

Efficacy and safety of nitrous oxide in alleviating pain and anxiety during painful procedures

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Abstract

Aims—To evaluate the efficacy and safety of nitrous oxide for children undergoing painful procedures.

Methods—Ninety children requiring repeated painful procedures (lumbar puncture, bone marrow aspirate, venous cannulation, or dressing changes) were given nitrous oxide at a variable concentration of 50–70%. Procedure related distress was evaluated using the Observational Scale of Behavioral Distress-Revised (OSBD-R). OSBD-R scores were obtained for each of the following phases of the procedure: phase 1a, waiting period; phase 1b, during induction with nitrous oxide; phase 2, during positioning and cleaning of the skin; phase 3, during the painful procedure; and phase 4, immediately following the procedure and withdrawal of nitrous oxide. Side effects were monitored and recorded by a second observer.

Results—OSBD scores reached a maximum during the induction phase with lower scores during subsequent phases. Children over the age of 6 showed a lower level of distress during nitrous oxide administration and the painful procedure. Eighty six per cent of patients had no side effects. The incidence of vomiting, excitement, and dysphoria was 7.8%, 4.4%, and 2% respectively. Eight patients developed oxygen desaturation ($SaO_2 < 95\%$), but none developed hypoxia, airway obstruction, or aspiration. Ninety three per cent of patients fulfilled the criteria for conscious sedation, and 65% had no recollection of the procedure. Mean recovery time was three minutes.

Conclusions—Inhalation of nitrous oxide is effective in alleviating distress during painful procedures, with minimal side effects and short recovery time.

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Keywords: nitrous oxide; pain; anxiety; painful procedure

Procedures such as venous cannulation, bone marrow aspiration, lumbar puncture, and dressing changes are painful and anxiety provoking in the paediatric population. Administration of sedative, hypnotic, amnesic, and analgesic agents, either alone or in combination have been used to diminish pain and anxiety during these procedures, with varying success.¹

Nitrous oxide is a potent inhalational agent that can provide analgesia, some sedation, and reduce anxiety. The effectiveness of 50% and

70% nitrous oxide in reducing the pain and anxiety associated with venous cannulation has been described.² It has also been reported that nitrous oxide is a well tolerated and effective analgesic in children for outpatient procedures.³⁻⁵ These reports compared the efficacy of nitrous oxide to placebo or an alternative pharmacological agent, and confirmed a significant reduction in pain scores when nitrous oxide was administered for painful procedures. However, they fail to describe the effect of nitrous oxide analgesia on children's emotional and behavioural response. Apart from efficacy, the adverse effects, side effects, and recovery characteristics of this agent must be considered in evaluating its success for painful procedures.

In a prospective study, we investigated the effects of nitrous oxide on children's behavioural responses to painful procedures. We planned to identify variables that related to high distress scores. The incidence of adverse effects and recovery characteristics was also evaluated.

Patients and methods

This study was approved by the institutional ethics committee. Following informed consent, patients were prospectively recruited into the study if it was planned that they undergo venous cannulation, bone marrow aspiration, lumbar puncture, or dressing change. Patients were recruited with medical, surgical, and oncological conditions. Ninety patients were enrolled in the study. Each patient was enrolled only once and 34 patients had more than one procedure performed. No premedication was used. Exclusion criteria included impaired level of consciousness, undrained pneumothorax, recent middle ear surgery, and a difficult airway. Patients were fasted from solids for four hours and clear fluids for two hours prior to the procedure. The apparatus used to administer nitrous oxide at a variable concentration consisted of the Quantiflex Mark II Relative Analgesia machine (Cyprane, Keighley, Yorkshire, UK) and a Bain circuit. The relative analgesia machine is a constant flow device and has a failsafe of a minimum of 30% oxygen at all times. The procedures were carried out in ward treatment rooms equipped with scavenging and monitoring facilities.

Nitrous oxide was administered by one of the nursing investigators who had been trained in the use of nitrous oxide by a member of the anaesthetic department. Nitrous oxide was administered at a variable concentration of 50–70% to achieve a level of consciousness that retained the patient's ability to maintain verbal

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Table 1 Sedation scoring system

Sedation score	Response
0	Unrousable
1	Asleep, rousable
2	Drowsy
3	Awake

Table 2 Mean rank of scores by age group

	1a	1b	2	3a	3b	4	Total
1-5	49.3	59.9	46.6	57.4	44.6	60.8	61.2
6-10	43.7	42.4	45.1	42.9	43.7	37.3	40.5
11+	41.5	30.2	42.9	32.7	47.4	36.4	31.4
p value	0.412	0.000	0.780	0.001	0.661	0.000	0.000

p < 0.05.

or tactile communication with the administrator. Children over the age of 3 received preprocedural teaching in correct use of the mask. Cognitive therapy that included imagery, distraction, and positive incentive was an integral part of the procedure and was provided by the administrator. Parents were encouraged to be present during the procedure. Nitrous oxide was administered for at least three minutes prior to the painful procedure and continuously throughout it. At the end of the procedure, the patient was allowed to breathe 100% oxygen for two to three minutes. Monitoring included pulse oximetry and end tidal gas analysis to measure the concentration of expired nitrous oxide and oxygen.

Procedure related distress was measured by trained observers using the scale of Observational Scale of Behavioral Distress-Revised (OSBD-R), an observation instrument with established reliability and validity that is used to evaluate distress.⁶ The presence or absence of eight operationally defined behaviours which indicate pain and anxiety (cry, scream, physical restraint, verbal resistance, seeks emotional support, information seeking, verbal pain, flail) is recorded by trained observers at 15 second intervals throughout the procedure and weighted according to the severity of distress. The weighted scores are summed during each 15 second interval and then divided by the number of intervals to obtain a mean score for each phase.

OSBD scores were obtained for each of the following phases of the procedures:

- Phase 1a—waiting period
- Phase 1b—during induction with nitrous oxide
- Phase 2—during positioning and skin cleaning
- Phase 3a—during the painful procedure
- Phase 3b—during the second procedure (where performed)
- Phase 4—immediately following the procedure and withdrawal of nitrous oxide.

Table 3 Mean rank of scores by procedure

Phase	1a	1b	2	3a	3b	4	Total
Lumbar puncture	44.5	41.9	44.2	43.6	45.6	41.2	41.2
Venous cannulation	38.9	48.9	40.4	35.9	42.1	47.7	42.8
Dressing	60.0	59.3	42.0	60.0	39.0	62.3	59.8
Bone marrow aspiration	44.9	38.6	51.3	44.4	57.3	37.4	44.2
p value	0.205	0.193	0.213	0.099	0.024	0.021	0.186

p < 0.05.

Prior to the study, two observers were trained in the use of OSBD-R until they obtained a minimum of 90% interobserver agreement.

A third observer recorded evidence of specified adverse effects: vomiting, excitement, dysphoria, and desaturation. Definition of desaturation was $SaO_2 < 95\%$. This was chosen as the patients were receiving an Fio_2 of 30–50%. Excitement was defined as uncontrolled laughing or hysteria and dysphoria was described as unpleasant dreams. The level of sedation was rated on a scale 0–3 (table 1) by noting the response to touch and voice during phase 2 and phase 3. The length of time for recovery was recorded as the time taken from phase 4 to sitting up on command. Children over the age of 3 were questioned for recollection of the procedure.

STATISTICS

Patients' ages were categorised into three groups: 1–5 years, 5–10 years, >11 years. The Kruskal–Wallis test was then used to examine the distribution of scores between the three categories. Distribution of scores with regard to previous experience with nitrous oxide for painful procedures was categorised as none, 1–5, or 6–10, and compared using the Kruskal–Wallis test. The primary procedure was recorded as lumbar puncture, cannulation, bone marrow aspiration, or dressing changes. The distribution of OSBD scores among these categories was compared using the Kruskal–Wallis test. These non-parametric tests are equivalent to *t* and F tests applied to the ranks of the data. Tables 2, 3 and 4 show the mean ranks. Higher means indicate a greater level of distress. Significance level was set at p < 0.05.

Results

Scores were obtained using the OSBD-R for 90 patients administered continuous nitrous oxide while undergoing painful procedures. Table 5 shows patient demographics and procedure characteristics. The OSBD-R scores were obtained for each of the six phases. The higher scores indicated a greater level of distress. Table 6 presents the median scores along with the lower and upper quartiles.

Significant differences in the mean ranks between the three age categories were seen for the total OSBD score (p = 0.000) and scores

Table 4 Mean rank of scores by number of previous experiences with nitrous oxide

Phase	1a	1b	2	3a	3b	4	Total
0	47.8	50.9	44.7	47.7	46.1	47.6	50.0
1-5	43.7	41.6	44.5	41.5	42.7	43.4	40.5
6-10	43.2	39.5	47.9	45.3	47.2	43.8	42.3
p value	0.652	0.136	0.777	0.627	0.603	0.695	0.288

p < 0.05.

Table 5 Patient demographics and procedure characteristics

Age (y)	Sex	Procedure	Number (n = 90)	% of children
7.32 (4.02)	42:48	Lumbar puncture	45	50
		Bone marrow aspiration	14	15.6
		Venous cannulation	14	15.6
		Dressing changes	17	18.8

Table 6 OSBD score for each phase, median (range)

	Lower	Median	Upper
Phase 1a	0	0	0.34
Phase 1b	0	0.41	2.02
Phase 2	0	0	0
Phase 3a	0	0.31	1.5
Phase 3b	0	0	0
Phase 4	0	0	0.71

Table 7 Frequency of previous experience with nitrous oxide

Number of previous exposures	Number of patients (n = 90)
0	42
1-5	24
6-10	24

Table 8 Incidence of adverse effects

Adverse effects	Incidence (%) (n = 90)
Vomiting	7.8
Excitement	4.4
Dysphoria	2.0
Desaturation	8.9

Table 9 Level of sedation

Sedation score	Incidence (%) (n = 90)
0 (unrousable)	0
1 (asleep, rousable)	1.1
2 (drowsy)	5.6
3 (awake)	93.3

Table 10 Recovery parameters

Amnesia	65% (n = 66)
Mean recovery time (SD)	3.08 (1.37) minutes

for phase 1b ($p = 0.000$), phase 3a ($p = 0.001$), and phase 4 ($p = 0.000$). In all cases, a gradient of higher mean rank for the younger children through to lower mean rank for the older children was observed.

There were significant differences between the various procedures in phases 3 and 4. Dressing changes scored highly in phases 3a and 4. Table 7 shows the frequency of previous experience with nitrous oxide for procedures. No significant difference between scores was found with regard to frequency of previous nitrous administration for painful procedures. Tables 8, 9, and 10 show incidence of adverse effects, level of sedation, and recovery parameters respectively.

Discussion

Procedures such as venous cannulation, bone marrow aspiration, lumbar puncture, and dressing changes are painful and provoke anxiety in the paediatric population. Pharmacological agents have been used alone and in various combinations with varying success.¹ The properties of an ideal agent include analgesia, anxiolysis, amnesia, and minimal side effects. The agent should have a rapid and predictable onset and characteristics that allow early recovery. A painless route of administration is also important. Venous cannulation is in itself painful and it is better if this can be avoided.

Inhaled nitrous oxide provides pain relief, sedation, and alleviation of anxiety. These benefits were shown in paediatric dentistry,⁷ and

more recently in relieving pain and anxiety associated with procedures in children in the emergency department.³⁻⁵

EFFICACY

Although the OSBD-R scale has been used to compare the effects of intervention in two different groups of patients,⁸ we used the scale to investigate the effect of intervention within a single group of patients. The numerical score during each phase describes the level of distress experienced by the child. Our scores revealed a significant elevation in the level of distress during the administration of nitrous oxide and a reduction during the subsequent phases of procedures, including the painful phase (table 6). This observation of increased score during phase 1b could be caused by numerous factors, including the application of the mask and nitrous oxide inhalation. Other potential causes are anticipation of the procedure and parental separation. The subsequent reduction in distress score during phases 2, 3, and 4 shows that continuous nitrous oxide administration decreases the level of distress to a minimal level. Studies which have evaluated the efficacy of ketamine and midazolam for painful procedures by using the OSBD-R scoring system show an elevation in scores during the painful phase of the procedure (phase 3).⁸⁻¹⁰

The efficacy of nitrous oxide is attributed to its analgesic and sedative properties, which produce a sense of euphoria and detached attitude towards pain and surroundings. However, this effect can be variable and nitrous oxide may fail to produce an analgesic effect in some patients.¹¹ Reasons for failure include poor technique of administration and the mask actually increasing the child's level of anxiety.

Previous studies of the use of nitrous oxide for venous cannulation,² laceration repair, and orthopaedic manipulation³⁻⁵ in the paediatric population have not discussed specific indications for or limitations of the use of the agent. However, this study was able to identify groups that consistently showed low level of distress during the administration of nitrous oxide and the painful procedure. Patients in the age groups >11 years and 6-10 years had lower scores during phase 1b (application of face mask), phase 3 (the painful procedure), and phase 4. This was also reflected in the total score.

Jay *et al* reported that age was the strongest predictor of children's distress during bone marrow aspirations.¹² Katz *et al* showed that young children tend to emit a greater variety of anxious behaviours over a longer period of time than older children do.¹³ Application of this information to our findings suggests that administration of nitrous oxide for painful procedures in very young children may not be as effective compared with older children. Our clinical impression is that older children have a better understanding of the correct technique of breathing into a facemask and also benefit from the cognitive therapy that accompanies this technique.

In our institution, imagery, distraction, and positive incentive are strategies that have

become an integral part of the technique of nitrous oxide administration for procedural pain. Jay *et al* reported equivocal results with respect to distress when cognitive therapy was compared with general anaesthesia for painful medical procedures in children.¹⁴ The suggestion that combination of cognitive behavioural intervention with general anaesthesia may diminish distress than either treatment alone was also raised.¹⁵ Ninety three per cent of the patients in this study were able to communicate with the administrator during inhalation of nitrous oxide and able to participate in imagery and positive incentive while benefiting from the euphoric and anxiety alleviating properties of nitrous oxide. We consider that cognitive therapy should be an integral part of the technique of nitrous oxide administration for alleviation of distress in children. With respect to procedures, patients undergoing dressing changes scored higher than those undergoing other procedures. The score remained high during the recovery phase. The higher score may be related to the longer length of the procedure and persisting pain.

The most favourable characteristic of nitrous oxide in this study was the effect on recovery parameters, namely short recovery time and amnesic effect. This characteristic is particularly beneficial to children with an oncological diagnosis who require repeated painful procedures. The amnesic effect allows repeated procedures to be conducted with minimal distress and the favourable recovery characteristics allow these procedures to be conducted on a day stay basis with minimal disruption to patient and family.

SAFETY

The safety of the pharmacological agent of choice for painful procedures in ambulatory patients relies on minimal adverse effects and favourable recovery characteristics. The safety of nitrous oxide for dental surgery in paediatric patients was reported by Roberts and colleagues.⁷ Griffin *et al* also described a technique for safe utilisation of nitrous oxide-oxygen sedation in 3000 children undergoing minor surgical procedures.¹⁶ Some clinicians discourage the use of nitrous oxide for alleviating pain and distress during painful procedures for fear of inappropriate use that may lead to hypoxia, loss of consciousness, and gastric aspiration.

The definition of desaturation in this study ($\text{Sao}_2 < 95\%$) was higher than in other studies which have used $\text{Sao}_2 < 92\%$ as their definition. Although eight patients in our study developed episodes of relative desaturation ($\text{Sao}_2 < 95\%$), none were observed to develop airway obstruction or hypoxia. All the patients in our study were unpremedicated and our results revealed that 93% of the patients were in communication with the administrator during the procedure and thus fulfilled the criteria of conscious sedation.¹⁷ The remaining patients were drowsy

but rousable. The reported incidence of nausea and vomiting during nitrous oxide administration is 14–19%¹⁸ and can place patients at risk if they are unable to protect their airway. In this study, the incidence of vomiting was low (7.8%) compared to other studies and there was no aspiration. While this study indicates that vomiting and aspiration may not be a problem, as was previously thought, it should be noted that more than 90% of our patients fulfilled the criteria of conscious sedation.

CONCLUSION

In summary, this study shows that administration of nitrous oxide/oxygen for painful procedures in children maintains low distress scores during the painful phase. Its most appropriate application is to children over the age of 6 and for short procedures. The low incidence of adverse effects and short recovery time in unpremedicated children allow safe administration by non-anaesthetists outside the operating theatre.

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