Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

ORIGINAL RESEARCH CONTRIBUTION

Intranasal Fentanyl and High-concentration Inhaled Nitrous Oxide for Procedural Sedation: A Prospective Observational Pilot Study of Adverse Events and Depth of Sedation

Robert W. Seith, MBChB, MRCPCH, FRACP, FACEP, Theane Theophilos, RN, MPH, and Franz E. Babl, MD, MPH, FRACP, FAAP

Abstract

Objectives: Nitrous oxide (N_2O) is an attractive agent for pediatric procedural sedation and analgesia (PSA) with rapid onset and offset of sedation. However, it has limited analgesic efficacy. Intranasal fentanyl (INF) provides nonparenteral analgesia. There are currently no data on the combined use of N_2O and INF for PSA in children. The authors set out to prospectively assess the depth of sedation and incidence of adverse events when N_2O and INF are used in combination in pediatric patients.

Methods: This was a prospective observational pilot study of combined N_2O and INF for PSA at a tertiary children's hospital emergency department (ED). INF was administered at a precalculated dose of 1.5 μg/kg for preascertained weight ranges. N_2O concentration, dose, timing of INF, adverse events, and sedation depth were recorded. Sedation depth was recorded using the University of Michigan Sedation Scale (UMSS).

Results: A total of 41 patients, aged 1 to 14 years, received INF within 2 hours prior to N_2O. N_2O was administered at a maximal concentration of 70% in 40 patients, and at 50% in one patient. Most patients (80%) were minimally to moderately sedated (sedation score 1 or 2). Deep sedation (sedation score 3) was recorded in 14.6% of patients (95% confidence interval [CI] = 3.4% to 24.6%). No patients had serious adverse events; vomiting was recorded in 19.5% (95% CI = 7.4% to 31.6%). There were two patients (4.9%) who were deeply sedated and vomited during the procedure.

Conclusions: There were no serious adverse events identified in this pilot study of combined N_2O and INF. However, there was an increased incidence of vomiting and deeper levels of sedation when compared to published data of single-agent use of N_2O, which could lead to more serious adverse events. Further investigation is needed to establish the analgesic efficacy of combining N_2O and INF and to clarify the safety profile before this combination can be recommended for PSA in children.

ACADEMIC EMERGENCY MEDICINE 2012; 19:31–36

Nitrous oxide (N_2O) is commonly used in emergency departments (EDs) around the world for procedural sedation and has a very good safety profile.[1–9] N_2O fulfills many of the criteria for an ideal sedative agent, with rapid onset and offset, ease of nonparenteral administration, a favorable adverse events profile, and high patient satisfaction.[7] However, the efficacy of N_2O as a sole agent in very painful procedures is limited, in particular, in fracture reduction.[1,7–9]

From the Emergency Department, Royal Children's Hospital (RWS, TT, FB), Parkville, Victoria; and the Emergency Department, Monash Medical Centre (RWS), Murdoch Children's Research Institute (TT, FEB), University of Melbourne, (FEB) Melbourne, Victoria, Australia.

Received April 16, 2011; revision received June 14, 2011; accepted June 15, 2011.
The authors acknowledge grant support from the Murdoch Children's Research Institute, Melbourne, Australia.
The authors have no potential conflicts of interest to disclose.
Supervising Editor: James W. Fox, MD.
Address for correspondence and reprints: Franz E. Babl, MD, MPH, FRACP, FAAP, FACEP; e-mail: franz.babl@rch.org.au.

doi: 10.1111/j.1553-2712.2011.01241.x
ISSN 1069-6563
PII ISSN 1069-6563583

Intranasal fentanyl (INF) provides rapid, powerful analgesia, and in the ED setting is particularly useful in children without intravenous (IV) access. Pediatric ED data indicate an analgesic efficacy similar to that of IV morphine.[10] Other studies in children also have shown INF to be safe and effective.[11–14]

Theoretically, combining N_2O and INF could provide improved analgesic efficacy to create an ideal nonparenteral regimen for procedural sedation. However, there are currently no data investigating the safety profile and efficacy of these drugs when used together for procedural sedation and analgesia (PSA). Our primary objective was to characterize the depth of sedation and incidence of adverse events associated with the combined use of N_2O and INF for pediatric PSA in the ED. Secondary objectives included identifying associations with sedation depth and adverse events.

METHODS

Study Design

We conducted a prospective observational pilot study of depth of sedation and adverse events for the combination of N_2O and INF in pediatric patients. Approval for the study was obtained from the hospital's human research ethics committee, and patients were enrolled with documented verbal consent.

Study Setting and Protocol

The study was set in the ED of the Royal Children's Hospital (RCH), Melbourne, Australia, a large, urban children's hospital with an annual ED census of 69,000 patients. All consecutive children presenting to the ED for a period of 6 months who received inhaled N_2O for PSA within 2 hours of INF were eligible for enrollment. The formal exclusion criteria were the use of additional sedative agents, acute/chronic nasal problems, hemodynamic instability, respiratory distress, associated head injury or decreased level of consciousness, known opiate allergy, and exclusions based on the component agents as set out in the RCH ED Sedation Manual.[15]

PSA was performed using standardized presedation assessment, monitoring during the procedure, and postsedation discharge criteria. As part of standard sedation practice, a sedation checklist, which forms part of the medical notes, was used.[16,17] For N_2O sedation, minimum ED fasting times for solids and liquids were 2 hours.[15] Monitoring during N_2O and INF sedation included continuous oxygen saturation, heart rate, and sedation depth with recording every 5 minutes by the nursing staff on the observation chart until the child had returned to his or her preprocedural state.[15] There was an accredited trained senior nurse or physician to provide airway support in addition to the proceduralist. The sedation checklist, which doubled as a case report form, was used to record data before, during, and after PSA with N_2O and INF. This included age, past medical history, fasting status, procedures undertaken, highest concentration of N_2O used, dose of INF used, additional sedatives or opiates used, deepest level of sedation, and adverse events. The sedation checklist was completed by the nursing staff and/or physician involved in the PSA. Patients were consented and enrolled 24 hours a day. To ensure that consecutive data were collected, study sedation checklists were photocopied and placed in the ED research box after the procedure by the treating clinician. Sedation checklists for all PSA were routinely separately filed by the ED clerks and therefore allowed the tracking of all patients receiving INF and N_2O.

Nitrous oxide was administered via several fixed wall mounted Quantiflex MDM (Matrx, Orchard Park, NY) machines, which deliver a continuous flow of 0 to 70% N_2O. In the study ED, N_2O is almost exclusively administered at concentrations of 50% to 70% via a full-face mask. This technique requires an additional health care provider to administer the N_2O, as it can achieve moderate to deep levels of sedation and is associated with higher levels of emesis compared with self-administered demand-valve methods.[1] INF was administered at a precalculated dose of 1.5 μg/kg for weight ranges (increments of 2 kg from 10 to 20 kg and then increments of 5 kg to a maximum of 50 kg). An IV 200 μg/2 mL formulation of fentanyl citrate (Janssen-Cilag Pty. Ltd, North Ryde, NSW Australia) was administered through a mucosal atomizer device (MAD300, Wolfe Tory Medical, Salt Lake City, UT) attached to a syringe. The 50 μg/mL concentration has been shown to have analgesic efficacy.[13,14,18] All doctors and nurses administering PSA in the RCH ED are sedation-accredited as laid out in the RCH ED Sedation Manual.[15]

Outcome Measures

Our primary objective was to characterize the depth of sedation and incidence of adverse events associated with the combined use of N_2O and INF in the ED. Secondary objectives included identification of procedures performed; comparison of depth of sedation and adverse events to those reported in the same-center study by Babl et al.[2] of N_2O as sole agent; and identifying associations with sedation depth and adverse events in relation to timing and dose of N_2O and INF used, age of the child, and length of time fasted before PSA.

Definitions

To measure the level of sedation, the validated University of Michigan Sedation Scale (UMSS) was used.[19] The scale has five levels of sedation ranging from 0 to 4 (0 = awake and alert; 1 = minimally sedated: may appear tired/sleepy, responds to verbal conversation and/or sounds; 2 = moderately sedated: somnolent/sleeping, easily roused with light tactile stimulation or simple verbal command; 3 = deep sedation: deep sleep, rousable only with deep or significant stimuli; 4 = unarousable). The deepest level of sedation attained was recorded on the sedation checklist.

Adverse events were defined as per the Consensus Panel on Sedation Research of Pediatric Emergency Research Canada (PERC) and the Pediatric Emergency Care Applied Research Network (PECARN).[20] They define nine categories of adverse events: 1) oxygenation, 2) ventilation, 3) clinically apparent pulmonary aspiration, 4) retching/vomiting, 5) cardiovascular events, 6) excitatory movements, 7) adverse behavioral reactions, 8) permanent complications, and 9) other not described.

Data Analysis

All data were entered into an Access software database (Microsoft, Redmond, WA). Median values are reported with interquartile ranges (IQR), means are reported with standard deviation (SD), and key percentages are presented with 95% confidence intervals (CIs) where appropriate. Categorical data were analyzed using chi-square testing; continuous data were analyzed using t-tests for parametric variables and Wilcoxon rank sum tests for non parametric variables. Based on multiple comparisons undertaken, $p < 0.01$ was considered statistically significant. Statistical calculations were performed on Stata 10.0 (StataCorp, College Station, TX).

RESULTS

During the 6-month period, 41 patients received N_2O and INF for PSA in the ED. There were no missed patients. Patient demographics are listed in Table 1. Most procedures were orthopedic (80.5%), with the majority of those being fracture reduction (61%), four of which were done by local anesthetic, manipulation, and plaster (LAMP) in addition to N_2O and INF.

All patients were fasted for at least 2 hours before commencing N_2O hours (mean = 3.6 hours, SD ± 2.0 hours; median = 3 hours, IQR = 2.3 to 4.0 hours). Forty (98%) of the patients received 70% N_2O and one (2%) received 50% N_2O. All patients received continuous-flow N_2O. N_2O was commenced within a mean of 14.5 minutes (SD ± 14.3 minutes; median = 10 minutes, IQR = 5–25 minutes) of INF administration. Most patients (78%) received one dose of INF. Eight patients (19.5%) received two doses of fentanyl. Five of those commenced N_2O within 2 hours of both doses. One patient received three doses of INF, of which two were within 2 hours of N_2O. The mean total dose was 2.3 μg/kg and the median was 2.1 μg/kg.

Table 1
Characteristics of ED Patients Receiving Inhaled Nitrous Oxide and INF for PSA (n = 41)

Characteristic	Value
Age, yr	
Mean (±SD)	6.7 (±2.9)
Median (IQR)	6.3 (5.2–8.8)
Sex, male, *n* (%)	29 (70.7)
Strength N_2O, *n* (%)	
70%	40 (98)
50%	1 (2)
Length N_2O, minutes	
Mean (±SD)	11.4 (±6.3)
Median (IQR)	10 (5.5–15)
INF, number of doses*(%)	
1	32 (78)
2	8 (19.5)
3	1 (2.4)
Time pre-N_2O, minutes†	
Mean (±SD)	14.5 (±14.3)
Median (IQR)	10 (5–25)
Procedures, *n* (%)	
Orthopedic	33 (80.5)
Reduction fracture	21 (51.2)
LAMP	4 (9.8)
Reduction dislocation	2 (4.9)
Application of plaster	6 (14.6)
Laceration repair	4 (9.8)
Facial	3 (7.3)
Nonfacial	1 (2.4)
Other	4 (9.8)
Abscess drainage	1 (2.4)
Removal foreign body	2 (4.9)
Burns dressing	1 (2.4)

INF = intranasal fentanyl; IQR = interquartile range; LAMP = local anesthesia, manipulation, and plaster; PSA = procedural sedation and analgesia.
*Within 2 hours of administering N_2O.
†If multiple doses of fentanyl, then dose closest to N_2O is used.

There were no serious adverse events: no patient became hypoxic; required assisted ventilation; or had clinically apparent pulmonary aspiration, laryngospasm, cardiovascular events, or permanent complications. Twenty-two percent of patients (95% CI = 9.3% to 34.7%) sustained mild and self-resolving adverse events, mostly vomiting (19.5%, 95% CI = 7.4% to 31.6%). One patient became agitated, which resolved on discontinuing the N_2O. There were no other adverse effects observed.

We investigated associations with vomiting and length of N_2O administration, fasting times, age of the patient, depth of sedation, and relationship to dose of fentanyl. No significant associations were found based on a priori definition of significance at $p < 0.01$. Mean length of N_2O administration in those who vomited was 10 minutes (SD ± 5.9 minutes), compared to 11.6 minutes (SD ± 6.4 minutes) in those who did not vomit ($p = 0.54$). Mean fasting time was 5.0 hours (SD ± 3.2 hours) for those who vomited compared to 3.2 hours (SD ± 1.2 hours) for those who did not vomit ($p = 0.03$). Mean age for those who vomited was 6 years (SD ± 2.5 years) versus 6.9 years (SD ± 3.0 years) in those who did not vomit ($p = 0.46$). Five of the eight patients who vomited (62.5%) had a UMSS of 1 (mildly sedated), one (12.5%) had a UMSS of 2, and two patients (25%) had a UMSS of 3. Six of the eight who vomited (75%) received a dose of INF 10 minutes or less before administration of N_2O. Of the other two, one was given INF 30 minutes prior to N_2O, and for the other patient the timing was not recorded. This gives a mean of 10 minutes (SD ± 9.6 minutes) in those who vomited compared to 15.5 minutes (SD ± 15.1 minutes) in those who did not vomit ($p = 0.36$). Three of the eight (37.5%) who vomited had received multiple doses of INF.

Of the eight patients who vomited, five vomited during the procedure and two after the procedure, and in one patient the time of vomiting was not recorded. Of the patients who were deeply sedated and vomited during the procedure, one was a 2-year-old girl undergoing a fracture reduction who was fasted for 3 hours, had 7 minutes of 70% N_2O, and received fentanyl immediately prior to reduction. The other was a 7-year-old boy undergoing application of plaster for a fractured arm who was fasted for 3 hours, had 3 minutes of 70% N_2O, and received two doses of INF 70 and 10 minutes before the procedure.

Table 2 shows the deepest level of sedation recorded and the associated incidence of emesis. Six patients (14.6%; 95% CI = 3.4% to 24.6%) were deeply sedated, and no patients were unrousable. Of the six deeply sedated patients, two (33.3%) had received multiple

Table 2
Depth of Sedation* in ED Patients Receiving Inhaled Nitrous Oxide and INF for Procedural Sedation and Analgesia (n = 41)

	Total (any concentration N_2O)		
Score	n	%	Vomiting
0	2	4.9	0
1	15	36.6	5
2	18	43.9	1
3	6	14.6	2
4	0	0	0
Total	41	100	8

INF = intranasal fentanyl; UMSS = University of Michigan Sedation Scale.
*Depth of sedation based on UMSS (see Methods for definitions).

doses of fentanyl. The mean length of time of N_2O administration for these six patients was 9.2 minutes (SD ± 4.0 minutes) versus 10.7 minutes (SD ± 6.6 minutes; p = 0.36); mean time from INF to commencing N_2O was 17.0 minutes (SD ± 9.1 minutes) versus 14.1 minutes (SD ± 15.0 minutes) (p = 0.7); and mean age was 6.9 years (SD ± 4.6 years) versus 6.7 years (SD ± 2.6 years; p = 0.9), respectively. The procedures performed in the deeply sedated patients were fracture reductions (n = 3), plaster applications (n = 2), and sutures (n = 1).

We extracted data of a previously published study by Babl et al.[2] on patients who received N_2O alone (n = 659) from the same center and compared vomiting rate and depth of sedation with data from this study. When combining N_2O and INF we found a higher rate of vomiting (19.5%, 95% CI = 7.4% to 31.6% vs. 5.7%, 95% CI = 4.1% to 7.4%; p < 0.001) and a higher rate of deep sedation (14.6%, 95% CI = 3.4% to 24.6%, vs. 2.9%, 95% CI = 1.6% to 4.2%; p < 0.001) compared to the patients who received N_2O alone.

DISCUSSION

The combination of high-concentration N_2O and INF is a seemingly attractive regimen for nonparenteral PSA in children that has not been investigated before. Our pilot study of 41 patients who received this combination indicated that patients had no or mild adverse events, mainly vomiting (19.5%), and most patients (80%) were minimally to moderately sedated (sedation score 1 or 2). However, this study identified a significant increase in vomiting and deep levels of sedation when compared to N_2O as the sole agent in a prior study from the same ED.[2] In 1,585 patients who received nitrous oxide, Zier et al.[21] found a rate of emesis of 1.8% in those who had received >50% N_2O. As with the study by Babl et al.,[2] this is lower than the incidence in this study, with the addition of INF. Of note, the patients in Zier's study received N_2O in the sedation unit, rather than in the ED, which could result in differences in vomiting rates not related to N_2O concentration.

This is particularly notable as INF as a sole agent has been found to be safe with a low incidence of emesis. Fentanyl has decreased histamine release compared to morphine, and therefore vomiting is less common.[1] In three studies, where a total of 166 patients received 1.5 μg/kg INF, there were no recorded incidents of emesis.[12–14] However, a randomized controlled trial (RCT) by Klein et al.[22] found vomiting in 25% of patients receiving oral transmucosal fentanyl when combined with midazolam, compared to 0% who had received midazolam alone. We could find no obvious association between vomiting and duration of inhaled N_2O, fasting times, age of the patient, or depth of sedation and the timing and dose of INF.

In IV fentanyl, emesis relates to peak serum concentration (T_{max}). Fisher et al.[23] showed that the T_{max} of INF was around 10 to 20 minutes postdose. This would fit with our observations where the mean time to introduction of N_2O was 14 minutes. N_2O is known to be a proemetic.[1,2] Concurrent administration of N_2O with fentanyl, at the time when fentanyl is at its T_{max}, would appear to make emesis more likely.

It may therefore be worth considering administering INF between 30 and 60 minutes prior to commencing N_2O. This may have the dual benefit of decreasing the rate of emesis and improving patient analgesia. INF has been shown to have maximum analgesic efficacy at 30 to 60 minutes postdose.[13]

This study also showed a significant increase in the depth of sedation when INF is used in combination with N_2O, compared to a study from the same hospital ED of 694 children who received N_2O alone.[2] However, there are limitations in comparing the studies as the study by Babl et al.[2] used the validated Children's Hospital of Wisconsin Sedation Scale.[24] Since its publication, the hospital-wide policy had changed to using the UMSS.

In the sole-agent use of N_2O, Babl et al. found 2.5% of patients to be deeply sedated compared to 14.6% in this study with the addition of INF. Zier et al.[21] found no incidence of deep sedation in 1858 administrations of N_2O. Increased depth of sedation has been shown to be associated with an increased rate of adverse events.[20] Of the six patients with a sedation score of 3, two had received more than one dose of INF. We could identify no association with length of N_2O administration, time from INF to N_2O, age of patient, or procedure undergone. We also noted that two of six deeply sedated patients vomited during the procedure. The potential combination of increased incidence of vomiting and depth of sedation raises the concern of increased risk of pulmonary aspiration. While aspiration may be a rare event in ED PSA[25] and responsiveness may be a crude surrogate marker for retention of protective airway reflexes,[25–27] the combined use of N_2O and INF should proceed with caution.

Two potential methods for trying to decrease emesis bear consideration: longer fasting times or introducing a premedication antiemetic such as ondansetron. Longer fasting times have not been shown to decrease the risk of vomiting with N_2O alone.[28] In fact, the literature provides no compelling evidence to support specific fasting periods prior to PSA, and existing guidelines for elective patients are based upon consensus opinion.[1,25–27] In this study, admittedly with low numbers, no association was found between fasting times and emesis, with the mean and median fasting

times in the group that vomited both greater than 4 hours. An RCT showed a significant reduction in the incidence of vomiting with the use of prophylactic IV ondansetron in children who received IV ketamine for ED PSA.[29] Due to the high number of patients needed to treat (NNT) to prevent a single episode of emesis (NNT = 13), the clinical applicability of this practice for ketamine. It should be investigated in a future RCT of the combined use of N_2O and INF. Future research should also investigate the analgesic efficacy of N_2O and INF for PSA in an RCT and the safety profile of the combination in a larger sample.

LIMITATIONS

The low numbers limit the ability to assess associations of variables with adverse events and depth of sedation. Recording of adverse events depended on accurate recording of information on the sedation record by staff involved, not by independent observers. It is possible that a number of mild, transitory adverse events were not recorded or occurred after discharge. The lack of postdischarge follow-up may have resulted in fewer episodes of vomiting being recorded as emesis following N_2O can occur after discharge.[28] Some procedures using INF and N_2O for PSA may have been missed. Assignment of sedation scores, although used and taught for a number of years in the study ED in a standardized sedation program,[16,17,30] is open to some interpretation, and the interrater reliability of staff-determined sedation depth was not assessed. We did not track N_2O sedations without INF, but based on past data,[30] we would estimate an expected 300 PSA during this study period overall, and 250 of those would use N_2O. We did not investigate why clinicians decided to use or not use INF with N_2O.

CONCLUSIONS

In this prospective, observational pilot study we found no serious adverse events when combining inhaled nitrous oxide and intranasal fentanyl. However, there was an increased incidence of vomiting and deep sedation when compared to published data on single-agent use of N_2O. This increase in vomiting in combination with deeper levels of sedation could lead to more serious adverse events. Further investigation is needed to establish the analgesic efficacy of combining N_2O and intranasal fentanyl and clarify the safety profile before this combination can be recommended for procedural sedation and analgesia in children.

The authors thank the families and the medical and nursing staff of the ED for participation in the study.

References

1. Krauss B, Green SM. Procedural sedation and analgesia in children. Lancet. 2006; 367:766–80.
2. Babl FE, Oakley E, Seaman C, Barnett P, Sharwood L. High-concentration nitrous oxide for procedural sedation in children: adverse events and depth of sedation. Pediatrics. 2008; 121:e528–32.
3. Burton JH, Auble TE, Fuchs SM. Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. Acad Emerg Med. 1998; 5:1191–8.
4. Hennrikus WL, Simpson RB, Klingelberger CE, Reis M. Self-administered nitrous oxide analgesia for pediatric fracture reductions. J Pediatr Orthoped. 1994; 14:538–42.
5. Luhmann JD, Schootman M, Luhmann SJ, Kennedy RM. A randomized comparison of nitrous oxide plus hematoma block versus ketamine plus midazolam for emergency department forearm fracture reduction in children. Pediatrics. 2006; 118:e1078–86.
6. Annequin D, Carbajal R, Chauvin P, Gall O, Tourniaire B, Murat I. Fixed 50% nitrous oxide oxygen mixture for painful procedures: a French survey. Pediatrics. 2000; 105:E47.
7. Krauss B. Continuous-flow nitrous oxide: searching for the ideal procedural anxiolytic for toddlers. Ann Emerg Med. 2001; 37:61–2.
8. Krauss B, Green SM. Sedation and analgesia for procedures in children. N Engl J Med. 2000; 342:938–45.
9. Babl FE, Oakley E, Puspitadewi A, Sharwood LN. Limited analgesic efficacy of nitrous oxide for painful procedures in children. Emerg Med J. 2008; 25:717–21.
10. Borland M, Jacobs I, King B, O'Brien D. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. Ann Emerg Med. 2007; 49:335–40.
11. Borland ML, Bergesio R, Pascoe EM, Turner S, Woodger S. Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. Burns. 2005; 31:831–7.
12. Borland ML, Jacobs I, Geelhoed G. Intranasal fentanyl reduces acute pain in children in the emergency department: a safety and efficacy study. Emerg Med. 2002; 14:275–80.
13. Crellin D, Ling RX, Babl FE. Does the standard intravenous solution of fentanyl (50μg/ml) administered intranasally have analgesic efficacy? Emerg Med Australas. 2010; 22:62–7.
14. Finn M, Harris D. Intranasal fentanyl for analgesia in the paediatric emergency department. Emerg Med J. 2010; 27:300–1.
15. Babl FE. Sedation Manual. 2nd ed. Children's Hospital, Melbourne. Available at: http://www.rch.org.au/emplibrary/emerg_rch/SedationManualDec2008_final.pdf. Accessed Oct 7, 2011.
16. Babl F, Priestley S, Krieser D, et al. Development and implementation of an education and credentialing program to provide safe paediatric procedural sedation in emergency departments. Emerg Med Australas. 2006; 18:489–97.
17. Babl FE, Krieser D, Belousoff J, Theophilos T. Evaluation of a paediatric procedural sedation training and credentialing program: sustainability of change. Emerg Med J. 2010; 27:577–81.
18. Borland M, Milsom S, Esson A. Equivalency of two concentrations of fentanyl administered by the intranasal route for acute analgesia in children in a

paediatric emergency department: a randomized controlled trial. Emerg Med Australas. 2011; 23:202–8.
19. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Scale (UMSS). Br J Anaesth. 2002; 88:241–5.
20. Bhatt M, Kennedy RM, Osmond MH, et al. Consensus-based recommendations for standardizing terminology and reporting adverse events for emergency department procedural sedation and analgesia in children. Ann Emerg Med. 2009; 53:426–36.
21. Zier JL, Tarrango R, Liu M. Level of sedation with nitrous oxide for paediatric medical procedures. Anesth Analg. 2010; 110:1399–405.
22. Klein EJ, Diekema DS, Paris CA, Quan L, Cohen M, Seidel KD. A randomized, clinical trial of oral midazolam plus placebo versus oral midazolam plus oral transmucosal fentanyl for sedation during laceration repair. Pediatrics. 2002; 109:894–7.
23. Fisher A, Watling M, Smith A, Knight A. Pharmacokinetic comparisons of three nasal fentanyl formulations; pectin, chitosan and chitosan-poloxamer 188. Int J Clin Pharmacol Ther. 2010; 48:138–45.
24. Hoffman GM, Nowakowski R, Troshynski TJ, Berens RJ, Weisman SJ. Risk reduction in pediatric procedural sedation by application of an American Academy of Pediatrics/American Society of Anesthesiologists process model. Pediatrics. 2002; 109:236–43.
25. Green SM, Krauss B. Pulmonary aspiration risk during ED procedural sedation: an examination of the role of fasting and sedation depth. Acad Emerg Med. 2002; 9:35–42.
26. Green SM, Roback MG, Milner RM, Burton JH, Krauss B. Fasting and emergency department procedural sedation and analgesia: a consensus-based clinical practise advisory. Ann Emerg Med. 2007; 49:454–61.
27. Green SM. Fasting is a consideration–not a necessity–for emergency department procedural sedation and analgesia. Ann Emerg Med. 2003; 42:647–50.
28. Babl FE, Puspitadewi A, Barnett P, Oakley E, Spicer M. Pre-procedural fasting state and adverse events in children receiving nitrous oxide for procedural sedation and analgesia. Paediatr Emerg Care. 2005; 21:736–43.
29. Langston WT, Wathen JE, Roback MG, Bajaj L. Effect of ondansetron on the incidence of vomiting associated with ketamine sedation in children: a double-blind, randomized, placebo-controlled trial. Ann Emerg Med. 2008; 52:30–4.
30. Babl FE, Belousoff J, Theophilos T, Hopper S, Deasy C. Paediatric procedural sedation based on nitrous oxide and ketamine: data from an Australian sedation registry. Emerg Med J. 2010; 27: 607–12.