A Randomized Clinical Trial of Continuous-Flow Nitrous Oxide and Midazolam for Sedation of Young Children During Laceration Repair

Jan D. Luhmann, MD[*‖]
Robert M. Kennedy, MD[*‖]
Fran Lang Porter, PhD[‡‖]
J. Philip Miller, AB[§]
David M. Jaffe, MD[*‖]

From the Division of Emergency Medicine,[*] the Department of Psychology,[‡] and the Division of Biostatistics,[§] Washington University School of Medicine, and St. Louis Children's Hospital,[‖] St. Louis, MO.

Received for publication July 26, 1999. Revisions received March 27, 2000, July 27, 2000, and August 22, 2000. Accepted for publication September 29, 2000.

Presented at the Pediatric Academic Societies' annual meeting, New Orleans, LA, May 1998, and at the Society for Academic Emergency Medicine annual meeting, Chicago, IL, May 1998.

Address for reprints: *Jan D. Luhmann, MD, St. Louis Children's Hospital, One Children's Place, Room 4S50, St. Louis, MO 63110; 314-454-2341, fax 314-454-4345; E-mail luhmann_j@kids.wustl.edu.*

0196-0644/2001/$35.00 + 0
47/1/112003
doi:10.1067/mem.2001.112003

See editorial, p. 61.

Study objective: To compare the efficacy and complication profile of oral midazolam therapy and continuous-flow 50% nitrous oxide in alleviating anxiety during laceration repair in children 2 to 6 years old.

Methods: We conducted a prospective, randomized clinical trial using 4 study groups who required laceration repair: (1) children who received standard care alone, which included comforting and topical anesthesia augmented with injected lidocaine if needed; (2) children who received standard care and oral midazolam; (3) children who received standard care and nitrous oxide; and (4) children who received standard care, oral midazolam, and nitrous oxide. Videotapes were blindly scored using the Observational Scale of Behavioral Distress-Revised (OSBD-R) to assess distress during baseline, wound cleaning, lidocaine injecting, suturing, and recovery. Adverse effects were noted during suturing and by parent questionnaires completed 24 hours after suturing and at suture removal. OSBD-R data were analyzed using repeated-measures analysis of variance. Adverse effect data were analyzed using categorical models.

Results: Two hundred four subjects were enrolled (midazolam plus nitrous oxide 52, midazolam 51, nitrous oxide 51, standard care 50; mean patient age was 4.1 years; 66% were boys). Mean OSBD-R scores were lower for groups that received nitrous oxide during wound cleaning by 2.2 points (95% confidence interval [CI] 1.1 to 3.2), lidocaine injecting by 2.5 points (95% CI 1.4 to 3.5), and suturing by 2.9 (95% CI 1.8 to 3.9). Adverse effects occurred more frequently, and recovery times were longer for groups that received midazolam.

Conclusion: For facial suturing in 2- to 6-year-old children, regimens including continuous-flow nitrous oxide were more effective in reducing distress, and had fewer adverse effects and shorter recovery times than midazolam.

[Luhmann JD, Kennedy RM, Porter FL, Miller JP, Jaffe DM. A randomized clinical trial of continuous-flow nitrous oxide and midazolam for sedation of young children during laceration repair. *Ann Emerg Med.* January 2001;37:20-27.]

INTRODUCTION

Lacerations requiring sutures contribute to as many as half of emergency department visits by injured children.[1] Even with the availability of tissue adhesives, many still require suturing. Successful management in the ED requires effective relief of pain and anxiety as these visits are often stressful for the patient, parent, and health care worker. Advances in analgesic regimens such as the use of topical and buffered injected anesthetics can make suturing almost painless.[2-4] However, anxiety during both wound preparation and suturing continues to be a significant problem, especially among young children and their parents.

Many agents for pharmacologic sedation during suturing in children have been studied.[5-12] Desirable characteristics include nonpainful routes of administration, predictable and titratable effects, lack of significant adverse effects, and rapid onset and recovery. Oral midazolam and inhaled nitrous oxide (N_2O) are 2 agents that meet most of these criteria and have commonly been used for outpatient procedures.[5-8,13-17] The purpose of this study was to compare the efficacy and complication profile of midazolam and continuous-flow N_2O in alleviating anxiety during laceration repair in young children. Our primary study hypotheses were (1) N_2O would produce more effective sedation than midazolam or standard care during wound preparation and suturing, and (2) differences in adverse effects between groups related to the known mechanisms of action would occur. In addition, our secondary hypotheses were (1) patients receiving N_2O would recover more rapidly from sedation than patients receiving midazolam, and (2) suturers would be more satisfied with N_2O sedations compared with midazolam or standard care.

MATERIALS AND METHODS

To compare the efficacy and complication profile of midazolam and continuous-flow N_2O, the following 4 treatment groups were defined: standard care alone, which includes comforting and topical anesthesia augmented with injected lidocaine if needed; standard care and oral midazolam; standard care and N_2O; and standard care and oral midazolam plus nitrous oxide. Children ages 2 through 6 years who presented to the ED at St. Louis Children's Hospital for repair of facial lacerations and met the American Society of Anesthesiologists (ASA) class I or II criteria[18] were invited to participate in the study between July 1, 1996, and September 1, 1997. Exclusion criteria were previous laceration repair; solid or liquid oral intake within 2 hours of evaluation[19]; abnormalities of airway, cardiac, hepatic, renal, or central nervous systems; bowel obstruction; otitis media; history of adverse reaction to the study drugs; or lacerations that would inhibit use of the mask for N_2O delivery (eg, nasal lacerations). Demographic data were recorded for patients who were eligible but not enrolled. Informed written consent was obtained from parents by the emergency physician before randomization. Research protocol, study design, and consent forms were approved by the institutional review board at Washington University School of Medicine.

Subjects were randomly assigned in blocks of 20 to receive standard care; standard care and oral midazolam; standard care and N_2O; or standard care, oral midazolam, and N_2O. Randomization sequences were predetermined by a random number generator and maintained in sealed envelopes until consent was obtained. For subject safety and because study medication delivery is easily distinguishable, physicians performing sedation were not blinded to the study regimens. Suturing and recovery were performed in an ED treatment room equipped for monitoring, resuscitation, and audiovisual recording.

Before and throughout sedation, levels of consciousness (A=alert, V=responsive to voice, P=responsive to pain, U=unresponsive),[20] heart rate, respiratory rate, blood pressure, and oxygen saturation were monitored continuously in all patients, and end-tidal N_2O levels were monitored continuously in the patients who received N_2O and both oral midazolam and N_2O using a Spacelabs model PC-2 monitor (Spacelabs Medical, Redmond, WA) and documented by the nurse at 5-minute intervals. After suturing, when cardiopulmonary functions were determined to be stable and adequate, documentation intervals were increased to 10 minutes until discharge. Also documented were subject age, weight, sex, race; location of laceration; ASA classification; allergies; time of last oral intake and presedation medications; study medication doses and administration times; and descriptions and times of adverse effects and interventions. Criteria for discharge were normal cardiopulmonary function, return to presedation level of responsiveness, and ability to talk, sit unaided, or walk with minimal assistance.[20] Recovery time was defined as

the time of placement of the last suture to the time of discharge.

All study medications were administered by 14 attending or fellow emergency physicians familiar with the medications and protocol. Sedators directly observed subjects throughout the procedure and until adequate cardiopulmonary functions were verified during recovery. Registered nurses remained with subjects throughout the procedure and recovery periods.

All patients received standard care, which included a topical anesthetic combination of lidocaine, epinephrine, tetracaine (LET),[2] supplemented after 20 minutes by injected buffered lidocaine[3,4] using a 30-gauge needle if needed as determined by the suturing physician. Parents or emergency staff provided age-appropriate comforting techniques, such as watching videotapes or reading books. Patients who received oral midazolam were given 0.5 mg/kg (maximum dose of 20 mg based on current practice in our institution) 20 minutes before suturing.[21,22] Patients who received N_2O were given a mixture of 50% N_2O/50% O_2 through a nasal mask just before wound preparation.

A customized continuous-circuit apparatus allowed continuous delivery of N_2O by emergency physicians, who were not involved with suturing.[23] This apparatus delivers a continuous flow of N_2O and is equipped with a valve that prohibits administration of N_2O flow unless oxygen delivery is at least 30% and has a scavenging system to minimize escaped gas exposure in health care personnel. An appropriately sized clear, disposable, cushioned nose mask scented with bubble gum, elbow connector with a gas sampling line, and a disposable Humidivent HME (heat moisture exchanger) filter (Airflow Developments Ltd, Buckinghamshire, England) to conserve exhaled heat and humidity and serve as a bacterial/viral filter[24] were connected to the respiratory circuit. A sidestream gas analyzer and Spacelabs Medical capnograph (model 90513) were used to measure O_2 and N_2O levels. The gas flow meter was set from 6 to 10 L/min and after achieving mask acceptance, the blender was dialed to 50% N_2O. The circuit and tanks were checked for proper functioning before each use. Routine room air sampling by the Environmental Safety department confirmed levels to be within standards established by the Occupational Safety and Health Administration.[25]

The primary outcome measure for efficacy was the Observational Scale of Behavioral Distress-Revised (OSBD-R),[26,27] which was scored from videotapes made during laceration repair. After informed consent was obtained, videotaping of subjects began and continued until discharge. The OSBD-R has been validated during procedures for children of ages within our sample range.[26] The presence of each of 8 behaviors (information seeking, cry, scream, restraint, verbal resistance, emotional support, verbal pain, and flail) was noted continuously every 15 seconds during the following intervals: baseline (3 minutes before intervention); local anesthetic injection, if needed; cleaning; suturing; and recovery. OSBD-R scores range from 0 to 23.5 per interval and higher scores indicate greater distress. Fifteen-second scores for each category were compiled, averaged, and weighted in a standard manner.[26] One of 2 trained observers who were blinded to study purpose and design scored the videotape of each subject. The scorers were not health care professionals and were instructed that various equipment and monitoring were being evaluated. Interrater reliability for each behavior of the OSBD-R was assessed by 2 trained observers before scoring study videotapes and midway during the scoring process.

Secondary outcome measures were visual analog scale (VAS) ratings completed by suturers. At the completion of suturing, suturers completed a 10-point VAS questionnaire to rate satisfaction with the sedation. The endpoints were "not satisfied" and "highly satisfied," with higher scores indicating greater satisfaction.

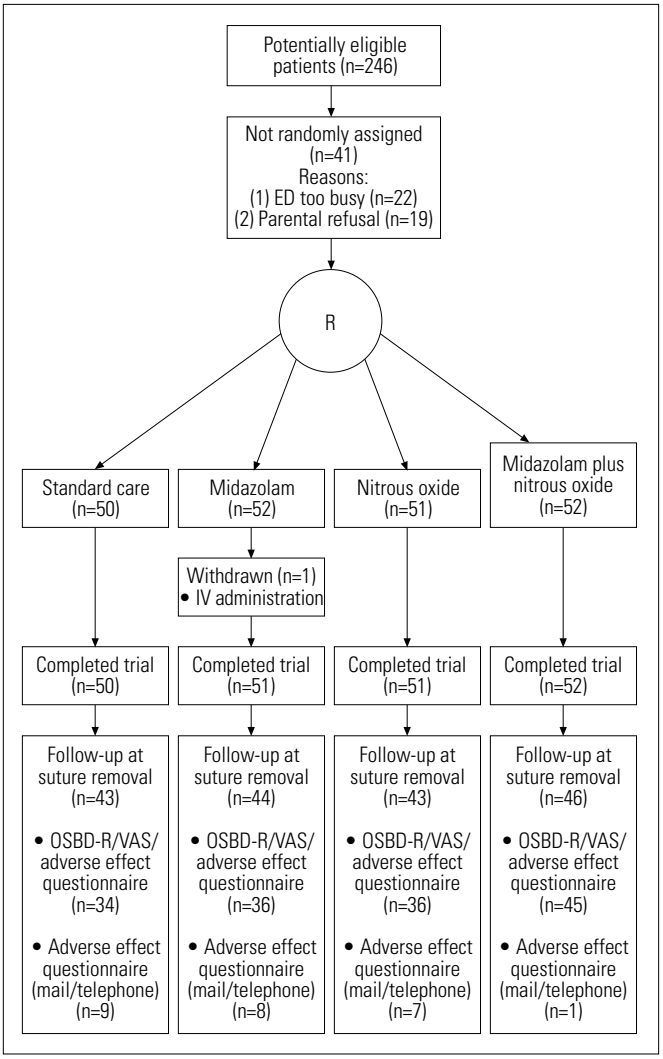
Primary outcome measures for adverse events were abnormalities in cardiopulmonary function as measured by oxygen saturation less than 93%, alterations in heart rate and blood pressure of more than 15% from baseline, clinical signs of hypoperfusion (eg, diminished peripheral pulses, cool and pale distal extremities, or delayed capillary refill), or need for supportive care, such as supplemental oxygen or positive-pressure ventilation.[28] Secondary measures of adverse events were frequency of adverse events, including vomiting, during sedation and recovery. Oversedation was defined as a level of consciousness of U (unresponsive) based on the nursing score. Parents completed questionnaires regarding adverse effects 1 day after suturing and at the time of suture removal. Parents who did not return to our institution for suture removal returned questionnaires by mail or were contacted by telephone.

Calculations of the anticipated power for the study were based on estimates of means and SDs. Assuming that the population mean OSBD-R was 1.75±1.85 OSBD units[26] with a power of 0.80 and α of .05, a change in the mean of 1.05 OSBD units could be detected by a *t* test with a sample of 50 children in each treatment group. Because no cardiopulmonary adverse effects associated with the use of 50% N_2O in large numbers of children

have been published, we did not conduct a formal power analysis for adverse effects and chose to evaluate comparative complication profiles of standard care with either oral midazolam or N_2O.

Descriptive statistics were used to examine the demographic data (sex, age, race, ASA class, laceration length, and number of sutures). Primary data analysis for efficacy compared mean OSBD-R scores for the 4 treatment groups using a repeated-measures analysis of variance (ANOVA) with oral midazolam and N_2O as the between-subjects factors. Suturer satisfaction scores and recovery times were also compared as a function of group assignment with 2-way ANOVA. Cardiorespiratory and other adverse effects were compared using an analogous categorical model using the weighted least square solution. Odds ratios and 95% confidence intervals (CIs) were computed from the estimated effects. All statistical analyses were performed using SAS software (version 8.0, SAS Institute, Inc, Cary, NC, 1996) with a value of *P* less than .05 as the criterion for statistical significance.

Figure 1.
Participant flow chart.



RESULTS

Two hundred five subjects (83% of eligible) were enrolled in the study (Figure 1). Patients eligible but not enrolled were similar to those enrolled in terms of age, sex, race, and laceration length. One subject enrolled was given midazolam intravenously and was excluded from analysis because of protocol violation. The mean patient age was 4.1 years; 66% were boys; 66% were black; and 92% were in ASA class I. There were no differences in age, sex, race, ASA classification, laceration length, or number of sutures between the groups (Table 1).

Mean OSBD-R scores were significantly lower for the groups that received N_2O during injecting lidocaine, cleaning, and suturing (Table 2, Figure 2). Although there was no similar systematic effect for midazolam, there were significant interactions for these periods. The general pattern of this interaction was for the midazolam group to have lower OSBD-R scores than the standard care group, but for the midazolam plus N_2O group to have no advan-

Table 1.
Subject characteristics.

Variable	Standard Care	Midazolam	N_2O	Midazolam+ N_2O
No.	50	51	51	52
Age, y (mean±SD)	4.0±1.4	4.2±1.4	4.2±1.4	4.0±1.4
Male sex, No. (%)	33 (66)	33 (65)	35 (69)	34 (65)
Race, No. (%)				
Black	35 (70)	37 (73)	34 (67)	29 (56)
White	15 (30)	14 (27)	17 (37)	23 (44)
ASA class, No. (%)				
I	46 (92)	44 (86)	47 (92)	50 (96)
II	4 (8)	7 (14)	4 (8)	2 (4)
Laceration				
Length (cm, mean±SD)*	1.5±0.9	1.7±1	1.5±0.9	1.5±0.7
No. of sutures (mean±SD)	5±3	6±3	5±2	5±2
Baseline OSBD-R score (mean±SD)	0.3±0.1	0.1±0.3	0.3±0.8	0.2±0.9

tage over the N_2O alone group. κ Coefficients of OSBD-R behaviors ranged from 0.66 (information seeking) to 1.0 (flail) on a sample of 5 randomly selected tapes at the midway point. Mean recovery times were longer for groups that received midazolam (Table 2), and suturer satisfaction VAS scores were higher for groups that received N_2O compared with midazolam (Table 2, Figure 3).

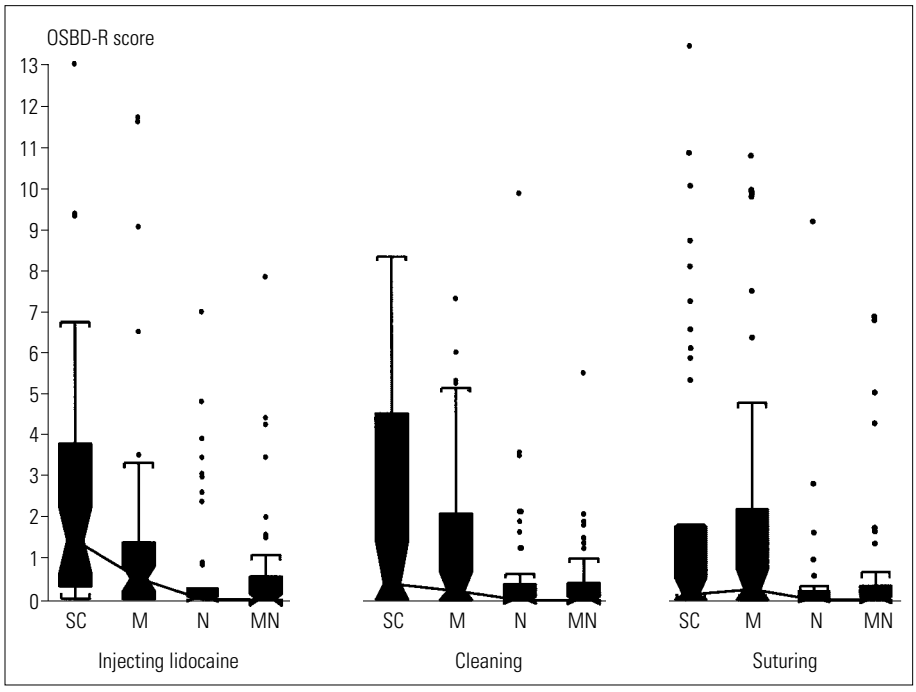
No cardiorespiratory adverse events including hypotension, hypertension, hypoperfusion, and hypoxia occurred in any subject at any time. No patient was

Table 2.
Analysis of variance tables.

	Least Square Means				*P* Value		
Period	**M**	**MN**	**N**	**SC**	**M**	**N**	**MN**
OSBD scores*							
Baseline	0.1	0.2	0.3	0.33	(.63)	.86	(.73)
Inject lidocaine	1.5	0.7	0.7	2.4	(.09)	.0001	(.0001)
Cleaning	1.2	0.4	0.6	2.0	(.04)	.0001	(.001)
Suturing	1.9	0.7	0.4	2.0	(.63)	.0001	(.01)
Recovery	0.1	0.6	0.3	0.3	(.86)	.48	(.71)
Suturer satisfaction†	7.5	8.0	8.2	6.6	(.41)	.02	(.22)
Recovery time (min)‡	30	28	21	20	(.01)	.90	(.63)

M, Midazolam; **MN,** midazolam and N_2O; **N,** N_2O; **SC,** standard care.
*Contrasts extracted from a repeated-measures ANOVA with tests of M, N, and their interaction (MN) done for each period. The pooled estimate of the within-cell SD was 1.58.
†From a simple 2-way ANOVA. The pooled within-cell SD for the Suturer Satisfaction VAS was 3.04.
‡The analysis of recovery time was done with a square root transformation because of a highly skewed distribution and then the least square means were back-transformed. The pooled within-cell SD (on the square root scale) was 2.38.

Figure 2.
OSBD-R intervals. ***SC,*** *Standard care;* ***M,*** *midazolam;* ***N,*** *N_2O;* ***MN,*** *midazolam and N_2O.*



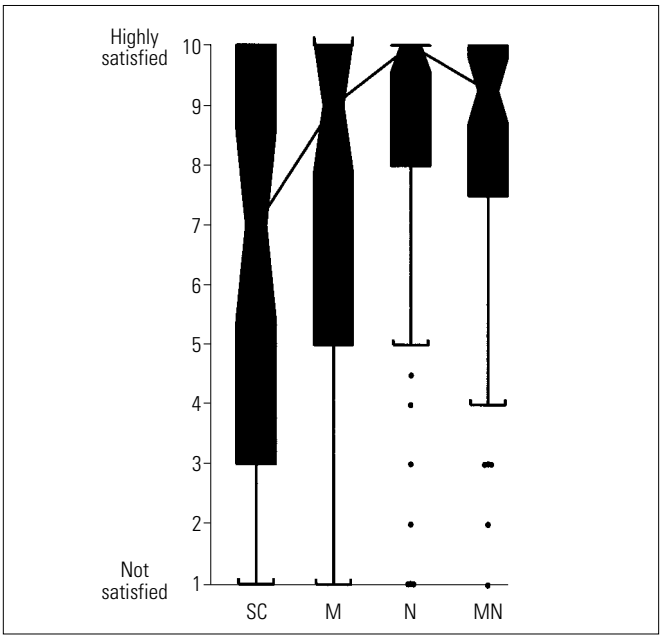
determined to be unresponsive, and the deepest level of consciousness observed in each group was as follows: standard care alone (A=50); standard care and oral midazolam (A=39, V=13); standard care and N_2O (A=14, V=34, P=3); standard care, midazolam, and N_2O (A=12, V=35, P=5).

Adverse effect questionnaires were completed in 176 (86%) of children. Parents of the 25 of 53 children who did not return for suture removal completed the questionnaire by mail or telephone. Children who received midazolam were more likely to have adverse events up to 24 hours after suturing, including ataxia, dizziness, difficulty walking, and crying more than usual (Table 3). Adverse events were not reported in any group at the time of suture removal.

Vomiting occurred in 6 children who received N_2O (standard care and N_2O 5; standard care, oral midazolam, and N_2O 1; Table 3). Three patients vomited during suturing and 3 after the last suture was placed but before oral intake. In the 3 children who vomited during suturing, the oropharynx was suctioned while the nasal mask was maintained; however, the N_2O administration was terminated and 100% oxygen was given for 1 to 3 minutes or until the end-tidal N_2O level was zero. The 3 patients who vomited during sedation were described as responsive to voice, and the 3 who vomited during recovery were alert. No clinically apparent aspiration occurred, and there were no reports of respiratory symptoms at 1 day and suture removal follow-up.

Two of the 3 patients in whom treatment failed were in the midazolam group. The other patient was randomly assigned to the standard care group. There was no difference in baseline OSBD-R scores for these patients compared with others. In addition, 2 patients in the midazolam group had inconsolable agitation consisting of loud crying, emotional lability, and resistance to comforting by parents during suturing, requiring recovery in the ED for 3 and 5 hours. Thirteen patients (5 standard care; 2 standard care and midazolam; 3 standard care and N_2O; 3 standard care, midazolam, and N_2O) were restrained at the discretion of the suturer with a papoose board. There was no difference in group assignment or baseline OSBD-R scores according to whether children were restrained.

Figure 3.
Suturer satisfaction. ***SC,*** *Standard care;* ***M,*** *midazolam;* ***N,*** *N_2O;* ***MN,*** *midazolam and N_2O.*



DISCUSSION

This study demonstrates that in our sample, continuous-flow 50% N_2O is more effective for relief of anxiety in young children during wound preparation and suturing, has fewer adverse effects, and shorter recovery times than oral midazolam. Although vomiting occurred more frequently in groups that received N_2O, there were no incidents of clinically apparent aspiration. In addition, suturer satisfaction with the sedation was highest when N_2O was used.

Few studies in children using N_2O for anxiety and pain relief during procedures have been undertaken. Procedures prospectively studied include suturing,[7,8] venipuncture,[14,29] fracture reduction,[13,17] and dental procedures.[30,31] During emergency suturing, Gamis et al[7] demonstrated safety and mild efficacy of 30% N_2O in children 8 years and older, and Burton et al[8] reported safety and efficacy of 50% N_2O in 17 children 2 to 7 years old. In 2 reports of children undergoing dental procedures, Litman et al[30,31] evaluated the ventilatory effects and levels of sedation achieved with the combination of oral midazolam (0.5 to 0.7 mg/kg) and 15% to 60% N_2O. In the first study of a small group of children 1 to 3 years old, there were no significant changes in end-tidal carbon dioxide tension with increasing concentrations of N_2O from 15% to 60% and a progression from conscious to deep sedation in 45% of children who received 30% to

60% N_2O.[30] In the second study, the authors demonstrated that the addition of 40% N_2O to 0.7 mg/kg oral midazolam in a small group of children 1 to 9 years old did not result in respiratory depression or upper airway obstruction, but did cause an increase in the level of sedation in some children beyond conscious sedation.[31] Vomiting has been reported in none to 6% of the aforementioned outpatient studies of N_2O and is similar to our incidence of 6%.[7,8,13,30,31]

Traditionally, N_2O has been self-administered in the outpatient setting by a device that delivers a fixed mixture of 50% N_2O and oxygen through a demand valve (eg, Nitronox). In our experience, children do not consistently achieve acceptable analgesia and sedation with this device. The demand valve requires an inspiratory effort of –3 to –5 cm H_2O to activate gas flow. This is difficult for young children who are crying, have weaker respirations than adults, or cannot follow instructions. In collaboration with the Departments of Anesthesiology, Dentistry, and Respiratory Therapy, we constructed and used in this study an inexpensive portable, continuous-flow system for delivery of N_2O and oxygen to young children.[23]

Other studies have compared children inhaling N_2O with a control group inhaling oxygen.[7,8] We believe that oxygen administration by nasal mask to an agitated young child likely increases the child's anxiety. This iatrogenically induced distress may increase the difference in distress between groups and does not represent a true control. Therefore, we chose as the control group our standard of care for suturing, which includes comforting activities, topical LET and, if needed, injected buffered lidocaine. Because we chose not to use oxygen as a control, we were unable to blind parents and sedators to the agent used.

Furthermore, most modalities of sedation involve a noxious stimulus associated with administration. In the case of N_2O, the facemask in some children may be perceived as noxious. Flavoring the mask and incorporating the mask into story-telling in young children were used to enhance acceptance of the nasal mask. Although the nasal mask alone may be noxious, OSBD-R scores for children who received N_2O and the accompanying nasal mask were lower than groups that did not receive N_2O.

Because this study was conducted in an ED staffed by nurses and physicians experienced in the care of critically ill and injured children and because only subjects 2 to 6 years old were studied using a continuous delivery system of N_2O, caution in generalization of these results to other clinical settings, equipment, and children of different ages is warranted.

Table 3.
Adverse effects.

Adverse Effects	Standard Care*	Midazolam*	N_2O*	Midazolam+ N_2O*	Midazolam Odds Ratio (95% CI)†	N_2O Odds Ratio (95% CI)†
Ataxia						
During ED visit‡	0	2	0	1	2.0 (0.7–6.2)	0.8 (0.3–2.0)
First 24 h§	0	12	1	14	6.0 (2.2–16.5)	1.1 (0.7–1.7)
Dizziness						
During ED visit	0	1	0	0	1.4 (0.4–4.9)	0.7 (0.2–2.5)
First 24 h	0	6	0	6	3.8 (1.4–10.6)	0.9 (0.5–1.5)
Difficulty walking first 24 h	0	10	0	8	4.7 (1.7–13.1)	0.7 (0.5–1.2)
Vomiting during ED visit	0	0	5	1	0.6 (0.3–1.3)	2.5 (0.9–7.5)
Crying more first 24 h	0	5	0	5	3.4 (1.2–9.6)	0.9 (0.5–1.6)
Hallucinations first 24 h	0	1	0	3	2.1 (0.7–6.4)	1.3 (0.5–3.1)
Sleeping more first 24 h	4	11	4	6	1.4 (0.9–2.2)	0.7 (0.5–1.1)
Headache						
During ED visit	0	0	1	0	0.7 (0.2–2.5)	1.4 (0.4–4.8)
First 24 h	3	1	4	4	0.8 (0.5–1.4)	1.3 (0.7–2.3)

*Frequency data.
†All interactions were insignificant, so a main-effect only/weighted least squares categorical model was computed, adding 0.5 to each cell because of the observed cells with a frequency of 0.
‡Two hundred four questionnaires completed during ED visit.
§One hundred fifty-six questionnaires completed at 24 h after ED visit.

Our results indicate that the addition of oral midazolam has no advantage over N_2O alone. However, in groups that did not receive N_2O, there seems to be an anxiety-reducing effect of midazolam during wound preparation, including the steps of lidocaine injecting and wound cleaning. The minor side effects of dizziness, ataxia, and irritability occurred only in children who received midazolam and were reported by some parents to persist for up to 24 hours after discharge. Furthermore, because the addition of midazolam to N_2O did not confer added benefit in reducing distress but increased adverse effects, the use of N_2O alone appears to be optimal.

We conclude that 50% N_2O, administered by a continuous-flow system, is more effective than midazolam and standard care for relief of anxiety during emergency suturing in young children. Furthermore, adverse effects occurred less frequently, recovery was shorter, and suturer satisfaction was greatest during suturing in groups that received N_2O.

REFERENCES

1. Alcock DS, Feldman W, Goodman JT, et al. Evaluation of child life intervention in emergency department suturing. *Pediatr Emerg Care.* 1985;1:111-115.

2. Schiling CG, Bank DE, Borchert BA, et al. Tetracaine, epinephrine (adrenaline), and cocaine (TAC) versus lidocaine, epinephrine, and tetracaine (LET) for anesthesia of lacerations in children. *Ann Emerg Med.* 1995;25:203-208.

3. Christoph RA, Buchanan L, Begalia K, et al. Pain reduction in local anesthetic administration through pH buffering. *Ann Emerg Med.* 1988;17:117-120.

4. McKay W, Morris R, Mushlin P. Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. *Anesth Analg.* 1987;66:572-574.

5. Hennes H, Wagner V, Bonadio W. The effect of oral midazolam on anxiety of preschool children during laceration repair. *Ann Emerg Med.* 1990;19:1006-1009.

6. Fatovich DM, Jacobs IG. A randomized, controlled trial of oral midazolam and buffered lidocaine for suturing lacerations in children (the SLIC Trial). *Ann Emerg Med.* 1995;25:209-214.

7. Gamis AS, Knapp JF, Glenski JA. Nitrous oxide analgesia in a pediatric emergency department. *Ann Emerg Med.* 1989;18:177-181.

8. Burton JH, Auble TE, Fuchs SM. Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. *Acad Emerg Med.* 1998;5:112-117.

9. Schutzman SA, Liebelt E, Wisk M, et al. Comparison of oral transmucosal fantanyl citrate and intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation of children undergoing laceration repair. *Ann Emerg Med.* 1996;28:385-390.

10. Qureshi FA, Mellis PT, McFadden MA. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. *Pediatr Emerg Care.* 1995;11:93-97.

11. Hollman GA, Perloff WH. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. *Pediatr Emerg Care.* 1995;11:399.

12. Green SM, Rothrock SG, Lynch EL, et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. *Ann Emerg Med.* 1998;31:688-697.

13. Wattenmaker I, Kasser JR, McGravey A. Self-administered nitrous oxide for fracture reduction in children in an emergency room setting. *J Orthop Trauma.* 1990;4:35-38.

14. Vetter TR. A comparison of EMLA cream versus nitrous oxide for pediatric venous cannulation. *J Clin Anesth.* 1995;7:486-490.

15. Griffin GC, Campbell VD, Jones R. Nitrous oxide-oxygen sedation for minor surgery: experience in a pediatric setting. *JAMA.* 1981;245:2411-2413.

16. Stewart RD. Nitrous oxide sedation/analgesia in emergency medicine. *Ann Emerg Med.* 1985;14:139-148.

17. Hennrikus WL, Simpson RB, Klingelberger CE, et al. Self-administered nitrous oxide analgesia for pediatric fracture reductions. *J Pediatr Orthop.* 1994;14:538-542.

18. Dripps RD, Lamong A, Eckenhoff JE. The role of anesthesia in surgical mortality. *JAMA.* 1961;178:261-266.

19. Gabriel MJ, Barker DS. *Paediatric Acute Pain Management Handbook.* 4th ed. North Adelaide, South Australia: Women's and Children's Hospital; 1998.

20. Committee on Drugs, American Academy of Pediatrics. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. *Pediatrics.* 1992;89:1110-1115.

21. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. *Anesthesiology.* 1990;73:831-834.

22. Connors K, Terndrup TE. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. *Ann Emerg Med.* 1994;24:1074-1079.

23. Luhmann JD, Kennedy RM, Jaffe DM, et al. Continuous flow delivery of nitrous oxide and oxygen: a safe and cost effective technique for inhalation and sedation of pediatric patients. *Pediatr Emerg Care.* 1999;15:388-392.

24. Dorsch J, Dorsch S. *Understanding Anesthesia Equipment.* 3rd ed. Baltimore, MD: Williams & Wilkins; 1994:167-189.

25. National Institute for Occupational Safety and Health (NIOSH). Nitrous oxide level recommendation: criteria for a recommended standard. Occupational exposure to waste anesthetic gases and vapors [NIOSH] publication No. 77-140]. Cincinnati, OH: Department of Health and Human Services; 1998.

26. Jay SM, Ozolins M, Elliott CH, et al. Assessment of children's distress during painful medical procedures. *Health Psychol.* 1983;2:133-147.

27. Jay SM, Elliot C. Behavioral observation scales for measuring children's distress: the effects of increased methodological rigor. *J Consult Clin Psychol.* 1984;53:1106-1107.

28. Marx CM, Stein J, Tyler MK, et al. Ketamine-midazolam versus meperidine-midazolam for painful procedures in pediatric oncology patients. *J Clin Oncol.* 1997;15:94-102.

29. Henderson JM, Spence DG, Komocar LM. Administration of nitrous oxide to pediatric patients provides analgesia for venous cannulation. *Anesthesiology.* 1990;72:269-271.

30. Litman RS, Berkowitz RJ, Ward DS. Levels of consciousness and ventilatory parameters in young children during sedation with oral midazolam and nitrous oxide. *Arch Pediatr Adolesc Med.* 1996;150:671-675.

31. Litman RS, Kottra JA, Berkowitz RJ, et al. Breathing patterns and levels of consciousness in children during administration of nitrous oxide after oral midazolam premedication. *J Oral Maxillofac Surg.* 1997;55:1372-1377.