Original Contribution

A randomized controlled study in reducing procedural pain and anxiety using high concentration nitrous oxide

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1. Introduction

Over the past 10 years, pediatric emergency departments (PED) throughout the country have adopted the concept of an “ouchless” PED, using both pharmacologic and non-pharmacologic methods to achieve this goal [1]. Despite our interest in an “ouchless” PED, many routine procedures are performed without full attention to patient comfort. Some procedures, such as laceration repair, require local anesthesia, while others, such as intravenous catheter placement, are usually performed without local anesthesia. All of these minor procedures, however, are ones in which the risk of parenteral procedural sedation outweighs the benefit.

As the concept of creating a pain-free PED experience has grown, the use of high-concentration nitrous oxide [HC-N₂O] (>50%) in the pediatric outpatient setting and PEDs has increased throughout the country. N₂O is a colorless, non-narcotic, analgesic gas and its efficacy and safety have been well documented in anesthesia and dental literature [2].

Several studies have been published on the use of HC-N₂O in decreasing pain and anxiety in the pediatric emergency setting; however, previous investigations have been either observational, focused on a narrow age range, studied for use with a single procedure type, or included procedures associated with moderate to severe pain such as fracture reduction [1,3-5].

1.1. Objective

The objective of this study was to assess whether the use of HC-N₂O in addition to standard management increased the comfort level in pediatric patients undergoing minor procedures compared to standard management alone.

2. Materials and methods

2.1. Study design and selection of participants

This was a randomized controlled trial conducted in an inner city, academic PED. Children 3–12 years of age presenting to the PED, who required a minor procedure were assessed for eligibility. Minor procedures were defined as any procedure in which the standard management involved providing local anesthetic and/or holding the child in order to successfully accomplish the procedure. These procedures are those in which the potential risks associated with parenteral anesthesia would outweigh the benefits. Minor procedures included simple incision and drainage of an abscess, intravenous catheter placement, foreign body removal, suture/staple removal and simple laceration repair. A local anesthetic, such as injectable lidocaine, or a topical anesthetic, such as eutectic mixture of local anesthetics (EMLA) or lidocaine epinephrine and tetracaine (LET), was used at the discretion of the provider performing the procedure. The decision of whether to use topical anesthesia was made by the provider before group randomization of the patient.

The nitrous oxide machine was the Porter AVS 5000 with concentration titratable from 30% to 70% NO delivered by a full facemask, which was held in position by the provider administering the NO. The machine...
includes a Porter Scavenging System involving a non-rebreathing valve and emergency air intake allowing room air into the circuit and the inability to re-inspire exhaled carbon dioxide. A protocol was developed for the administration of nitrous oxide to standardize the delivery. A flow rate was determined based on the weight of patient, and 100% oxygen was administered 2–3 min prior to nitrous oxide administration. The machine allowed for slow titration of nitrous oxide to the desired sedation level. The nitrous oxide was dialed to a steady state percentage reached within 4–6 min of delivery. During the most painful or distressful part of the procedure nitrous oxide was dialed 20% higher than the steady state percentage. Once the procedure was completed the NO concentration was dialed down slowly over 4 min. The patient was placed on 100% oxygen for 5 min post procedure.

Exclusion criteria included patients with medical conditions in which HC-N₂O is contraindicated, those who were unable to communicate reliable levels of pain (e.g., developmental delay, autism, or psychiatric conditions), and those who had low to no anxiety demonstrable by the Modified-Yale Pre-operative Anxiety Scale (M-YPAS) [6] as a score < 10. This initial M-YPAS score was obtained in the examining room by one of sixteen recruiting physician after the procedure was described. All recruiting physicians were previously trained in using the scoring system.

M-YPAS is a validated scale that measures anxiety by assessment of activity, vocalization, emotional expressivity, state of arousal, and use of parents. All categories have a maximum score of 4 except for vocalization, which has a maximum score of 6. The scores within each category are totaled and a total anxiety score is reported ranging from 5 (no anxiety) to 22 (highest level of anxiety). A score <10 indicates normal behavior in at least 1 of the 5 measured categories and the risk of sedation may outweigh the benefit in this group. After obtaining parental consent/child assent, using a scripted text, eligible patients were randomized using a random number table to group 1 (standard management alone) or group 2 (HC-N₂O plus standard management). Because younger children experience significant anxiety before and during procedures, which can negatively affect the success of the procedure, we used block randomization by groups of six for two separate age groups in order to ensure equal representation in both groups. The sample was separated into preschool age (3 years to <6 years) and school age (≥6 years to 12 years) children.

### 2.2. Outcome measures

Data collection occurred at three time points: pre- procedure, intra-procedure, and post-procedure. The pre-procedural data collection included: 1) a pain score using a standard number scale ranging from 0 to 10 for children ≥6 years or the 10-point Wong-Baker faces pain scale for children <6 years measured at the time of triage by the triage nurse 2) clinical information including age, gender, procedure type, time to last oral intake, any previous experience with the procedure, adjuvant pain medication (including the use of local anesthesia) and 3) an anxiety score using m-YPAS. Intra-procedural data collection included: 1) pain score from 0 to 10 (0 = no pain) measured on the FLACC Pain Scale and 2) an anxiety score measured using m-YPAS. All intra-procedural scoring was done by the recruiting physician.

The FLACC Scale is a 10 point scoring system that assesses five categories: Face, Legs, Activity, Cry and Consolability; each category is scored from 0 to 2 resulting in a total score of 0–10. The post-procedure data collection included: mask tolerance, length of procedure, highest HC-N₂O concentration used, patient recovery time back-to-baseline, adverse events, a parental satisfaction survey, and an independent rating of the success of the procedure by both the provider performing the procedure and the provider administering the HC-N₂O or by second provider observing the procedure. Parental survey and provider rating were both based on a 5-point Likert Scale.

The primary outcome was the intra-procedural FLACC pain score. Secondary outcomes included the intra-procedural m-YPAS score, the change in m-YPAS (pre vs. intra-procedural), parent satisfaction with the comfort level of the patient, and independent scores by two providers regarding the success of the procedure.

### 2.3. Analysis

Based on a pre-study sample of children undergoing minor procedures using standard care, the mean FLACC Pain Scale score was 7.25/10. In various published articles, a clinically important change in pain score was noted with the use of HC-N₂O between 20% and 40% [4,7]. We determined that a 25% difference in the mean FLACC scores between the two groups would be clinically relevant. At an alpha of 0.05 and a power of 80%, we estimated a sample size of 42 patients in each arm.

Statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY). All continuous variables were non-normally distributed and therefore were described using medians and interquartile ranges (IQR) and compared using Mann-Whitney tests. Normality was

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### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Standard care</th>
<th>Standard care + Nitrous oxide</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>5 (4, 8)</td>
<td>6 (4, 9)</td>
<td>0.63</td>
</tr>
<tr>
<td>Pre-procedural pain score, median (IQR)</td>
<td>14 (36)</td>
<td>17 (40)</td>
<td>0.73</td>
</tr>
<tr>
<td>Pre-procedural MYPAS anxiety score, median (IQR)</td>
<td>3 (0, 6)</td>
<td>4 (0, 6)</td>
<td>0.91</td>
</tr>
<tr>
<td>ASA classification I</td>
<td>12 (12, 18)</td>
<td>14 (12, 18.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>Previous experience with procedure</td>
<td>10 (28)</td>
<td>10 (24)</td>
<td>0.69</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laceration repair</td>
<td>19 (49)</td>
<td>18 (42)</td>
<td>0.53</td>
</tr>
<tr>
<td>Abscess drainage</td>
<td>3 (8)</td>
<td>4 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>IV placement</td>
<td>11 (28)</td>
<td>15 (35)</td>
<td>0.52</td>
</tr>
<tr>
<td>Other</td>
<td>6 (15)</td>
<td>6 (14)</td>
<td>0.86</td>
</tr>
<tr>
<td>Adjunct pain medications</td>
<td>7 (18)</td>
<td>2 (5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Oral or topical anesthetic</td>
<td>21 (54)</td>
<td>21 (49)</td>
<td>0.65</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0.48</td>
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### Table 2

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Standard care</th>
<th>Standard care + Nitrous oxide</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-procedural FLACC score</td>
<td>8 (5, 10)</td>
<td>2 (0, 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intra-procedural MYPAS anxiety score</td>
<td>20 (15, 22)</td>
<td>10 (5, 15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in MYPAS anxiety score</td>
<td>3 (0, 7)</td>
<td>-4 (-8, -1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of procedure, minutes</td>
<td>11 (5, 20)</td>
<td>11 (5, 16)</td>
<td>0.80</td>
</tr>
</tbody>
</table>
assessed using histograms. Categorical variables were prescribed using frequencies and percentages and compared using Chi-squared tests and Fisher’s exact tests, where appropriate. Inter-rater reliability was computed using the Kappa statistic. The study was approved by the Institutional Review Board at the Albert Einstein College of Medicine and was registered at clinicaltrials.gov (NCT01911351).

3. Results

Eighty-two patients were enrolled and randomized, 39 to the standard care group and 43 to the HC-N2O group. Patient characteristics are demonstrated in Table 1. There was no difference between the groups in terms of procedure type. The majority of the procedures in both groups were laceration repairs and IV placement. There were 19 laceration repairs (49%) and 11 IV placements (26%) in the standard care group and 18 (42%) and 15 (35%) respectively in the N2O group. Among the entire sample, the median intra-procedural FLACC score, the median intra-procedural mYPAS score, and the median change between pre and intra procedural mYPAS scores were all significantly higher for the standard care group compared to the N2O group (Tables 2). There was no difference between the groups in terms of the length of the procedure. When stratified by age a significant difference persisted except in the intra-procedural FLACC score in the 6–12 year olds (Table 3).

Three patients experienced adverse events with administration of HC-N2O; emesis (n = 2), and hallucinations (n = 1). There were no mechanical complications or failures with the nitrous oxide delivery system. Eighty-eight percent of providers reported that children in the N2O group tolerated the procedure well compared to 56% in the standard care group. Eighty-eight percent of providers reported that children in the N2O group tolerated the procedure well compared to 56% in the standard care group. However, when stratified by age a significant difference persisted except in the intra-procedural FLACC score in the 6–12 year olds (Table 3).

Table 3 shows secondary clinical outcomes specific to the HC-N2O group stratified by age.

3.1. Limitations

There are some limitations to our study. Many children did not meet the criteria for enrollment based on the pre-procedural anxiety score but who, during the procedure, were unable to cooperate due to pain and/or anxiety. Although the level of anxiety during the procedure cannot be consistently predicted, we needed to use a standard measure of exclusion for the study participants in order not to randomize children to a sedation arm who in fact may not require sedation. In a non-study setting, many clinicians would have chosen to use the HC-N2O, anticipating that the child’s anxiety and/or pain would have increased during the actual procedure. Additionally, many parents opted not to participate because of the randomization process. Parents had predetermined views regarding wanting or not wanting their child to be sedated and would not consent to the study. Finally, neither the participants nor the providers were blinded to the intervention. Although the FLACC and M-YPAS scales are validated, they involve subjective measures of the patient’s behavior. We did not, however, believe it was ethical to introduce the potentially noxious stimuli of a facemask delivering oxygen alone without the possible benefit of HC-N2O. Furthermore, doing so would have likely skewed the results even more favorably toward the HC-N2O intervention group if the child had a negative reaction to the facemask.

4. Discussion

Providers caring for children in PEDs and urgent care centers are aware of the increase of anxiety and pain associated with the medical environment. There is, however, a gap between the recognition of the increase in distress and active methods to reduce anxiety. N2O has been documented for use in dental procedures since 1844 [8]. Today,

Table 4

Provider and Parent Survey Results by Randomization Assignment.

Table 5
Anxiety in young children, even in the absence of painful stimuli, may nonetheless be painful and/or anxiety provoking for young children. In our study, no patients experienced hypoxia during administration of 60% and the other at 70%. No airway compromise or aspiration arising due to the possible depth of sedation the patient may have obtained with HC-N2O. Airway compromise or aspiration has not been reported in the literature in relation to the depth of sedation attained during the administration of HC-N2O [3,12]. Two patients in our study experienced emesis during administration of HC-N2O, one at a concentration of 60% and the other at 70%. No airway compromise or aspiration was noted in these patients.

The translation of the use of HC-N2O to the outpatient setting has grown in the last thirty years. Several of the earlier studies evaluated the use of 30%–50% N2O, with a N2O e-oxygen supply system, in children as young as 16 months of age until adulthood [8]. The largest of these early studies, with a sample size over 3000, was an observational report showing procedural success in a pediatric office setting using N2O [8]. Other earlier prospective studies focused on decreasing pain measured on the Children’s Hospital of Eastern Ontario Pain Scale (CHEOPS) with patients undergoing laceration repairs. They noted a clinically and statistically significant decrease in pain scores during the procedure in children >8 years old while using 30% N2O [12]. In children less than 8 years old, a higher concentration of 50% N2O was needed to achieve a decrease in pain scores [7,12]. Another study by Kanagasundaram, demonstrated moderate sedation levels without airway compromise, and reported a decrease in behavioral distress score during the painful phase of the procedure with HC-N2O (>50%). Patients in this study were undergoing painful procedures such as, bone marrow aspirations or lumbar punctures [3]. Other studies report the use of HC-N2O for fracture reductions and other painful procedures [3,11,13,14]. Although significant findings were reported, these studies were limited by a small sample size, the use of single procedure type, and/or a behavior rating that did not include the patient’s response to infiltration of local anesthetic [10].

Our study included a variety of minor procedures that are routinely performed in a PED, in which parenteral sedation would not be used but are nonetheless painful and/or anxiety provoking for young children. Anxiety in young children, even in the absence of painful stimuli, may lead to the child being physically restrained in order to perform an otherwise simple and minor procedure. The effects of the noxious stimuli and restraints can create a negative association with future medical procedures and personnel which can cause lifetime effects of post-traumatic stress and avoidance of health care as an adult. Also the developmental stage of the brain at the time of distress can be related to the permanence of a painful memory and long-term effects [15]. Therefore, the younger population is further at risk for traumatic memories that can develop into long-term distress cycles in relation to med-ical procedures [13].

We chose an age range of 3–12 years in order to capture the age group that may be particularly disposed to a negative experience while undergoing a medical procedure, and in whom the safety of HC-N2O has been previously demonstrated. By doing this we attempted to replicate the practice in a busy PED and assess the feasibility of providing sedation for minor procedures.

Significantly more providers reported that children in the HC-N2O group tolerated the procedure well; similarly, parents of children in the HC-N2O group were significantly more likely to report that their child appeared comfortable during the procedure. Satisfaction regarding other survey questions, however, was similar for parents in both groups. Although anecdotally providers thought that parents in the nitr-ous group exhibited a positive response to the sedation, this was not reflected in the parental survey. The structure of the parental survey and a lack of previous comparison may be the reason for this inconsistency.

Pain and anxiety are closely related in the behavior of a child undergoing a procedure. It is sometimes difficult to determine what proportion of their behavior response is due to pain. Previous studies have used a variety of validated scaling systems to measure pain and anxiety during procedures. The FLACC Pain Scale was initially developed for post-operative pain, but has been evaluated in both healthy and cognitively impaired school-aged children for procedural pain [16]. A systematic review by von Baeyer and Spagrud recommend the use of the FLACC Scale as a validated measure of procedural pain [17]. We chose the intra-procedural FLACC scale score as our primary outcome due to its simplicity and strength of validity for procedural pain in our target age group. We did not use the FLACC scale as a pre-procedural measurement because patients requiring minor procedure are unlikely to present with significant initial pain levels, but may have substantial anxiety. To account for the fact that the FLACC pain scale does not measure anxiety, we added the M-YPAS. This scale has shown to have good to excellent inter-observer reliability and high concurrent and construct validity in the perioperative setting [6]. To our knowledge, the M-YPAS has not been validated in the procedural pain setting and therefore was used as an adjunct. Our goal would be to add information to strengthen the use of both FLACC and M-YPAS in the procedural setting, and perhaps have a scale that would account for both.

In conclusion, we found a substantial decrease in pain and anxiety in children undergoing minor procedures when receiving HC-N2O and standard care versus standard care alone. Additional studies are needed.

Table 5

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Overall</th>
<th>3 to 5 years old</th>
<th>6 to 12 years old</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since last food or drink, minutes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>165 (90, 445)</td>
<td>183 (105, 387)</td>
<td>150 (57, 903)</td>
<td>0.98</td>
</tr>
<tr>
<td>Tolerated mask, n (%)</td>
<td>40 (93)</td>
<td>20 (95)</td>
<td>20 (91)</td>
<td>1.00</td>
</tr>
<tr>
<td>Highest percentage of NO used</td>
<td>60 (50, 65)</td>
<td>60 (50, 65)</td>
<td>60 (50, 65)</td>
<td>0.82</td>
</tr>
<tr>
<td>Total NO time, minutes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 (10, 25)</td>
<td>15 (10, 25)</td>
<td>20 (10, 21)</td>
<td>0.46</td>
</tr>
<tr>
<td>Recovery time, minutes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (4, 7)</td>
<td>5 (4, 5)</td>
<td>5 (5,10)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are presented as median (IQR) unless otherwise indicated.
<sup>b</sup> Total number of participants with data available was 17 for 3–5 year old age group and 14 for 6–12 year old age group.
<sup>c</sup> Total number of participants with data available was 20 for 3–5 year old age group and 22 for 6–12 year old age group.
<sup>d</sup> Total number of participants with data available was 19 for 3–5 year old age group and 19 for 6–12 year old age group.
to confirm our findings and to further document the feasibility of the routine use of HC-N₂O for minor procedures in the attempt to create an “ouchless” PED.

References


