Safety and efficacy of a nitrous oxide procedural sedation programme in a paediatric emergency department: a decade of outcomes

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ABSTRACT

Background Nitrous oxide (N_2O) has multiple benefits in paediatric procedural sedation (PPS), but use is restricted by its limited analgesic properties. Analgesic potency could be increased by combining N_2O and intranasal fentanyl (INF). We assessed safety and efficacy data from 10 years (2011–2021) of our N_2O PPS programme.

Methods Prospectively collected data from a sedation registry at a paediatric emergency department (PED) were reviewed. Total procedures performed with N_2O alone or with INF, success rate, sedation depth and adverse events were determined. Contributing factors for these outcomes were assessed via regression analysis and compared between different N_2O concentrations, N_2O in combination with INF, and for physician versus nurse administered sedation. A post hoc analysis on factors associated with vomiting was also performed.

Results 831 N_2O procedural sedations were performed, 358 (43.1%) involved a combination INF and N_2O. Nurses managed sedation in 728 (87.6%) cases. Median sedation depth on the University of Michigan Sedation Scale was 1 (IQR 1–2). Sedation was successful in 809 (97.4%) cases. Combination INF/N_2O demonstrated higher median sedation scores (2 vs 1, p<0.001) and increased vomiting (RR 1.8, 95% CI 1.3 to 2.5), with no difference in sedation success compared with N_2O alone. No serious adverse events (SAEs) were reported (desaturation, apnoea, aspiration, bradycardia or hypotension) regardless of N_2O concentration or use of INF. 137 (16.5%) minor adverse events occurred. Vomiting occurred in 113 (13.6%) cases and was associated with higher concentrations of N_2O and INF use, but not associated with fasting status. There were no differences in adverse events (RR 0.98, 95% CI 0.97 to 1.04) or success rates (RR 0.93, 95% CI 0.56 to 1.7) between physician provided and nurse provided sedation.

Conclusion N_2O can provide effective PED PPS. No SAEs were recorded. INF may be an effective PPS adjunct but remains limited by increased rates of vomiting.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although nitrous oxide (N_2O) can be safely administered by staff without advanced airway skills, it is not commonly used as a first-line sedative for painful procedures due to concerns surrounding its limited analgesic potency.
⇒ Combining N_2O and intranasal fentanyl (INF) may help overcome the limitations of N_2O alone; however, data remain limited and there are concerns for increased respiratory depression.

WHAT THIS STUDY ADDS

⇒ In this review of 10 years of prospectively collected procedural sedation data at a paediatric ED in Ireland, use of N_2O alone or combined with INF achieved a 97.4% successful sedation rate with no serious adverse events (SAEs).
⇒ 87.6% of sedations were performed by nurses. Success rate and adverse event rates were not different between nurses and physicians.
⇒ Despite the absence of SAEs, vomiting was a significant issue occurring in 13.6% of patients, which is higher than with other agents.
⇒ Combining N_2O with INF provided deeper sedation but increased the risk of vomiting. There was no difference in sedation success rate between combined N_2O/INF and N_2O alone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Nurse-delivered sedation using N_2O could ease physician workload demands in busier departments.
⇒ In appropriate settings, N_2O can be an alternative to parenteral agents, even for painful procedures such as fracture manipulation.
⇒ Combination of INF with N_2O enhances sedation depth, compensating for N_2O's limited sedative effect with no recorded increase in SAEs.

INTRODUCTION

The safety and efficacy of paediatric procedural sedation (PPS) delivered by emergency physicians has been widely confirmed.[1–3] However, expertise in Europe is variable compared with North America, Australia and New Zealand.[4–6] Barriers including provider skillset, credentialing, monitoring requirements, drug choice and methods of delivery may account for regional differences.[5 7 8] There have been calls for further data detailing PPS practices.[4 5 7 8]

Nitrous oxide (N_2O) is a sedative agent that can potentially decrease barriers to PPS. It eliminates

the need for parenteral access, has a rapid onset and offset, and consistently demonstrates high patient satisfaction due to its euphoric and amnesic effects.[9] Importantly, its favourable safety profile compared with parenteral agents, facilitates administration by staff without extensive airway training.[10–15]

Despite these benefits, N_2O is not widely used as a first-line agent.[1 2 5 14] Its popularity is predominantly confined to Australian EDs, where ketamine remains the preferred agent for procedures such as fracture manipulation.[16] The preference for ketamine over N_2O may arise from concerns regarding the variability of sedation provided by N_2O and its limited analgesic potency. However, N_2O can provide effective sedation, even for highly painful procedures, when administered in combination with other agents.[12 13 17] Intranasal fentanyl (INF) is one such agent. It is a high potency, short acting opioid that can be administered without parenteral access. INF has been explored as an effective adjunct to N_2O PPS.[18–20] Yet widespread combination remains uncommon, due to fears of increased respiratory depression.[2 3 6]

A PPS training programme has been delivered in the Paediatric Emergency Department (PED) at Children's Health Ireland—Crumlin since 2011. The programme was conceived at a time when clear PPS guidance was lacking and as a result, features unique aspects, tailored to institutional requirements including:

- A locally created training and certification process, analogous to previously described programmes.[15]
- Sedation delivered primarily by nursing staff.
- Use of up to 70%, N_2O, via continuous flow as the primary agent.
- Frequent coadministration of N_2O with INF.

The aim of this study is to describe our experience under this PPS programme, focusing on safety and efficacy. Secondary objectives were to identify factors associated with adverse events in PPS and to compare efficacy data, along with adverse event rates for N_2O alone, varying N_2O concentrations and N_2O in combination with INF. Finally, we aimed to assess whether outcomes differed between nurse- and physician-delivered sedation.

METHODS

Study design

Retrospective review of prospectively collected registry data on paediatric sedations between 8 March 2011 and 25 January 2021.

Setting

Data were collected in the PED of a tertiary hospital in Ireland, with ~40 000 annual attendances. Sedation practice, documentation, staff certification and monitoring requirements were structured according to local departmental guidelines, similar programmes have been described.[15] Documents governing the programme are available on request.

Participants

All children between 1 and 16 years of age who received N_2O for procedural sedation were eligible for inclusion. Written parental consent and patient assent were obtained prior to sedation; all parents consented to data collection and retention for the purpose of audit.

Interventions

N_2O PPS was provided to patients who required sedation as part of their PED care. Our programme mandates the sedation provider be separate to the proceduralist. Nursing staff who had completed our certification process facilitated physician performed procedures by providing sedation when additional physicians were unavailable.

N_2O was delivered via a continuous flow system, the Porter MXR flowmeter (Porter Instruments, Hatfield, Pennsylvania, USA), capable of delivering N_2O at concentrations of 0–70% via a Bain circuit with a full facemask. If administered, INF was given at a dose of 1.5 mcg/kg via a mucosal atomiser device before initiation of sedation. N_2O and fentanyl required a physician prescription.

Definitions

'Depth of sedation' was recorded using the University of Michigan Sedation Scale (UMSS) which has been previously defined and validated.[19–21] The scale scores sedation depth from 0 (awake and alert) to 4 (unrousable). Scores 1–3 correspond to minimal (responds to voice), moderate (responds to light tactile stimulation) and deep sedation (responds only to significant physical stimulation), respectively. The score was allocated by the provider performing the sedation at the time of the procedure.

A 'successful sedation' was defined by consensus as: A sedation event whereby the patient was comfortable and co-operative, enabling the required procedure to be undertaken.

'Combination therapy' with INF required fentanyl to be administered within 60 min of sedation with N_2O. This timeframe was chosen based on data regarding the duration of clinical effect of fentanyl.

'Nurse-provided sedation' occurred when a nurse who had completed our certification process, administered sedation and was responsible for titrating sedation and managing the airway, if required.

'Adverse events' were defined as per published guidelines.[22] 'Serious adverse events (SAEs)' were defined as: oxygen saturation <94%, apnoea, stridor, airway malalignment requiring repositioning, laryngospasm, cardiovascular instability, aspiration pneumonia, endotracheal intubation, permanent neurologic injury and death.

'Major procedures' were fracture manipulation and joint reduction, all other procedures were classified as minor.

Data abstraction procedures

The registry was populated with data gathered prospectively via a paper sedation proforma which was mandated for every sedation event (online supplemental material—Sedation Proforma). The proforma was completed contemporaneously by the team providing sedation, then stored in a secure location. Staff independent from this research project would enter data into a Microsoft Access database (Microsoft Corp, Redmond, Washington, USA) as a part of their non-clinical duties. N_2O sedations were stored in a separate database to other sedation agents. All data were pseudonymised once uploaded. Variables stored within the database, their definition and their format are available in the supplementary material (online supplemental material—Codebook). Wherever possible binary values or fixed categories were used to ensure data consistency. For entries detailing adverse event type, additional analgesic agents, procedure type and sedation provider free text entries were permitted to ensure maximal data capture. These entries were then later assessed and recategorised, with addition of new categories if required by research staff (SC).

Outcomes of interest

The key outcomes were sedation success and adverse event rates. Secondary outcomes were demographic and procedural factors associated with adverse events and sedation success. Adverse event rates and sedation efficacy for N_2O alone, high (51–70%) versus low (50%) N_2O concentrations and N_2O in combination with INF were compared. Success rates and adverse event data for physician- versus nurse provided sedation were also analysed.

Statistical analysis

Data were exported to Microsoft Excel (Microsoft Corp). Discrepancies were validated against the original record. Complete case analysis was used for missing data.

Descriptive data are presented with frequencies and percentages. Measures of central tendency are reported as median with IQR and mean with SD. Categorical variables were analysed using Fisher's exact test. Parametric continuous variables were analysed using Student's t test. Non-parametric and ordinal variables were assessed via the Mann-Whitney U test. Variables found to be significant in univariate analysis or considered clinically relevant were entered into multivariate regression models for further analysis. Multicollinearity was assessed via variance inflation factors. CIs were calculated by the modified Wald method or Koopman asymptotic score. All tests were two-tailed and performed at the 5% level of significance. Statistical analysis was performed using Prism (GraphPad Software, Boston, Massachusetts, USA).

Patient and public involvement

Patients were not involved in the design or conduct of either the PPS programme or manuscript.

RESULTS

Over a 10-year period, 831 N_2O PPS cases were recorded. 7.4% of registry datapoints were missing. Combination therapy with INF occurred in 358 (43.1%) patients and trends over time are shown in online supplemental table 1. Successful sedation occurred in 809 (97.4%, 95% CI 96.0% to 98.3%) cases. The median age was 9 years (IQR 6–12). Patient characteristics are listed in table 1.

Most children (n=727, 87.5%) were discharged home following sedation. Ninety-seven (11.7%) patients required admission for ongoing care. Predominantly, this occurred when the procedure performed was temporising, rather than definitive. Unsuccessful sedation necessitated admission in 6 (0.7%) children (table 1). The remaining unsuccessful sedations (n=11) did not require admission.

Median depth of sedation was 1 (IQR 1–2). 2.5% (n=21) of patients experienced deep sedation (UMSS 3+4), none of whom required airway interventions or suffered a SAE. Vomiting (n=9) was the only recorded adverse event in this subgroup. Total duration of N_2O exposure, use of higher concentrations of N_2O and combination INF/N_2O therapy were associated with increased sedation depth (online supplemental table 2).

Sedation was unsuccessful for 17 (2%) patients (table 2). The most common reason being inability to tolerate the facemask. Regression analysis found successful sedation was associated with use of 70% N_2O (OR 3.8, 95% CI 1.2 to 12.6) and longer duration of exposure to N_2O (OR 1.3 95% CI 1.1 to 1.5). Use of INF, fasting status, age and sex had no effect on sedation success (table 3; online supplemental table 3). Sedation was provided by a nurse in 87.6% (n=728) of cases. Of the 17 unsuccessful sedations, 14 (82.4%) were nurse delivered. Provider status was

Table 1 Characteristics of patients (N=831)

Characteristics	n	%
Age (years)		
Median (IQR)	9 (6–12)	
Mean (SD)	8.7 (±3.6)	
Age range (years)		
1–3	66	7.9
4–6	172	20.7
7–9	239	28.8
10–12	200	24.1
>12	152	18.3
Not recorded	2	0.2
Sex		
Male	526	63.3
Female	304	36.6
Not recorded	1	0.1
Procedure		
Fracture manipulation	445	53.6
Wound repair	127	15.3
Foreign body removal	91	11.0
Joint reduction	87	10.5
Minor surgical procedure	33	4.0
Wound care	22	2.7
Lumbar puncture	12	1.4
Other*	10	1.2
Not recorded	4	0.5
Fasting status		
Not fasting	79	9.5
0.1–2 hours	118	14.2
2.1–4 hours	142	17.1
4.1–6 hours	87	10.5
>6 hours	68	8.2
Not recorded	337	40.5
Sedation provider		
Nurse	728	87.6
NCHD†	44	5.3
Consultant	16	1.9
Not recorded	43	5.2
Agent used		
N_2O alone	473	56.9
N_2O and INF	358	43.1
Not recorded	0	0
Concentration of N_2O used		
70%	603	72.5
60%	63	7.6
50%	132	15.9
Not recorded	33	4
Depth of sedation		
Median (IQR)	1 (1–2)	
Mean (SD)	1.4 (±0.6)	
UMSS 0	17	2.0
UMSS 1	390	46.9
UMSS 2	298	35.9
UMSS 3	20	2.4
UMSS 4	1	0.1
Not recorded	105	12.6
Duration of sedation (minutes)		
Median (IQR)	10 (7–15)	

Continued

Table 1 Continued

Characteristics	n	%
Mean (SD)	13.2 (±9.5)	
Sedation success		
Successful sedation	809	97.4
Unsuccessful sedation	17	2.0
Not recorded	5	0.6
Patient outcome		
Admitted	97	11.7
Discharged without follow-up	178	21.4
General Practtioner (GP) follow-up	73	8.8
Referred to fracture clinic	388	46.7
Other outpatient follow-up	88	10.6
Not recorded	7	0.8

*Other procedures included intravenous cannulation, urinary catheterisation and physical examination.
†Non-consultant hospital doctor/trainee doctor.
UMSS, University of Michigan Sedation Scale.

not documented for the remaining three cases. One hundred and twenty-two (16.7%) patients reported adverse events during nurse-delivered sedation compared with 11 (18%) patients who received physician-led sedation. When comparing provider status, there was no significant difference between physicians or nursing staff for sedation success (RR 0.98, 95% CI 0.97 to 1.04) or adverse events (RR 0.93, 95% CI 0.55 to 1.6).

There were no SAEs (95% CI 0% to 0.6%) and 137 (16.5%, 95% CI 14.1% to 19.2%) minor adverse events reported over the 10-year period. (table 2). Two children experienced multiple adverse events (bradycardia with vomiting and paradoxical agitation with vomiting). Vomiting was the most common adverse event experienced by patients (n=113, 13.6%, 95% CI 11.4% to 16.1%) accounting for 82.5% of all adverse events. Increasing fasting duration showed a slight association with total adverse event risk (OR 1.03, 95% CI 1.001 to 1.07) on

Table 2 Characteristics of unsuccessful sedations and adverse events

Characteristic	n	%
Unsuccessful sedation (N=17)		
Mask not tolerated	8	47.1
Paradoxical response to sedation	2	11.8
Lack of sedation effect	3	17.6
Vomiting	2	11.8
Parental distress	1	5.9
Not documented	1	5.9
Adverse events		
No adverse event	678	81.6
Any adverse event	137	16.5
Multiple adverse events	2	0.2
Not recorded	16	1.9
Serious adverse events		
Any	0	0
Minor adverse events (n=137)		
Vomiting	113	82.5
Paradoxical response to sedation	15	10.9
Unpleasant recovery reactions	3	2.2
Other*	6	4.4

*Bradycardia, nausea, hallucinations, vertigo.

Table 3 Results of multivariate logistic regression analyses for sedation success, adverse events and vomiting

Variable	OR	95% CI
Factors associated with sedation success		
Use of 70% N_2O	3.8	1.20 to 12.62
Duration of exposure to N_2O (per minute)	1.3	1.09 to 1.50
Combination INF/N_2O therapy	1.1	0.34 to 4.00
Factors associated with any adverse event		
Combination INF/N_2O therapy	1.1	0.62 to 1.78
Use of 70% N_2O	1.1	0.54 to 2.10
Depth of sedation (per grade on UMSS)	1.1	0.67 to 1.65
Fasting duration (per hour)	1.03	1.00 to 1.07
Duration of exposure to N_2O (per minute)	1.02	0.98 to 1.07
Factors associated with vomiting		
Use of 70% N_2O	2.3	1.03 to 5.87
Combination INF/N_2O therapy	1.7	1.09 to 2.73
Sedation depth (per grade on UMSS)	1.5	1.05 to 2.21
Duration of exposure to N_2O (per minute)	1.1	1.04 to 1.12

INF, intranasal fentanyl; N_2O, nitrous oxide; UMSS, University of Michigan Sedation Scale.

regression analysis. No other factor was significantly associated with adverse event risk (table 3; online supplemental table 3).

Given the high incidence of vomiting, we performed a separate regression analysis to investigate contributing factors. In univariate analysis, vomiting was associated with use of 70% N_2O (compared with 50% N_2O) (OR 3.4, 95% CI 1.7 to 8.3), longer duration of exposure to N_2O (OR 1.1, 95% CI 1.0 to 1.1), administration of INF (OR 2.0, 95% CI 1.3 to 3.0) and greater sedation depth (OR 1.9, 95% CI 1.3 to 2.6). Fasting status, procedure indication, age, sex and provider status did not contribute to the risk of vomiting (online supplemental table 3). These findings persisted on multivariate analysis (table 3).

Characteristics of patients who received 51–70% versus 50% concentration N_2O are compared in table 4. Six hundred and sixty-six (80.1%) patients received 51–70% N_2O while 132 (15.9%) patients received 50% N_2O. Concentration was not documented for 33 (4%) patients. Higher concentrations were more likely to be used for major procedures (RR 2.3, 95% CI 2.0 to 2.8) and in combination with INF (RR 1.8, 95% CI 1.6 to 2.0). Use of higher concentrations of N_2O was associated with increased depth of sedation (median UMSS 2 vs 1, p<0.0001). Sedation success rate was also increased (RR 1.04, 95% CI 1.1 to 1.1), probably due to better facemask tolerability (RR 0.06, 95% CI 0.01 to 0.24). There was no increase in overall adverse event rates (RR 1.2, 95% CI 0.8 to 1.9); however, the incidence of vomiting was significantly higher in those receiving 51–70% N_2O compared with 50% (RR 3.0, 95% CI 1.5 to 6.3). These findings persisted when other factors associated with sedation success, sedation depth and vomiting risk were considered in multivariate analysis (table 3; online supplemental table 2).

Combination INF/N_2O therapy was used in 358 (43%) cases and became increasingly common between 2012 and 2020 (24–48%) (online supplemental table 1). Characteristics of patients who received combination INF/N_2O versus N_2O alone are compared in table 5. Children receiving combination therapy had higher median sedation scores than children receiving N_2O alone (median UMSS 2 vs 1, p<0.0001). In comparison to high concentration N_2O, combination therapy did not demonstrate a statistically significant reduction in sedation failure (RR 0.55, 95% CI 0.2 to 1.5), despite increasing sedation depth; perhaps

Table 4 Comparison of low versus high concentration N_2O (N=798)

Characteristic	N_2O 50%	N_2O 51–70%	P value
n			
Total	132	666	
Age (years)			
Mean (SD)	8.3 (±3.7)	8.8 (±3.6)	
Procedure indication			
Wound repair (%)	56 (42.4%)	69 (10.4%)	
Fracture manipulation (%)	25 (18.9%)	402 (60.4%)	
Minor surgical procedure (%)	12 (9%)	19 (3.9%)	
Joint reduction (%)	19 (14.4%)	74 (11.1%)	
Foreign body removal (%)	10 (7.5%)	69 (10.4%)	
Other (%)	10 (7.55)	33 (5.0%)	
Procedure classification			
Major*	44 (33.3%)	476 (71.5%)	<0.01†
Minor	88 (66.7%)	190 (28.5%)	
Coadministration of INF			
Not used	120 (90.9%)	336 (50.5%)	<0.01†
INF used	12 (9.1%)	330 (49.5%)	
Sedation success			
Unsuccessful sedation (%)	7 (5.3%)	10 (1.5%)	0.01†
Not tolerating mask (%)	7 (5.3%)	2 (0.03%)	<0.01†
Sedation depth			
Median (IQR)	1 (1–1)	2 (1–3)	<0.01‡
Mean (SD)	1.05 (±0.47)	1.5 (±0.59)	<0.01§
Adverse events			
No adverse events (%)	111 (85.4%)	548 (82.3%)	
Not documented (%)	2 (0.1%)	10 (0.2%)	
Any adverse events (%)	19 (14.4%)	118 (17.7%)	0.45†
Vomiting (%)	7 (5.3%)	106 (15.9%)	<0.01†

*Fracture manipulation and joint reduction.
†Fisher's exact test.
‡Mann-Whitney U test.
§Student t-test.

Table 5 Comparison of N_2O alone versus combination with INF (N=831)

Characteristic	N_2O	Combination INF+N_2O	P value
n			
Total	473	358	
Age (years)			
Mean (SD)	8.1 (±3.7)	9.6 (±3.3)	
Procedure indication			
Wound repair (%)	118 (25.0%)	9 (2.5%)	
Fracture manipulation	165 (34.9%)	280 (78.2%)	
Minor surgical procedure	30 (6.3%)	3 (2.5%)	
Joint reduction	30 (6.3%)	57 (15.9%)	
Removal of foreign body	87 (18.4%)	4 (1.1%)	
Other	43 (9.1%)	5 (1.4%)	
Procedure classification			
Major*	195 (41.2%)	337 (94.1%)	<0.01†
Minor	278 (58.8%)	21 (5.8%)	
Sedation success			
Unsuccessful sedation	12 (2.5%)	5 (1.4%)	0.32†
Not tolerating mask	9 (2%)	0 (0%)	0.01†
Sedation depth			
Median (IQR)	1 (1–2)	2 (1–2)	<0.01‡
Mean (SD)	1.3 (±0.6)	1.6 (±0.6)	<0.01§
Sedation provider			
Nurse	410 (56.3%)	318 (43.7%)	0.50†
Physician	37 (61.7%)	23 (38.3%)	
Adverse events			
No adverse events	397 (83.9%)	281 (78.5%)	
Not documented	9 (0.2%)	7 (0.2%)	
Any adverse events	67 (14.2%)	70 (19.6%)	0.047†
Vomiting	48 (10.1%)	65 (18.2%)	<0.01†
Serious adverse events	0	0	

*Major procedures are fracture manipulation and joint reduction.
†Fisher's exact test.
‡Mann-Whitney U test.
§Student t-test.
INF, intranasal fentanyl; N_2O, nitrous oxide.

due to being associated with more difficult procedures (RR major procedure 7.6, 95% CI 5.5 to 10.8).

No SAEs (95% CI 0 to 1.3%) occurred with the use of INF. Fischer's test and univariate regression analysis suggested minor adverse events were higher in the combination INF/N_2O group (RR 1.4, 95% CI 1.02 to 1.9); however, this effect was not robust and did not persist on multivariate analysis (tables 3 and 5; online supplemental table 3). Much of this excess risk was due to higher rates of vomiting associated with combination therapy (RR 1.8, 95% CI 1.3 to 2.5), this effect persisted in multivariate analysis (table 3).

INF use was strongly associated with coadministration of 51–70% N_2O (RR 2.3, 95% CI 2.0 to 2.8). However, multivariate analysis confirmed INF remained an independent predictor for vomiting risk and sedation depth, even when the effects of 70% N_2O were accounted for (table 3; online supplemental table 2). Direct comparison showed 70% N_2O had a larger effect on sedation depth and improved sedation success rates when compared with INF but was also associated with a greater risk of vomiting (table 3; online supplemental table 2).

DISCUSSION

In this review of predominantly nurse-delivered N_2O PED sedations, 97.4% (95% CI 96.0 to 98.3%) of sedation events were successful. There were no SAEs recorded, with an upper 97.5% CI for SAEs of 0.6%. Other studies have reported SAE rates of ~0.5%, ranging from 0.3 to 15% depending on the definition and agent.[1–3 14 23] Our data suggest the rates of SAEs using N_2O alone or in combination with INF are similar.

Our incidence of minor adverse events, in particular vomiting, was high. Large mixed studies report vomiting in ~5%.[1 23] When limited to studies using continuous flow N_2O, the incidence of vomiting is 2.2–8.5%.[10 11 24–27] Vomiting occurred in 13.6% (95% CI 11.4% to 16.1%) of our cohort which is significantly higher. Possible explanations include our use of higher N_2O concentrations and coadministration of INF; both of which were independently associated with increased vomiting. Our finding of increased risk of emesis with higher concentrations of N_2O conflicts with previous work suggesting no association between N_2O concentration and emesis risk.[24 25 27 28] Our analysis showed higher concentrations of N_2O remained a risk factor even when accounting for the effects of INF. One hypothesis is that our use of continuous flow N_2O circuits rather than demand valve circuits could cause gastric insufflation and increased vomiting. Unfortunately, there is no published literature comparing the effects of demand valve versus continuous flow N_2O systems.

Fasting duration and emesis risk with N_2O is a controversial area, with one study reporting a reduction in emesis rates when patients were given a light meal prior to sedation.[29] Observational data have also suggested an increased risk of emesis when fasting.[24] However, studies specifically addressing the question failed to find an association.[28] Similarly, we did not find a relationship between fasting and emesis risk (OR 1.0, 95% CI 0.97 to 1.13). We found some association between increased fasting duration and risk of adverse events (OR 1.03, 95% CI 1.00 to 1.07) but the clinical significance of this effect is questionable, given the low magnitude of effect and borderline statistical significance. In general, our results should be interpreted with caution as fasting status was recorded in only 59.4% of patients.

Regarding combination INF/N_2O use, a randomised controlled trial (RCT) of 402 patients compared combination INF/N_2O with N_2O alone and found no differences in analgesia, sedation depth or vomiting.[30] In contrast, observational data report increased vomiting but improved sedation.[19 20] Our study mirrored the results of earlier observational studies, finding that INF increases both sedation depth (median UMSS 1 vs 2) and emesis risk (OR 2.3, 95% CI 1.03 to 5.87). The absence of any SAEs in our study suggests that combination therapy could be a safe sedation adjunct, but the 97.5% upper CI for SAE is 1.3%; preventing definitive exclusion of a small increased risk.

Use of 70% N_2O and INF both independently increased sedation depth compared with 50% N_2O alone (online supplemental table 2). This effect likely accounts for our ability to achieve high PPS success rates despite N_2O's lack of potency. Despite increasing sedation depth, combination INF/N_2O did not increase sedation success (OR 1.1, 95% CI 0.34 to 4.0), this may be because INF/N_2O use was predominantly confined to the difficult major procedures (RR 7.6, 95% CI 5.5 to 10.8). Combination INF/N_2O and 70% N_2O were both more likely to be used for major procedures, which suggests that clinicians actively tailor the agents used to balance the depth of sedation required against risk of emesis to achieve an optimal, individualised sedation profile.

87.6% of sedations were provided by nursing staff. There was no evidence of a difference between nurse- and physician-delivered sedation for adverse event rate or sedation success. This suggests that our model enables trained nurses to provide safe and effective sedation, even with the higher patient acuity and procedural difficulty of our cases compared with previous studies.[11 27] Our model could offer an attractive alternative to physician-led, parenteral sedation for PEDs lacking this skillset. Additionally, staff allocation could be improved by reducing the number of physicians required to perform PPS. However, assessment of safety must be balanced against the wide CIs we report for adverse events, low overall numbers of unsuccessful sedations and the single site nature of our study, which limits definitive conclusions.

Our study is subject to limitations in several areas. The observational nature limits our ability to account for unobserved confounders or control allocation of sedation agents between patients. The incidence and type of adverse events depended on accurate recording in the sedation record; this may have introduced bias as completion of the record was reliant on the PPS provider and some providers may have been hesitant to document complications. Multiple providers completed the forms, and no formal assessment of inter-rater variability was calculated. We attempted to mitigate this concern through our formalised training programme and the use of objective definitions and fixed reporting guidelines wherever possible. The pragmatic nature of data collection also meant that some emergent sedations were not recorded and not all forms were completed in full, with 7.4% of total datapoints missing from the final registry. Finally, we only recorded sedation depth, there was no attempt to record any subjective or objective indicators of patient pain. Given the increasingly recognised difference between analgesia and sedation, this could be a relevant limitation when considering the effectiveness of sedation.

In conclusion, we demonstrated effective PPS using continuous flow N_2O with no SAEs. N_2O can provide effective sedation; even for highly painful procedures such as fracture manipulation. Combination of N_2O with INF can increase sedation depth but increases emesis risk. Vomiting was a common minor adverse event and was significantly associated with use of 70% N_2O and INF. High concentration N_2O, either alone or in combination with INF was safely and effectively administered by nursing staff after appropriate training in a PED setting.

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Data availability statement Data are available upon reasonable request. Any data pertaining to the research may be obtained in a de-identified format from the corresponding author, provided a reasonable request is made within an acceptable timeframe.

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HCR NUMBER

SURNAME
NAME
DOB
AFFIX ADDRESSOGRAPH LABEL HERE

Record of sedation for Emergency Department procedures only

This is not a medication order. Use this form for ALL procedural sedations in ED or delivered by ED staff eg, in CT

Date: ___/_____/____ Time procedure started (24hr clock): _____ Type of procedure: _____

( )* NUMBER CORRESPONDS TO THE INFORMATION PROVIDED ON THE REVERSE		
PRIOR TO SEDATION		
Risk assessment and exclusion criteria checked (1)*	Yes	
List if any:		
If using ketamine/IV midazolam ED consultant must be informed (name of ED consultant):		
Prepare patient/parents Last ate (2)* Solids ___HRS Liquids ___HRS (PLEASE RECORDED FOR EVERY SEDATION, EVEN IF FASTING NOT REQUIRED)		
Sedation handout discussed with patient/parent	Yes	
Informed written consent obtained: indications discussed adverse events discussed/documented in HCR	Yes	
Adequate staff available (3)* Nurse NCHD Consultant	Yes	
Baseline observations (sedation score, HR, RR, $Sa0_2$) performed immediately prior to administering sedation (BP for Ketamine)	Yes	
Sedation agent prescribed on Medication Chart	Yes	
Weight and allergies documented on medication chart	Yes	
Non-pharmacological techniques planned (e.g. TV/distraction box)	Yes	No
Other analgesic/sedative agents administered. If yes, specify	Yes	No
Prepare venue (4)* Equipment is present and functioning: procedure equipment, emergency equipment	Yes	No
"TIME OUT" or "Positive Patient Identification" (5)*	Yes	
	Yes	

ABOVE SECTION SHOULD BE COMPLETED PRIOR TO THE PATIENT PROCEEDING TO THE "SEDATION PERIOD"

DURING SEDATION PERIOD		
Drugs administered by ED-trained staff member	Yes	
Vital signs/Sedation Score documented every 5 minutes (on Obs sheet)	Yes	
POST-PROCEDURE		
Patient returned to baseline Sedation Score	Yes	
Observation within normal limits	Yes	
Discharge criteria met (7)*	Yes	
Post-sedation care discussed (Sedation handout) (N.B. safety and injury prevention highlighted)	Yes	

SUMMARY OF SEDATION EPISODE (PLEASE CIRCLE)

Sedation used (please circle): nitrous oxide ketamine midazolam other (specify) _____

Route: Inhaled IV IM Intranasal PO

Additional Anaesthesia: Local (infiltrative lignocaine) Topical (Ametop) LAT
Total dose:_____ mg OR N_2O_____% for_____minutes
Deepest level of sedation:_____(indicate University of Michigan Sedation Score (UMSS)) (6)*
Side effects/adverse events: No Yes
(specify)_____

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Staff members identification Print Name_____ Signature_____IMC No/ABA PIN_____ Print Name_____ Signature_____IMC No/ABA PIN_____	Time Out completed by: (5)* Tick box by staff member listed

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1. RISK ASSESSMENT

If any child meets the risk assessment criteria OR if you have reservations, contact the Emergency Department consultant for further discussion before using a sedation agent

Significant risk of delayed gastric emptying or vomiting e.g. bowel obstruction, gastro-oesophageal reflux
.....
Significant respiratory disease e.g. upper airway obstruction, airway infection, apnoea, exacerbation of asthma, pneumonia
.....
Significant cardiovascular impairment e.g. pulmonary hypertension, cardiomyopathy, hypovolaemia
.....
Abnormal conscious state/risk of raised ICP e.g. head injury, meningitis, space occupying lesion
.....
Acute systemic infection e.g. sepsis
.....
Immunosuppression e.g. post-op transplant, neutropenia
.....
Significant liver disease/liver failure e.g. biliary atresia
.....
Prior adverse event
.....
Prior allergic reaction
.....
Patient receiving opioids or other sedative agents
.....
Age less than or equal to 6 months (oral agents) or less than or equal to 1 year (nitrous oxide and ketamine)
.....
Significant neuromuscular disease/kyphoscoliosis

	NITROUS OXIDE	KETAMINE
EXCLUSION CRITERIA	< 1 year Abnormal homocysteine metabolism Pneumothorax or Lung cyst Bowel obstruction History of Bleomycin administration B12 folate deficiency Middle ear disease	< 1 year Glaucoma Head injury, CNS lesion, epilepsy, ADHD, psychosis

2. FASTING TIMES	NITROUS OXIDE	ORAL AGENTS	KETAMINE
	No fasting required	2 hours solids and liquids	4 hours solids or milk 2 hours clear liquids
3. STAFF LEVELS	2 staff required 1 ED-sedation trained staff	2 staff required 1 ED-sedation trained staff	3 staff required (incl. ED Consultant) 2 ED-sedation trained staff

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4. LOCATION AND EQUIPMENT CHECK	Location: nitrous oxide in procedure room, ketamine in resuscitation Equipment: this equipment should be in the room at all times, turned on and functioning during the sedation period • suction device; bag/valve/mask for size of patient with correct mask • oxygen available by mask • monitoring equipment (HR, RR, SaO_2, BP) • access to resuscitation trolley with appropriate sized airway equipment
5. "TIME OUT" OR POSITIVE IDENTIFICATION"	Both staff involved in the procedure will confirm the following: • the patient's identity checked by ID band or positive identification with parent/guardian or HCR • confirm or mark site (if applicable) • procedure to be performed and appropriate sedation agent prescribed
6. DETAILS OF SEDATION SCORE (UMSS)	0 = Awake and alert – THIS IS NOT SEDATED 1 = Minimally sedated: may appear tired/sleepy, responds to verbal conversation and/or sound 2 = Moderately sedated: sleeping, easily roused with light tactile stimulation or simple verbal command 3 = Deep sedation: deep sleep, rousable only with deep or significant physical stimulation 4 = Unrousable
7. DISCHARGE CRITERIA	• return to pre-sedation level of consciousness • resumption of purposeful neuromuscular activity • ability to ambulate or sit without support (if appropriate) • ability to verbalise (if appropriate) • final set of vital signs within normal limits for patient's age • ability to tolerate oral fluids

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Value Name	Explanation	Units	Possible Values
Patient ID	Sample Study Number.	Integer	1 to XXX corresponding to study sample size.
			Total Sample Size 831
Date of Procedure	Date Sedation Event was completed.	Date	DD/MM/YYYY
Duration of Sedation Event	Total duration for which the patient was sedated before returning to UMSS 0.	Minutes	Whole integer. Cell is left blank for missing data.
Duration of Exposure	Total duration for which the patient was exposed to Nitrous Oxide.	Minutes	Whole integer. Cell is left blank for missing data. Maximum value set to 90 minutes; higher values trigger manual review.
Sedation Status	Parameter to indicate whether the patient was sedated to allow successful completion of the procedure.	Binary	Successful
			Failed
			Cell is left blank for missing data
Adverse Event	If an adverse occurred.	Binary	TRUE
			FALSE
			Cell is left blank for missing data
Adverse Event Type	Description of the type of adverse event experienced. "Other" subcategory, initially entered as free text by sedation provider to ensure maximal data capture, then re-categorised by research staff as appropriate.	Fixed Categories	No Adverse Events
			Vomiting
			Nausea
			Not Tolerating Mask
			Agitation
			Vertigo
			Hallucination
			Bradycardia
			Other
			Cell is left blank for missing data
Airway Intervention	Were any Airway repositioning or more advanced techniques required.	Binary	Not Required
			Required
			Cell is left blank for missing data

Additional Analgesia	Did the patient require additional analgesia before or during the procedure	Free text	A free text description of analgesia given
Intranasal Fentanyl	Was Intranasal Fentanyl given in addition to Nitrous Oxide for the sedation event. Will be true if fentanyl, IN fentanyl or INF listed in the additional analgesia subsection after review by research staff.	Binary	TRUE
			FALSE
			Cell is left blank for missing data
Pain Score	0-10 Pain score provided by patient	Integer	Whole integer from 0-10
Age	Age of the patient receiving sedation	Integer	Age in years. Possible values 0-16.
Gender	Sex of the patient being sedated.	Binary	M = Male
			F = Female
			Cell is left blank for missing data
Procedure Type	Type of procedure performed during sedation. "Other" subcategory, initially entered as free text by sedation provider to ensure maximal data capture, then categorised into fixed categories by research staff.	Fixed Categories	Fracture Manipulation
			Joint Reduction
			Suturing
			Wound care
			Surgical
			Removal of Foreign Body
			Lumbar Puncture
			Other
			Cell is left blank for missing data
Discharge Criteria	Did the patient meet the discharge criteria post sedation.	Binary	TRUE
			FALSE
			Cell is left blank for missing data
Discharge Outcome	Description of the final discharge disposition of the patient.	Fixed Categories	Admitted
			Discharged Home
			Discharged to ED Review Clinic
			Discharged to OPD
			Discharged to Fracture Clinic
			GP follow up
			Blank if none of the above
Fasting Duration	Number of hours for which the patient was fasting prior to sedation	Integer	Whole integer representing hours fasting. Cell is left blank for missing data.

Sedationist	Title/Grade of provider of sedation.	Free Text	Free text descriptor of staff member who provided sedation
Nurse Led	Indicator of whether sedation was provided by nurse. Considered true if details in "sedationist" consistent with sedation delivery by a member of nursing staff, ie ANP, ED ANP, ED nurse, ED CRN, ED staff nurse, staff nurse.	Binary	TRUE
			FALSE
			Blank if unclear or not recorded
Maximum Nitrous Dose	Maximum Concentration of Nitrous Oxide used at any point during sedation.	Fixed Categories	50% = 50% Nitrous Oxide
			60% = 60% Nitrous Oxide
			70% = 70% Nitrous Oxide
			Cell is left blank for missing data
UMSS	Scale that assesses the level of sedation. Values range from 0-4. Assigned by the sedation provider at the time of sedation.	Integer	Single 0-4 integer corresponding to UMSS category. Cell is left blank for missing data
	0 = Awake and alert 1 = Minimally sedated, appropriate response to voice. 2 = Moderate sedation, around with tactile stimulation 3 = Deeply sedated, requires significant physical stimulation to rouse 4 = Unrousable		

Supplemental Material

***Supplementary Table 1**: Temporal trends in nitrous oxide and intranasal fentanyl use*

Year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Total	71	75	54	45	31	42	109	154	108	139	3
N_2O Alone	71	57	44	33	20	21	40	70	43	72	2
Combination Therapy (%)	0 (0%)	18 (24%)	10 (19%)	12 (26%)	11 (35%)	21 (50%)	69 (63%)	84 (55%)	65 (60%)	67 (48%)	1 (33%)

***Supplementary Table 2**: Result of Multivariate Linear Regression Analysis for Sedation Depth (UMSS score).*

Variable	Estimate	95% CI
Factors Associated with Sedation Depth		
Use of 70% Nitrous Oxide	0.45	0.34 – 0.57
Use of 60% Nitrous Oxide	0.30	0.13 – 0.48
Use of Intranasal Fentanyl	0.13	0.05 – 0.22
Duration of Exposure to N_2O (per minute)	0.01	0.005 – 0.02
Age	0.002	-0.01 – 0.02
Male Sex	0.04	-0.06 – 0.14
Fasting Duration (per hour)	0.003	-0.01 -0.01

***Supplementary Table 3**: Result of Univariate Logistic Regression Analysis*

Variable	Odds Ratio	95% Confidence Interval
Factors Associated with Sedation Success		
Use of 70% Nitrous Oxide	4.2	1.44 - 11.81
Use of 60% Nitrous Oxide	1.7	0.40 – 11.69
Duration of Exposure to N_2O (per minute)	1.3	1.09 - 1.51
Use of Intranasal Fentanyl	1.8	0.67 - 5.82
Female Sex	1.8	0.61 - 6.31
Fasting Duration (per hour)	1.1	0.90 - 1.40
Age (per year)	1.1	0.94 - 1.25
Factors Associated with Adverse Events		
Duration of Exposure to N_2O (per minute)	1.04	1.01 – 1.08
Fasting Duration (per hour)	1.0	1.00 – 1.07
Use of Intranasal Fentanyl	1.4	0.99 – 2.1
Use of 70% Nitrous Oxide	1.3	0.80 – 2.31
Use of 60% Nitrous Oxide	1.1	0.47 – 2.54
Sedation Depth (per point UMSS)	1.1	0.79 – 1.49
Age (per year)	1.0	0.92 – 1.02
Nurse Delivered Sedation	0.9	0.49 – 1.92
Major Procedure	0.9	0.63 – 1.35
Female Sex	0.8	0.50 – 1.10
Factors Associated with Vomiting		
Use of 70% Nitrous Oxide	3.4	1.66 – 8.31
Use of 60% Nitrous Oxide	2.9	1.06 – 8.75
Use of Intranasal Fentanyl	2.0	1.32 – 2.96
Sedation Depth (per point UMSS)	1.9	1.32 – 2.64
Duration of Exposure to N_2O (per minute)	1.1	1.03 – 1.11
Major Procedure	1.5	0.97 – 2.34
Nurse Delivered Sedation	1.2	0.57 – 2.41
Fasting Duration (per hour)	1.0	0.97 – 1.13
Age (per year)	1.0	0.92 – 1.03
Female Sex	0.7	0.43 – 1.02