Intranasal fentanyl and inhaled nitrous oxide for fracture reduction: The FAN observational study

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Abstract

Introduction: Procedural sedation and analgesia (PSA) are frequently used for fracture reduction in pediatric emergency departments (ED). Combining intranasal (IN) fentanyl with inhalation of nitrous oxide (N2O) allow for short recovery time and obviates painful and time-consuming IV access insertions.

Methods: We performed a bicentric, prospective, observational cohort study. Patients aged 4–18 years were included if they received combined PSA with IN fentanyl and N2O for the reduction of mildly/moderately displaced fracture or of dislocation. Facial Pain Scale Revised (FPS-R) and Face, Leg, Activity, Cry, Consolability (FLACC) scores were used to evaluate pain and anxiety before, during and after procedure. University of Michigan Sedation Score (UMSS), adverse events, detailed side effects and satisfaction of patients, parents and medical staff were recorded at discharge. A follow up telephone call was made after 24–72 h.

Results: 90 patients were included. There was no difference in FPS-R during the procedure (median score 2 versus 2), but the FLACC score was significantly higher as compared to before (median score 4 versus 0, Δ2, 95% CI 0, 2). Median UMSS was 1 (95% CI 1, 2). We recorded no serious adverse events. Rate of vomiting was 12% (11/88). Satisfaction was high among participants responding to this question 85/88 (97%) of parents, 74/83 (89%) of patients and 82/85 (96%) of physicians would want the same sedation again.

Conclusion: PSA with IN fentanyl and N2O is effective and safe for the reduction of mildly/moderately displaced fracture or dislocation, and has a high satisfaction rate.

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1. Introduction

Fractures are common injuries in children [1–3]. Closed reduction of fractures is often a painful procedure associated with a degree of physical force, and is one of the main indications for procedural sedation and analgesia (PSA) in a pediatric emergency department (ED) [4–7].

The use of intranasal (IN) fentanyl to treat acute pain in children has been studied in different settings, showing comparable analgesic effects to intravenous (IV) morphine [8–10]. Obtaining IV line insertion in children requires special skills and is often a painful and time consuming process. Providing analgesia with IN fentanyl allows for analgesia without the tedious process of obtaining IV access.

Nitrous oxide (N2O)-oxygen mixtures have been used for PSA in the ED for many years [11]. It has few side effects, and its use in the pediatric emergency setting is well established for mildly painful and/or distressing procedures [12,13]. Although the exact mechanism of action is unknown, sedation is usually explained due to a noncompetitive inhibition of the NMDA-receptor, and analgesia via central opioid–as well as opioid-like-receptors [12]. Usually, concentrations between 50 and 70% are used [11]. Best results as far as effect/side effect ratio are for inhalation time of <15 min [14]. However, its analgesic effect for painful procedures remains limited [15,16].

Theoretically, the combination of inhaled N2O and the IN administration of fentanyl is attractive as it would support the use of N2O in more painful procedures, such as fracture reduction, and maintain the advantages of a short recovery time without IV access. This would be especially valuable in the setting of mildly to moderately displaced forearm fractures or dislocation, where manipulation time is known to be short. Additionally, using a narcotic with N2O enhances sedative and anxiolytic effects while allowing the patient to talk and follow commands [17].

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So far, the reported use on this combination is sparse. To date, only one observational study has been published evaluating IN fentanyl and N₂O as PSA: Seith et al. [18] prospectively studied sedation depth and adverse events in 41 patients undergoing PSA for painful procedures. This study did not assess the analgesic efficacy of the combined agents.

Thus, we aimed to evaluate the analgesic efficacy and the safety of combined IN fentanyl and N₂O as PSA for reduction of mildly to moderately displaced fractures and dislocation in children seen in pediatric ED.

2. Methods

We performed a prospective, observational study at two tertiary pediatric children’s hospitals in Canada and Australia. In center 1, patients were recruited in the pediatric ED as well as in the orthopedics’ clinic from September 2014 to October 2015. In center 2, ED patients were recruited from April 2015 to October 2015. Patients between the age of 4 and 18 years were eligible if PSA consisted of a combination of IN fentanyl and N₂O for reduction of the following: mildly or moderately displaced fractures of the forearm, fractures of the wrist or the hand, dislocation of a finger or of the patella, or application of traction on displaced femur fractures.

Patients received IN fentanyl 1.5 mcg/kg (100 mcg max) via atomizer using the 50 mcg/ml concentration. Additional doses of 0.5 mcg/kg were administered for pain control up to a total of 2 mcg/kg (100 mcg max total) at the discretion of the physicians performing the PSA. N₂O was delivered as fixed 50/50% nitrous oxide/oxygen mixture via the Nitronox™ system (Porter Instruments) at center 1 and as a variable mixture with N₂O at 0%–70% oxygen mixture via the Entonox™ system (BOC Health Care UK) at center 2 (but always using a 70%/30% mixture). Both are on-demand flow systems: patients self-administer the gas by inhaling through the mask. Manipulation was started after 3 min of N₂O administration. During the procedure, patients were monitored continuously by pulse oximetry and heart rate in both centers, and by capnography in center 1. Monitoring ended after an oxygen wash out period of 2–5 min following the use of N₂O administration when the patient had returned to his or her pre-procedural state. 100% oxygen was delivered via nasal flow until patient was able to sit up by him- or herself. Discharge was based on local guidelines.

2.1. Measures

For patient assigned pain scores, the Facial Pain Scale Revised (FPS-R) was used to evaluate the efficacy of the procedural sedation. The FPS-R scale consists of 6 faces, each representing a degree of pain, and corresponding numbers 0–2–4–6–8–10 (0 being “no pain”, 10 being “very much pain”) (Fig. 1). It has been validated to quantify pain and pain relief following analgesia in children as young as 4 years in different settings including the pediatric ED [19–21], its French translation to evaluate acute pain evaluation is supported by the French Haute Autorité de Santé [22], and this acceptance allows its use in a center with mostly French speaking patients (center 1). Data were collected immediately before and 10 min after the end of the sedation - when patients were asked about pain scores during the procedure and about pain score at that moment. Patients were also asked about recall of the procedure, and were given the option to state ‘no recall’.

We also used the Face, Leg, Activity, Cry, Consolability Pain and Anxiety (FLACC) score to evaluate the observer based efficacy of PSA (Fig. 2) [23]. While it has limitations in procedural use it is a widely accepted observational score for postoperative pain and for acute procedures in children [20,21,23–25]. The scale was applied by a researcher or a trained researcher assistant before, during and 10 min after procedural sedation. Furthermore, sedation depth was recorded using the University of Michigan Sedation Scale (UMSS) during the sedation and 10 min after the end of sedation (Fig. 3) [26].

Side effects were recorded through a questionnaire to patients and parents after the procedure. Adverse events were recorded and categorized as suggested by the Consensus Panel on Sedation of the Research of Pediatric Emergency Care (PERC) and the Pediatric Emergency Care Applied Research Network (PECARN) [27]. Additionally, all other side effects were recorded, and a follow-up telephone call was made 24–72 h later to evaluate late side effects and adverse events.

Using surveys, general satisfaction of patients, parents and health care providers were collected separately. For the different surveys, different scales were used: Patients were asked on a scale of 0–10 with corresponding faces (0 = no satisfaction at all, 10 = very satisfied) how satisfied they were with the PSA. Parents were asked to determine their satisfaction on a scale from 0 to 5 (0 = very satisfied, 5 = not satisfied at all). Both parties also were asked if they would want the same sedation in the future for a similar procedure (yes or no). The surveys also included questions on sedations in the past as well as side effects. Health care provider questions included details on the fracture/dislocation type, overall satisfaction on a scale from 1 (not satisfied at all) to 5 (very satisfied), comparison with other PSA, and interest in future PSA with this drug combination for similar procedures (yes or no) as well as free text for additional comments.

2.2. Data collection and statistical analysis

For the purpose of data analysis, all data were entered in an Excel database (Microsoft Inc., Richmond, WA) and analyzed with SPSS v20 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Median differences of FPS-R and FLACC before, during, and after procedure were analyzed. Median depth of sedation and mean or median results for each question of the surveys were calculated. Responded questions were used to determine denominator or n, respectively. Percentages were calculated using these numbers. Key categorical data are presented with 95% confidence intervals.

The primary outcome was the difference between the FPS-R score prior to and during the procedure. We also compared the FLACC score prior to and during the procedure. For FLACC score of >6, we compared time interval between fentanyl and N₂O administration. For the main side effect (vomiting), we compared duration of N₂O, time interval

![Fig. 1. Faces Pain Scale-Revised (FPS-R).](https://www.iasp-pain.org/fpsr. Copyright ©2001, International Association for the Study of Pain®. Reproduced with permission.[19]).
between fentanyl intranasal and N₂O, concentration of N₂O, and patient age as possible confounding factors.

Sample size was convenience-based: There was no literature to base a sample size on. Thus, we used previous data from center 1 to predict the number of patients undergoing the procedure during one year: In 2013, around 100 patients per year underwent reduction of mildly or moderately displaced forearm fractures. We expected about 50 patients or 50% of them to be approached and reduced with N₂O and IN fentanyl. Data of center 1 were extrapolated to include around 50 patients per center during one year, or a total of about 100 patients.

3. Results

A total of 95 parents and patients were approached during the study period, from them, 90 were included (Fig. 4).

Details on the study population, type of injury sustained, and the procedure used are shown in Table 1. Mean age of the patients enrolled was 9.6 years. Most fractures were metaphyseal forearm fractures with angulation of 11–20° and <50% fracture displacement. The average fentanyl dose was 1.55 mcg/kg and mean time between IN fentanyl and N₂O was 21 min.

There was no difference between the median FPS-R score during the procedure as compared to before: median patient reported FPS-R score at 10 min after procedure was 1/10 (95% CI 0, 2). A total of 9/88 (10%) patients scored FPS-R per procedure higher than 6. In 6/9 (67%) of these patients, fentanyl was administered <15 min before initiating N₂O. All of these 9 patients had a score of 4 or less 10 min after.

The median FLACC score was higher during the procedure than prior to the procedure, 4/10 and 0/10, respectively: (a difference of 2 [95% CI 1, 3]). FLACC score was higher than 6 in 18/88 (20%) patients during the procedure. Ten of these patients (56%) had a time interval of <15 min after the IN fentanyl administration and the beginning of N₂O. The median FLACC 10 min after the procedure was 0/10, (95% CI 0, 0) and one patient (1%) had a persisting FLACC ≥6/10.

FPS-R and FLACC score did not necessarily correspond to each other. Three of nine patients with FPS-R ≥6 also had a FLACC score of ≥6. There were no significant differences for patients having scores of ≥6/10 in either FPS-R or FLACC when looking at concentration of N₂O and delay of introducing N₂O after fentanyl administration (Table 2).

The median UMSS was 1 (95% CI 1, 2) during the procedure for the whole group. While the reported median UMSS for patients with the score reported by research assistants during the procedure for these patients with no recall was 3/10. For all patients, the median patient reported FPS-R score at 10 min after procedure was 1/10 (95% CI 0, 2).

Fig. 2. Face, Leg, Activity, Cry, Consolability Pain and Anxiety Score [23].
Table 1
Study population.

| Center 1 total | Department | Age (mean, SD) | Gender | Type of injury (n = 90)
|----------------|------------|---------------|--------|----------------------|
| 61 (67.8%) | Orthopedics’ clinic | 9.6 ± 3.0 | Female | Fractures 85 (94.4%)
| 50 (55.6%) | ED | 64 (70%) | Male | - Forearm/wrist 1 bone 41 (45.6%)
| 11 (12.2%) | Center 2 | 36 (40%) | | - Metacarpal 31 (34.4%)

Table 2
Breakdown of the PSA characteristics for patients with FFS-R or FLACC scores of ≥6.

<table>
<thead>
<tr>
<th>Fentanyl/N2O &lt; 15 min (n = 43)</th>
<th>Fentanyl/N2O ≥ 15 min (n = 46)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFS-R &gt; 6 (n = 9)</td>
<td>6 (14%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>FLACC &gt; 6 (n = 18)</td>
<td>10 (23%)</td>
<td>8 (17%)</td>
</tr>
</tbody>
</table>

N2O: oxygen mixture of 70:30% was 2 (95% CI 1, 2), median for those with a mixture of 50:50 was 1 (95% CI 1, 1).

A minority of participants did not answer to all questions of questionnaire. Denominators stand for the number of participants responding to the individual question, and percentages are calculated accordingly.

Table 3
Side effects.

<table>
<thead>
<tr>
<th>In hospital (n = 84)</th>
<th>At follow-up (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia (self-resolved)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Paradoxical reaction</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (19%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>Urticaria/itchiness</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Double vision</td>
<td>5 (6%)</td>
</tr>
</tbody>
</table>

Other* | 7 (8%) | 11 (13%) |

* Information was not available for 1 fracture localization, 3 fracture angulations, and for 2 fracture displacements ED = emergency department, N2O = nitrous oxide, SD = standard deviation.

4. Discussion

In this study, we looked into detailed efficacy and satisfaction by patients, parents, and health providers for a combination of IN fentanyl and N2O, thus avoiding the insertion of an IV line. PSA with IN fentanyl and N2O for reduction of moderately displaced fractures or dislocations was effective when using patient assigned pain scores (FPS-R) as a surrogate marker for pain. Patients did not have a higher FPS-R score during the procedure compared to their reported pain scores prior to the painful procedure. Most patients had mild pain prior to reduction, and manipulation did not increase the pain level. In 17 (19%) patients, retrograde amnesia prevented self-evaluation with the FPS-R. However, median FLACC score was 3 for those patients, corresponding to a mild observer-assigned pain scale. This was the same for the patients who remembered the procedure.

There was a significantly higher observer-assigned FLACC score during the fracture or luxation reduction procedure than before (4 versus 0). This differs from our results for FPS-R. We had chosen both scores to get a broader picture, as no single score has been identified to best evaluate efficacy of PSA [28]: The disadvantage of self-evaluation is the risk of several factors influencing scoring: level of sedation, anxiety etc. [20,21,29]. On the other hand, observer related scores cannot differentiate distress from pain [20,21,24,25]. Reasons for higher FLACC scores could partly be explained by two factors: One, research assistants mentioned that their higher scoring was recorded during the few patients, and for 83 patients at follow-up. We recorded several mild side effects reported by patients: A total of 53/85 patients reported side effects in hospital (62%), and 38/83 (46%) at follow-up. Twenty-five patients reported no side effects at all (30%). These were not considered as adverse events, some of them being the desired effects of sedative use (Table 3).

In 11/85 patients, vomiting occurred during the ED stay (13%), and another 3/83 patients (4%) vomited after discharge. Vomiting was documented in 6/57 (10.5%) patients receiving the 50:50 N2O mixture, and in 8/27 (29.6%) patients receiving the 70:30 mixture: a difference of −18% (95% CI = 36, −1).

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seconds of the actual manipulation, rapidly returning to baseline. This short period of distress might have been too short to influence self-assessment. Also, leg movements and mild agitation can be related to euphoria when using N₂O, and both parameters are recorded with the FLACC score. Another explanation would be that higher FLACC score was due to inadequate self-reported pain by the participants: the amnestic properties of N₂O could influence the ability to accurately recall pain even when patient state having clear recall. We reduced effect by assessing the FPS-R score 10 min after the procedure: this assured that patients were awake and effect of nitrous oxide was over when they were asked about their pain score during procedure.

Also, we chose FPS-R as primary objective over FLACC for its validity in this setting, and for its possibility to differentiate distress from pain. To adequately assess efficacy, more than this one marker is needed. Using a self- as well as an observer-reported score plus questionnaires addressed to all participants allows for a multidimensional approach on evaluating effective PSA.

In terms of factors influencing the efficacy of the PSA, no differences were found when comparing higher FPS-R scores or FLACC scores ~6 to the delay between administration of IN fentanyl or the varying concentrations of nitrous oxide mixtures used during the procedures, nor with reduction of more severely displaced or angulated fractures. However, this might be due to the small sample size with overlapping confidence intervals. A short interval of fewer than 15 min between administration of fentanyl and N₂O was frequent. In center 1 the use of this PSA was relatively new, and optimal timing might have been less present by the treating physician trying to advance things in a busy ED.

Satisfaction of all participants was high: ~88% of patients, parents, and medical staff would want to use the same PSA in a future procedure. While encouragingly high, this observational study was based on a cohort where the decision to use the agents had already been made. Therefore the results may be more an evaluation of the appropriate choice of PSA by the treating physician than the specific PSA, especially knowing that 74% of patients had no previous experience with PSA to compare with.

So far, one study by Seith et al. has been published on side effects and sedation depth of the combination of IN fentanyl and N₂O [18]: No serious side effects were recorded, while the incidence of vomiting was elevated (19.5%) as compared to known data on N₂O alone. The incidence of deep sedation was also noted more frequently in that study when N₂O and IN fentanyl were administered in combination as compared to N₂O alone. Compared to this study, we found less ED vomiting (12%) [18]. Rate of vomiting was higher at center 2 where nitrous 70:30 was used (27.5%) versus center 1 where 50:50 was used (10%). While other factors may have played a role, the higher concentration of N₂O in combination with IN fentanyl may be the reason for a higher rate of emesis. Considering the increased emesis rate with higher N₂O concentration, the efficacy of ondansetron as an adjunct medication should be explored when it is used. Overall minor side effects were less common in the study by Seith et al. (22% versus 62% in our study). This may be due to a different methodology of specifically eliciting each of these possible symptoms from parents and patients. Also, follow-up data was not collected by Seith et al., adding to overall side effect rate, as well as follow up data in our study (not collected by Seith et al.) [18].

5. Limitations

The major limitation of our study was that it was observational, and non-randomized. Another limitation is recall bias when asking patients to assess their pain during the procedure 10 min later, and amnestic properties of nitrous oxide limits self-evaluation. Furthermore, most patients and parents did not have any experience with PSA, so it was impossible to compare with other medication as far as satisfaction goes. Another limitation is the fact that there is not an officially accepted method on how to measure efficacy of PSA, and we had to use different surrogate markers. A validated score to evaluate PSA should be developed for use in pediatric study in the ED.

6. Conclusion

Procedural sedation and analgesia with combined IN fentanyl and N₂O for the reduction of mildly to moderately displaced fractures and dislocations appears to have good analgesic efficacy as measured by patient assigned pain scores. Satisfaction among patients, parents, as well as medical staff was high. While no severe adverse events occurred, our study confirms an increased emesis rate for the combination compared to the use of fentanyl or N₂O alone when looking at literature [9,11,12, 30]. Finally, randomized controlled trials should be performed to evaluate and compare different medications in order to determine the best possible PSA for fracture reduction in children.

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