

Safety and effectiveness of nitrous oxide procedural sedation in a paediatric emergency department

Dear Editor,

Nitrous oxide (N₂O) produces dissociative euphoria, amnesia and analgesia, and is a common sedative for procedural sedation in paediatric emergency departments (EDs) due to its non-parenteral administration and good safety profile.¹⁻³ Suitable procedures include fracture reduction, toilet and suturing, incision and drainage, and application of burn dressings. The concentration of N₂O administered ranges from 30–70%, with maximum effect at 5 minutes, and rapid recovery upon discontinuation.^{1,4} Co-administered medications include intranasal fentanyl (1.5µg/kg, maximum 100µg/dose) administered 30–60 minutes prior to enhance analgesia,³ oral analgesics, topical anaesthesia or parenteral morphine.

Although N₂O is commonly used globally, there is no published report on its effectiveness and safety in paediatric patients in Singapore. We seek to identify the effectiveness of N₂O as a form of procedural sedation and analgesia for children requiring painful procedures in a tertiary paediatric emergency department (ED), study the incidence of adverse events, and evaluate the safety of co-administered opioids.

A retrospective analysis was performed on all patients less than 18 years who underwent procedural sedation with N₂O as a primary agent from 1 April 2013 to 31 September 2021, at the ED of KK Women's and Children's Hospital, Singapore. A prospective electronic database of all procedural sedations performed at the ED was set up in April 2013. All sedation-related adverse events and interventions were prospectively documented in the sedation forms in the medical records and extracted into the database. Data on demographics, diagnosis, procedures, types of sedatives, other co-administered medications, adverse events, and interventions were electronically extracted from the database. N₂O concentration, flow rate, start and end times, and sedation depth (Children's Hospital of Wisconsin Sedation Scale)⁵ were extracted manually from electronic medical records. The Children's Hospital of Wisconsin Sedation Scale has a scale of 0–6, with 6 being agitated. Data were anonymised in password-protected Excel (Microsoft Corp, Redmond, US) file.

Statistical analyses were performed using SPSS Statistics version 28.0 (IBM Corp, Armonk, US). Categorical variables were analysed using Fisher's

Exact test and continuous variables using independent t-test. Univariate regression analyses were performed to identify predictors of adverse events. Variables with *P* value ≤0.1 in the univariate analysis were included in a multivariate logistic model to identify independent predictors.

In the study period from April 2013 to September 2021, 918 children underwent N₂O sedation (Table 1). The median age was 11.91 (interquartile range [IQR] 9.26–13.90) years. Majority were male (75.4%). The most common diagnosis was fracture/dislocation requiring manipulation and reduction (98.3%). The mean duration of sedation was 15±9 minutes, and the mean duration of recovery was 3±4 minutes (n=511). A total of 93.1% received 50–70% N₂O, while 177 (19.3%) received pre-planned local/topical analgesia.

Nine hundred patients (98%) had their procedures successfully completed using N₂O sedation, with or without pre-planned oral, intranasal or topical analgesia. Most (97.2%) achieved a sedation scale of 3–5 (minimal to moderate sedation), with a mean decrease in sedation scale of 0.25±0.62 (n=386). Five (1.3%) had sedation scale ≤2. Of the remaining 18 patients, six (0.7%) received Bier's block (2 for inadequate sedation, 2 given prior to N₂O sedation and 2 given concurrently). Twelve (1.3%) patients required intramuscular (IM) ketamine subsequently. None received intravenous (IV) ketamine.

Sixteen (1.7%) patients had sedation-related adverse events, of whom 2 received IM ketamine subsequently, and 14 (1.5%) received N₂O only (Table 1). Most events were minor: emesis (n=14, 1.5%), desaturation (n=1, 0.1%), and agitation (n=1, 0.1%). Twelve required no intervention, 2 required supplemental oxygen (one given prophylactically for agitation), and 2 required oral ondansetron. None required assisted ventilation or cardiopulmonary resuscitation. None were admitted for sedation-related events. Patients with adverse events (median age 9.90, IQR 6.88–12.05) were significantly younger than those without (median age 11.95, IQR 9.51–13.91, *P*=0.009). There was no significance between N₂O concentration and adverse events (*P*=1.000).

In the univariate analysis (Table 1), intranasal fentanyl (odds ratio [OR] 2.692, 95% CI 0.587–12.346, *P*=0.202) or morphine (OR 1.519, 95% CI 0.194–11.879,

Table 1. Baseline characteristics, procedural details and adverse events for patients who underwent sedation with nitrous oxide

Variable	Number (%)			P value
	No adverse events (n=902)	Adverse events (n=16)	Total (n=918)	
Age, median (IQR), years	11.95 (9.31–13.93)	9.90 (6.88–12.05)	11.91 (9.26–13.90)	0.009 ^a
Sex				0.773
Female	222 (24.6)	3 (18.8)	225 (24.5)	
Male	678 (75.4)	13 (81.3)	693 (75.5)	
Ethnicity				0.663
Chinese	473 (52.4)	11 (68.8)	484 (52.7)	
Malay	159 (17.6)	2 (12.5)	161 (17.5)	
Indian	150 (16.6)	1 (6.3)	151 (16.5)	
Others	120 (13.3)	2 (12.5)	122 (13.3)	
Diagnosis				0.030
Fracture, dislocation	888 (98.5)	14 (87.5)	902 (98.3)	
Laceration, open wound	3 (0.3)	1 (6.3)	4 (0.4)	
Abscess, chalazion, styel	4 (0.4)	0	4 (0.4)	
Foreign body	3 (0.3)	0	3 (0.3)	
Nailbed injury	0	0	0	
Others ^b	4 (0.4)	1 (6.3)	5 (0.5)	
Site of procedure				0.141
Head, face	2 (0.2)	0	2 (0.2)	
Upper limb	780 (86.5)	13 (81.3)	793 (86.4)	
Lower limb	115 (12.8)	2 (12.5)	117 (12.8)	
Others	5 (0.6)	1 (6.3)	6 (0.7)	
Type of procedure				0.051
Manipulation and reduction	888 (98.5)	14 (87.5)	902 (98.3)	
Toilet and suturing	1 (0.1)	1 (6.3)	2 (0.2)	
Incision and drainage	4 (0.4)	0	4 (0.4)	
Removal of foreign body	3 (0.3)	0	3 (0.3)	
Debridement/dressing	2 (0.2)	0	2 (0.2)	
Others	4 (0.4)	1 (6.3)	5 (0.5)	
Co-administered medications/ analgesia ^c	191 (21.2)	8 (50.0)	199 (21.7)	0.011
Paracetamol or NSAIDs (ibuprofen/diclofenac)	86 (9.5)	1 (6.3)	87 (9.5)	1.000
Intranasal fentanyl	54 (6.0)	2 (12.5)	56 (6.1)	0.255
Morphine	43 (4.8)	3 (18.8)	46 (5.0)	0.042
Local anaesthesia (digital block/ subcutaneous lignocaine/LET gel)	10 (1.1)	2 (12.5)	12 (1.3)	0.021
None required	711 (78.8)	8 (50.0)	719 (78.3)	

Table 1. Baseline characteristics, procedural details and adverse events for patients who underwent sedation with nitrous oxide (Cont'd)

Variable	Number (%)			P value
	No adverse events (n=902)	Adverse events (n=16)	Total (n=918)	
Successful completion of procedure				
Yes	886 (98.2)	14 (87.5)	900 (98.0)	
Further modalities of pain management required				
Regional block (Bier's block)	6 (0.7)	0	6 (0.7)	1.000
Due to unsuccessful sedation	2 (0.2)	0	2 (0.2)	
Parenteral sedation (IM Ketamine)	10 (1.1)	2 (12.5)	12 (1.3)	0.017
Due to unsuccessful sedation	2 (0.2)	0	2 (0.2)	
Due to unsuccessful procedure or other reasons	8 (0.9)	2 (12.5)	10 (1.0)	
Nitrous oxide concentration, % (n=349) ^d				1.000
30	15 (4.4)	0	15 (4.3)	
50	56 (16.3)	1 (20)	57 (16.3)	
60	9 (2.6)	0	9 (2.6)	
70	264 (76.2)	4 (80)	268 (76.8)	
Sedation score (Children's Hospital of Wisconsin Sedation Scale) (n=386) ^{d,e}				0.043
1	1 (0.3)	1 (16.7)	2 (0.5)	
2	3 (0.8)	0	3 (0.8)	
3	10 (2.6)	0	10 (2.6)	
4	63 (16.6)	2 (33.3)	65 (16.5)	
5	297 (78.2)	3 (50.0)	300 (77.7)	
6	6 (1.6)	0	6 (1.6)	
Adverse events	Number (%)			
All patients (n=918)	16 (1.7)			
Emesis	14 (1.5)			
Oxygen desaturation	1 (0.1)			
Agitation	1 (0.1)			
N ₂ O alone (n=807)	11 (1.4)			
Emesis	10 (1.2)			
Oxygen desaturation	0			
Agitation	1 (0.01)			
N ₂ O with intranasal fentanyl (n=54)	2 (3.7)			
Emesis	2 (3.7)			
N ₂ O with morphine (n=44)	1 (2.3)			
Emesis	1 (2.3)			
N ₂ O with morphine and intranasal fentanyl (n=1)	0			

Table 1. Baseline characteristics, procedural details and adverse events for patients who underwent sedation with nitrous oxide (Cont'd)

Adverse events	Number (%)			
Patients with subsequent IM Ketamine sedation (n=16)				
N ₂ O without opioids (n=12)	0			
N ₂ O with intranasal fentanyl (n=2)	0			
N ₂ O with morphine (n=2)	2 (100)			
Emesis	1 (50)			
Oxygen desaturation	1 (50)			
Predictors of adverse events associated with nitrous oxide sedation				
Variable (n=918)	Univariate analysis		Multivariate analysis ^g	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, years (n=906) ^f	0.754 (0.631–0.903)	0.002		
Additional analgesia (n=906) ^f				
Morphine: Yes	1.519 (0.194–11.879)	0.690		
Morphine: No	Ref			
Use of intranasal fentanyl (n=906) ^f				
Fentanyl: Yes	2.692 (0.587–12.346)	0.202		
Fentanyl: No	Ref			
Use of other sedative				
IM ketamine	12.743 (2.554–63.581)	0.002	11.553 (2.227–59.943)	0.004
None	Ref		Ref	

CI: confidence interval; IM: intramuscular; IQR: interquartile range; LET: topical lidocaine/epinephrine/tetracaine; N₂O: nitrous oxide;

NSAIDs: non-steroidal anti-inflammatory drugs

^a $P < 0.05$ is considered statistically significant

^b Other procedures included 4 paraphimosis, 1 removal of K-wires

^c Some patients received more than one modality of analgesia

^d Data available after June 2016

^e Lowest sedation score documented for each patient:

0=Unresponsive to painful stimulus, 1=Arouses, but not to consciousness, with painful stimulus, 2=Arouses slowly to consciousness with sustained painful stimulus, 3=Arouses to consciousness with moderate tactile or loud verbal stimulus, 4=Drowsy, eyes open or closed, but easily arouses to consciousness with verbal stimulus, 5=Spontaneously awake without stimulus, 6=Anxious, agitated or in pain

^f Patients who required further management with IM ketamine were excluded from this analysis

^g Adjusted for age as a confounder

$P=0.690$) was not associated with increased adverse events. For patients receiving intranasal fentanyl and N₂O, 2/56 (3.6%) required ketamine due to unsuccessful procedures. Neither had adverse events. In contrast, for patients receiving morphine and N₂O, 2/46 (4.3%) required ketamine, and both had adverse events (one desaturation to 91% and one emesis) (OR 4.61, 95% CI 1.266–16.784, $P=0.020$).

Among patients who received subsequent IM ketamine, 2/12 (16.7%) had adverse events (OR 12.743, 95% CI 2.554–63.581, $P=0.002$). This was still significant (adjusted OR 11.553, 95% CI 2.227–

59.943, $P=0.004$) after adjusting for age as a covariate in multivariate analysis. Older children have been observed to have increased emesis risk with IM ketamine.⁶

The risk of emesis for co-administered intranasal fentanyl with N₂O was reported to be 10–27.5%, with increased rates at 70% N₂O.^{3,7} In our study, the emesis rate was 1.4% with N₂O alone, and 3.7% (2/54) for intranasal fentanyl with N₂O. This is also lower than the emesis rates (8.4%) with IM ketamine sedation reported.⁶ The risk of oxygen desaturation during N₂O sedation in our study was 0.1%, compared

to 1.9% with IM ketamine sedation.⁸ N₂O sedation is a safe and effective alternative with a short recovery time if only mild to moderate depth of sedation is required.

In our study, the risk of adverse events was higher when subsequent IM ketamine was given after N₂O sedation with co-administered parenteral morphine, compared with co-administered intranasal fentanyl. When additional analgesia with opioids is indicated with N₂O sedation, intranasal fentanyl is a preferred option compared to parenteral morphine.

A limitation of our study was that delayed events were not included as most patients were discharged after 30 minutes. However, the incidence is likely rare, as N₂O-related emesis is related to the duration of exposure, insignificant up to 1 hour.⁹

In summary, N₂O is safe for paediatric sedation, with or without adjunct opioids. However, caution should be taken when a third sedative is added. We experienced a low incidence of adverse events, likely also contributed by close supervision and adherence to department protocols.

REFERENCES

1. Krauss B, Green SM. Procedural sedation and analgesia in children. *Lancet* 2006;367:766-80.
2. Pedersen RS, Bayat A, Steen NP, et al. Nitrous oxide provides safe and effective analgesia for minor paediatric procedures—a systematic review. *Dan Med J* 2013;60:A4627.
3. Seith RW, Theophilos T, Babl FE. Intranasal Fentanyl and High-concentration Inhaled Nitrous Oxide for Procedural Sedation: A Prospective Observational Pilot Study of Adverse Events and Depth of Sedation. *Acad Emerg Med* 2012;19:31-6.
4. Yee R, Wong D, Chay PL, et al. Nitrous oxide inhalation sedation in dentistry: An overview of its applications and safety profile. *Singapore Dent J* 2019;39:11-9.
5. Hoffman GM, Nowakowski R, Troshynski TJ, et al. 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.
6. Suryaprakash S, Tham LP. Predictors of emesis in children undergoing procedural sedation with intramuscular ketamine in a paediatric emergency department. *Singapore Med J* 2017;58:660-5.
7. Seiler M, Staubli G, Landolt MA. Combined nitrous oxide 70% with intranasal fentanyl for procedural analgesedation in children: a prospective, randomised, double-blind, placebo-controlled trial. *Emerg Med J* 2019;36:142-7.
8. Lee JL, Tham LP. Incidence and predictors of respiratory adverse events in children undergoing procedural sedation with intramuscular ketamine in a paediatric emergency department. *Singapore Med J* 2020;63:28-34.
9. Peyton PJ, Wu CY. Nitrous Oxide-related Postoperative Nausea and Vomiting Depends on Duration of Exposure. *Anesthesiology* 2014;120:1137-45.

Si Qi Tan ^{1MD}, Lai Peng Tham ^{1,2,3,4MMed}

¹ Department of Emergency Medicine, KK Women's and Children's Hospital, Singapore

² Duke-NUS Medical School, Singapore

³ Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁴ Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Correspondence: Dr Si Qi Tan, KK Women's and Children's Hospital, 100 Bukit Timah Rd, Singapore 229899.

Email: siqi.tan@mohh.com.sg