children, nausea occurred at a high concentration of N_2O. This could be due of the regular fasting time we recommended, according to the fasting regulations for general anesthesia. Kupietzky *et al* found that the frequency of vomiting or nausea associated with 50% N_2O concentration was low, 0.5%. No studies have reported the frequency of vomiting and nausea in dental treatment using a high concentration of N_2O.[14] The overall adverse event rate of 22% with 60% N_2O concentration, and 64% with 70% concentration, reported in the present study is considerably more than the 8% reported by Babl *et al* [5] Our proportion of adverse events was also higher than that reported by Zeir *et al* [6] While the latter used N_2O for different procedures than in the current study, no adverse events were recorded in 96% of the pediatric patients. For most of the children (91% n=6947), N_2O was administered at a concentration above 50%. There was no difference in adverse event rates for N_2O of less than, equal to and greater than 50%. The higher occurrences of adverse events in our study may be due to the long duration of the treatment session (45 minutes). Accordingly, Zeir. reported more adverse effects in procedures that lasted longer than 15 minutes compared to those shorter than this time (a 4.9 times greater likelihood of having adverse effects).

Limitations of the study

The study was not conducted as a double-blind controlled study, in the manner that the pediatric dentist was aware of the type of sedation given by the anesthesiologist.

Only restorations were performed as extraction treatments were an excluding criteria, and it is well known that extractions are among the most difficult procedures in dentistry, this may explain the high scores of cooperation achieved. A disadvantage of using higher concentrations of N_2O is the greater occupational risk of exposure to ambient substance. Thus, an effective scavenging system must be implemented to reduce the known adverse effects of nitrous on the practitioner.[3]

The process used in the current study, of starting the sedation with a 50% N_2O concentration for ten minutes, and then increasing the concentration to 60% and 70%, may be considered time consuming.

This study was conducted under the supervision of an anesthesiologist to ensure safety. This is particularly important due to the risk of a child reaching a level of deep sedation and the possible compromise to the upper airway. The financial burden administrating high nitrous oxide concentrations is greater on the patient's family due to the fact that an anesthesiologist must be present. Nonetheless, the advantage of higher concentrations of N_2O over other types of

pharmacological sedation is the ability to titrate and to reverse the sedative effect rapidly if needed. Deep sedation with N_2O can be reversed quickly and easily by giving 100% oxygen or reducing the nitrous concentration. This can be useful for short procedures such as local anesthesia infiltration or extraction, in which it may be administered without an anesthesia provider. In such cases, the concentration must be decreased to 50% concentration.

CONCLUSION

Our findings confirm the benefit of higher concentrations of N_2O inhalator sedative agent in a pediatric dental treatment setting. This possibility provides the pediatric dentist, the patient and the parents a safe pharmacological technique that is an effective alternative to general anesthesia. However, it is stressed that when N_2O concentrations exceed 50% an anesthesia provider should be present, Though 60% and 70% N_2O concentrations were found to be equally effective, increased adverse events were observed in the use of 70% concentration. In addition, more than half of the children who received this concentration reached a state of deep sedation, which in itself may increase the risk of adverse events.

Considering these findings, N_2O at 60% concentration appears optimal and effective than 50% and safer than 70% for children who were not cooperative enough to complete dental treatment at 50% concentration.

Further studies should be conducted with more children to ensure the safety of higher concentrations of nitrous oxide as an inhalator sedative agent in the dental setting in the presence of pediatric anesthesiologist.

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