Efficient Intravenous Access Without Distress

A Double-blind Randomized Study of Midazolam and Nitrous Oxide in Children and Adolescents

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Objective: To determine whether treatment with midazolam or with nitrous oxide is more efficient in facilitating intravenous (IV) access in lean and obese children and adolescents.

Design: A prospective, double-blind, randomized trial of 90 children and adolescents.

Setting: Astrid Lindgrens Children’s Hospital, Karolinska University Hospital, Stockholm, Sweden.

Patients: A total of 60 obese children and adolescents and 30 growth-retarded children and adolescents, aged 5 to 18 years, with reported anxiety and/or difficulties with IV access.

Interventions: The patients were randomly assigned to receive midazolam (dose, 0.3 mg/kg; maximum dose, 15 mg), 50% nitrous oxide, or 10% nitrous oxide. All patients received lidocaine-prilocaine.

Main Outcome Measures: Efficiency, measured as total procedure time and number of attempts, which was defined as the number of attempts required to succeed in setting up 2 IV lines, with a successful procedure defined as 2 attempts for 2 IV lines. Secondary end points were patients’ and parents’ evaluations and procedure cancellations.

Results: Treatment with 50% nitrous oxide was the most efficient with regard to total procedure time ($P < .001$). An unfavorably long procedure time was observed after treatment with midazolam, especially in obese patients. An increased number of successful IV line procedures were obtained in the group of patients who received 50% nitrous oxide compared with the midazolam group and 10% nitrous oxide group ($P = .04$). The patients’ evaluations were significantly more positive for 50% nitrous oxide than for both midazolam and 10% nitrous oxide, whereas no such difference was observed between midazolam and 10% nitrous oxide.

Conclusions: Compared with treatment with midazolam, treatment with 50% nitrous oxide during IV line procedures results in a shorter total procedure time, improved rate of IV access, and a better experience for the child or adolescent. Only under rare circumstances should obese children or adolescents be treated with midazolam because of the long procedure time.

Trial Registrations: isrctn.org Identifier: ISRCTN33779750 and kctr.se Identifier: KCTR CT20090023.


Obese children and children with endocrine disorders are chronically affected patients in pediatric outpatient clinics in which diagnostic procedures often require blood samples or intravenous (IV) lines. These groups of children are increasing and so is the number of examinations needed to prevent and treat potential complications. Blood vessels in children who require repeated blood tests often become sensitive to pain, and the scars, which make the vessels hard and difficult to penetrate, frequently result in problems with using IV lines and other medical equipment. Consequently, conflicts can easily arise at pediatric outpatient clinics concerning the need for speed, efficiency, adequate pain reduction, personnel resources, and time spent at the clinic.

Observational and self-reported studies of children requiring IV access have demonstrated high levels of pain and distress among the children. Anesthetic creams and injection of buffered lidocaine hydrochloride (by needle or jet injector) are 2 well-described and well-established alternatives providing pain and anxiety reduction during IV line procedures, with anesthetic creams obviously being the less invasive. These treatments have significantly reduced the problems associated with IV lines, but they are not always effective enough when difficulties arise.
An ideal agent for a short-term procedure with no postprocedure pain should be noninvasive, should have a rapid onset and offset, should be without residual symptoms, should have minimal adverse effects, and, preferably, should be cost-effective. Midazolam hydrochloride, a benzodiazepine, is frequently used for outpatient procedures\textsuperscript{11,12} and provides anxiolysis, sedation, and some amnesia.\textsuperscript{13} Treatment with nitrous oxide is a well-established method for pain alleviation and sedation,\textsuperscript{14-16} but it is not frequently used in pediatric outpatient clinics.

Several authors have studied the effect of nitrous oxide on patients during painful procedures\textsuperscript{15,16} and also compared nitrous oxide with midazolam for sedation in young children, and both drugs have been proven to be safe and effective.\textsuperscript{17,18} In an open randomized study comparing treatment with 25 mg/g of lidocaine hydrochloride-prilocaine hydrochloride in an oil-in-water emulsion (EMLA cream; AstraZeneca, Södertälje, Sweden) vs treatment with 25 mg/g of lidocaine-prilocaine and 50% nitrous oxide, we found no prolongation of total procedure time when 50% nitrous oxide was added.\textsuperscript{19}

The aim of our study was to compare oral midazolam and nitrous oxide inhalation under double-blind conditions in children and adolescents with reported anxiety about or difficulties in establishing IV access. Efficiency, measured as total procedure time (from start of procedure to recovery) and number of attempts, which was defined as the number of attempts required to succeed in setting up 2 IV lines (with a successful procedure defined as 2 attempts for 2 IV lines), was the primary end point. Secondary end points were patients’ and parents’ evaluations and procedure cancellations.

### METHODS

#### STUDY DESIGN

Our study was a prospective, double-blind, randomized, stratified study including 90 children and adolescents, 60 obese and 30 growth-retarded children and adolescents aged 5 to 18 years, with expected difficulties in establishing IV access. They were randomly allocated to 1 of 3 treatments aimed to reduce problems during IV access. A total of 20 obese children and adolescents and 10 growth-retarded children and adolescents were stratified into 1 of the 3 treatment groups, because different body compositions provide different IV access problems (Figure 1).

Our study was approved by the ethical committee of the hospital (South Stockholm decision 050114). Children and adolescents who met the inclusion criteria were asked, consecutively, whether they wanted to participate in the study. Written informed consent was obtained from the parents, and the children and adolescents who were included gave their verbal assent. The study design was understood and accepted by all the children and adolescents who were included.

#### INCLUSION AND EXCLUSION CRITERIA FOR PATIENTS

There were 3 inclusion criteria that patients had to meet to enroll in our study: (1) Patients had to have had previous difficulties establishing IV access. These difficulties were defined as either previous requirement of several attempts before establishing IV access or children rating anticipatory anxiety greater than 4 using a numeric rating scale of 0 to 10, with 0 indicating no anxiety and 10 indicating worst possible anxiety.\textsuperscript{20} (2) Patients had to have an American Society for Anesthesia classification system status of 1 (ie, a normal healthy patient with no physiological disturbances [http://www.asahq.org]). (3) Patients had to have the ability to understand and contribute to the different treatments, including the ability to use a face mask and the ability to interpret the numeric rating scale (0-10) and the Likert scale (1-5). All patients were instructed on how to handle a face mask, and they were asked to use the scales to ensure that they understood the scales before inclusion. Patients were excluded from our study if they (1) did not have previous difficulties establishing IV access (numeric rating scale, ≤4); (2) had an American Society for Anesthesia classification system status of 2 or greater; and (3) were considered unable to collaborate.

#### INTERVENTION

There were 30 patients who were randomly assigned to receive midazolam (dose, 0.3 mg/kg; maximum dose, 15 mg) orally with 15 mL of syrup and use an oxygen mask, 30 patients who were randomly assigned to receive 50% nitrous oxide via oxygen inhalation with 15 mL of syrup, and 30 patients who were randomly assigned to receive 10% nitrous oxide via oxygen inhalation with 15 mL of syrup. All patients received lidocaine-prilocaine.

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Figure 1. Flowchart of enrollment, allocation, follow-up, and analysis of obese patients and growth-retarded (GR) patients, both with reported anxiety about or difficulties in establishing IV access. Efficiencies in children and adolescents with reported anxiety and nitrous oxide inhalation under double-blind conditions (EMLA cream; AstraZeneca, Södertälje, Sweden) vs treatment with 25 mg/g of lidocaine-prilocaine and 50% nitrous oxide inhalation with 15 mL of syrup. All patients received lidocaine-prilocaine.
ANAESTHESIA EQUIPMENT

Oxygen and nitrous oxide were mixed using the Engstrom 2024 (Engstrom Medical AB, Stockholm, Sweden) connected to 2.5-L nitrous oxide tubing and oxygen from the wall. The system incorporated a full face mask that covered the nose and mouth and that was held in place by the patient and, if necessary, assisted by the parent. The gas mixture was delivered by free flow (6 L/min), and no on-demand valve was used. The gas was delivered from the tube by a partial rebreathing system, a Bains circuit. Exhaled nitrous oxide was scavenged by a “double-mask” system (Medivent, Umeå, Sweden), and the scavenging system was attached to the face mask.21

PROCEDURE

The patients required 2 peripheral IV lines in preparation for IV tests. Three nurses (hereafter referred to as nurses N1, N2, and N3) were involved with each study patient. Nurses N1 and N2 did not switch assignments during our study. Nurse N1 was informed about our study and admitted the patients and reviewed their medical records. Nurse N2 performed the randomization and prepared and administered the midazolam mixture. Nurse N2 also set the mixing percentage of nitrous oxide and oxygen according to randomization and concealed the mixing device. When the child started to breathe into the mask, nurse N3 set up 2 IV lines using a 22-gauge catheter and evaluated the IV line procedure. Nurse N3 was actually 3 different nurses, all with many years of experience in pediatrics.

All patients received applications of lidocaine-prilocaine on the dorsum of both hands and over the cubital vein on both arms; thereafter, these 4 anatomic sites were covered with adhesive tape for 60 minutes before the procedure. All patients were given 13 mL of syrup with or without midazolam 40 minutes before the IV line procedure. Midazolam was dosed according to the standard procedure at the clinic (ie, 0.3 mg/kg with a maximum dose of 15 mg). Oxygen and nitrous oxide were administered 3 minutes before the IV line procedure was started.21 All patients breathed into the mask during the time needed to establish IV access. When the IV access was finished, the nitrous oxide valve was closed, and an additional 3 minutes were allowed for nitrous oxide washout with the child breathing 100% oxygen.

OUTCOME MEASUREMENTS

IV access time was defined as the time from the start of setting up the IV lines to the establishment of 2 IV lines. Recovery time was defined as the time from the establishment of the IV lines to the patient’s regaining alertness, measured by use of the finger tapping test. Alertness was defined as a finger tapping test result within 10% of the patient’s baseline value.23 During the finger tapping test, patients are instructed to tap a button as fast as they can during a 10-second interval. The baseline number was measured in connection with inclusion in our study. Attempts to measure recovery were made every 15 minutes after the IV line access. Blood samples were obtained during the first 10 minutes after IV access had been achieved, and thereafter after the finger tapping test was performed. Total procedure time was defined as IV access time plus recovery time. Number of attempts was defined as the number of attempts required to succeed in setting up double IV lines, with a successful procedure defined as 2 attempts for 2 IV lines. Patients’, parents’, and nurses’ evaluations of the IV line procedure were graded on a 5-point Likert scale, with 1 representing poor, 2 representing fair, 3 representing good, 4 representing very good, and 5 representing excellent.24 The patients performed the evaluation before the parents did, and the parents were present when the patients made their assessments. The nurses’ evaluations were done independently of patients’ and parents’ evaluations and were performed by nurse N3, who established the IV access. Pain was evaluated by the patient by means of a numeric rating scale of 0 to 10, with 0 representing no pain and 10 representing the worst pain imaginable.25 Sedation was assessed by nurse N1 using the Observer’s Assessment of Alertness/Sedation scale of 0 to 3, in which 0 means that the patient does not respond after squeezing the trapezius muscle, 1 means that the patient responds only after squeezing the trapezius muscle, 2 means that the patient responds only after mild prodding or shaking, 3 means that the patient responds only after his or her name is called loudly or repeatedly, 4 means that the patient has a lethargic response when his or her name is spoken in a normal tone, and 5 means that the patient responds readily to his or her name being name spoken in a normal tone (ie, he or she is alert).25 Heart rate and oxygen saturation (Datex-Ohmeda TuffSat, New York, New York) were monitored throughout the procedure. Hypoxia was defined as a saturation of less than 93%. Blood pressure was monitored throughout the procedure (NAIS blood pressure watch, Düsseldorf, Germany). Hypotension was defined as a decrease in blood pressure of more than 15% from baseline pressure.17 Side effects were recorded using a checklist in the protocol. Procedure cancellations were registered.

RANDOMIZATION

The opaque envelope technique was used. The envelopes were stored in a separate locked box, and nurse N2 performed the randomization. Nurse N2 was the only person who had access to the locked box.

STATISTICAL ANALYSIS

The power calculation was based on the results of an open randomized study with regard to procedure time for IV access.19 To ensure 80% power to identify a difference of 10 minutes between groups using α = .05, 30 patients were needed in each group. All analyses were performed on the population intended to treat. Technical failure is included with the value of the worst outcome (1 patient in the nitrous oxide group). All statistical analyses were performed using Statistica, release 8 (Statsoft Inc, Tulsa, Oklahoma). Descriptive data are presented as median values and ranges. The treatment groups were compared using nonparametric statistics pertaining to independent samples subjected to Kruskal-Wallis analysis of variance calculated by use of the Wilcoxon rank sum test and the Pearson χ² test. For post hoc analyses, pairwise comparisons were done using the Mann-Whitney U test. Body mass index was calculated as weight in kilograms divided by height in meters squared, and the body mass index standard deviation score was calculated according to the study by Rolland-Cachera et al.26

RESULTS

In our Table, we summarize the demographic and clinical characteristics of the patients studied, and we compare the data obtained from the 3 different treatment groups. The total procedure time (ie, the primary end point) was significantly longer in patients who received midazolam than in patients who received 50% or 10% nitrous oxide (P < .001). A subgroup analysis of total procedure times demonstrated a significant difference between obese children who received midazolam and growth-retarded children who received midazolam (P < .05).
There was no significant difference in the total number of attempts required for IV access between the treatment arms ($P = .09$). When obese and growth-retarded groups were analyzed separately, a significant difference in the number of attempts between the treatment arms was seen in the growth-retarded group ($P = .02$).

Furthermore, the percentage of successful IV line procedures was higher in patients treated with 50% nitrous oxide than in patients treated with 10% nitrous oxide or midazolam (67%, 40%, and 37%, respectively; $P = .04$).

Seven IV line procedures were not completed because there were too many unsuccessful attempts or because no attempt at all was allowed by the frightened patient: 3 IV line procedures in the midazolam group, 3 in the 10% nitrous oxide group, and 1 in the 50% nitrous oxide group. One patient did not receive 50% nitrous oxide because of a technical failure revealed when the code list was uncoding. Patients’ evaluations of the procedure were negatively correlated with the number of attempts ($r = 0.6$) and pain ($r = 0.7$). They were more positive for 50% nitrous oxide treatment than for either of the other 2 treatments ($P < .001$). No differences were found between patients’ evaluations of midazolam and patients’ evaluations of 10% nitrous oxide. A higher pain score was reported by patients who received either midazolam or 10% nitrous oxide ($P < .05$) than by patients who received 50% nitrous oxide. Evaluations were controlled for parental presence. Parents’ and nurses’ evaluation scores were significantly higher for patients who received 50% nitrous oxide than for patients who received either midazolam or 10% nitrous oxide, and no differences were seen between their evaluation of midazolam and their evaluation of 10% nitrous oxide.

Adverse effects were observed for 2 patients, dizziness after receiving midazolam and nausea after receiving 50% nitrous oxide.

### Table. Demographic and Clinical Characteristics of the Studied Children and Adolescents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients Studied</th>
<th>Treated With Midazolam (n=30)</th>
<th>Treated With 50% Nitrous Oxide (n=30)</th>
<th>Treated With 10% Nitrous Oxide (n=30)</th>
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<td>(n=30)</td>
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<td>13</td>
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<td>4.6 (−2.4 to 7.8)</td>
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<td>28</td>
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<td>4</td>
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<td>3</td>
<td>2</td>
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<td><strong>All Obese Patients</strong></td>
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<td>(n=20)</td>
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<td>BMI, median (range)</td>
<td>35.4 (26.5-53.8)</td>
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<td>35.7 (27.9-51.7)</td>
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<td>0</td>
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<tr>
<td><strong>All GR Patients</strong></td>
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<td>(n=10)</td>
<td>(n=10)</td>
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<td>Female</td>
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</tr>
<tr>
<td>BMI, median (range)</td>
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<tr>
<td>Without anxiety about IV access, No. of patients</td>
<td>3</td>
<td>1</td>
<td>2</td>
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</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GR, growth-retarded; IV, intravenous; SDS, standard deviation score.

a Calculated according to the study by Rolland-Cachera et al.28
In our study, we compared the level of efficiency when midazolam, 50% nitrous oxide, or 10% nitrous oxide was used for facilitating IV access in anxious patients; in an earlier open randomized study, we found positive effects when 50% nitrous oxide was used.\(^a\) These results needed to be confirmed under double-blind conditions and compared with midazolam, which is commonly used at pediatric outpatient clinics.\(^a\) The double-blind randomization scheme made it also possible to compare the effect of treatment on subjective parameters.

Treatment with 50% nitrous oxide effectively shortened the total procedure time compared with treatment with midazolam. An unfavorably long procedure time was observed after treatment with midazolam, especially in obese patients. The long recovery time is probably due to the fact that the lipophilicity of the drug caused a slow clearance from the adipose tissue.\(^a\) Four obese patients in the midazolam group reached a sedation level of 3 on the Observer’s Assessment of Alertness/Sedation scale, which requires monitoring not generally available in pediatric outpatient clinics. A long procedure time affects the working lives of both staff and parents and is to be avoided, if at all possible, in most outpatient clinics.

Treatmente with 50% nitrous oxide increased the number of successful IV line procedures compared with treatment with midazolam or 10% nitrous oxide. The importance of this difference for the experience of the patient is shown by the negative correlation (\(r=0.6\)) between number of attempts and the patients’ evaluations (ie, an increased number of attempts correlated with a worse evaluation by the patient). A significantly higher number of attempts for IV access were required for patients treated with midazolam in the growth-retarded group. No such difference was found among the obese children. This might be due to the different difficulties and technical problems experienced by obese, normal-weight, and growth-retarded children\(^a\) and, of course, to the deeper sedation found in the obese children.

Treatment with 50% nitrous oxide was rated higher than treatment with midazolam or treatment with 10% nitrous oxide by the patients, parents, and nurses, and their evaluations of the procedures were similar for treatment with 10% nitrous oxide and treatment with midazolam. Our results show that treatment with 50% nitrous oxide augments the quality of care, making it possible to complete procedures and examinations, compared with treatment with 10% nitrous oxide and treatment with midazolam.

There are pharmacological pros and cons for both pharmaceuticals used in our study. Midazolam, a benzodiazepine, has been widely used in recent years,\(^a\) being promoted for its good clinical effectiveness and low toxicity.\(^a\) Although effective, the interindividual variation in effect and elimination is high and dose-dependent,\(^a\) which may explain the variability in sedation levels observed among the patients who received midazolam in our study.

Several randomized controlled trials have compared treatment with midazolam with treatment with nitrous oxide during procedures of different designs, with the conclusions that the use of oral midazolam or nitrous oxide provides safe and effective sedation in children.\(^\text{17,18,33}\) In an open randomized crossover study, the children preferred midazolam to 30% nitrous oxide,\(^a\) and in a double-blind randomized study of children with cerebral palsy, no differences were seen in parents’ and nurses’ satisfaction between midazolam and 70% nitrous oxide.\(^\text{34}\) These results confirm our results, which are applicable to short procedures with no postprocedure pain.

The strength of our study is the prospective double-blind randomized design with a large group of children and adolescents (n=90). By comparing midazolam with nitrous oxide, we found that a dose-dependent effect could be demonstrated in the 2 nitrous oxide groups.

A potential weakness in our study was the blinding procedure. Nurse N1, who administered the nitrous oxide with oxygen, was not the person who evaluated the IV procedure. An argument can be made that, for a good blinding procedure, all of the treatments had to have had some pharmacologic effect, and at least for midazolam, a great variability in effect has been reported, and using
a low concentration of nitrous oxide improved the blinding procedure.

We used 0.3 mg/kg of midazolam (with a maximum dose of 15 mg), despite the fact that the therapeutic range is up to 0.5 mg/kg, and it is therefore possible that the effect of midazolam was not optimized. However, already with the dose chosen, an extremely long total procedure time was observed in obese patients. Most likely, therefore, higher doses should be avoided in obese patients.

We considered it unethical to have a pure placebo study arm, and, therefore, instead of placebo, we decided to use 10% nitrous oxide, based on the combination of weak analgesic efficacy and pain tolerance previously observed with this dose. It is also shown that there are no significant differences between air and 10% nitrous oxide in peak velocity of saccadic eye movements, which is a sensitive indicator of central nervous system depression by sedation.

We did not perform any long-term follow-up of the level of satisfaction or the amnesic benefits of midazolam by the parents or patients, as has been done in a previous study. This might have been of interest because the amnesia effect of midazolam mainly affects explicit memory but leaves implicit memory intact. The mechanism of conditioned anxiety in children associated with repeated medical procedures may be explained by the intact implicit memory in patients treated with midazolam.

It cannot be ruled out that the result obtained in the midazolam group was affected by the use of the face mask. Therefore, it is possible that, under optimal conditions, treatment with midazolam may be superior to treatment with 10% nitrous oxide.

In conclusion, compared with treatment with midazolam, treatment with 50% nitrous oxide resulted in a more efficient IV access procedure measured as shorter total procedure time and an increased number of successful IV line procedures, as well as a better experience reported by the patients. Treatment with 50% nitrous oxide is therefore preferable to treatment with midazolam for facilitating the IV line procedure in anxious children and adolescents. Only under rare circumstances should obese children or adolescents be treated with midazolam because of the long procedure time.

Accepted for Publication: February 9, 2011.
Published Online: May 2, 2011. doi:10.1001/archpediatrics.2011.56

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Author Contributions: Study concept and design: Ekbom, Jakobsson, and Marcus. Acquisition of data: Ekbom and Kalman. Analysis and interpretation of data: Ekbom, Kalman, and Marcus. Drafting of the manuscript: Ekbom, Kalman, Jakobsson, and Marcus. Critical revision of the manuscript for important intellectual content: Ekbom, Kalman, and Marcus. Statistical analysis: Kalman and Marcus. Obtained funding: Ekbom and Marcus. Administrative, technical, and material support: Ekbom. Study supervision: Kalman, Jakobsson, and Marcus.

Financial Disclosure: Dr Jakobsson reports that he is a paid consultant (safety physician) for Linde Healthcare.

Funding/Support: This project was funded by the Sven Jerring Foundation, the Swedish Order of Freemasons, and the Swedish Council for Working Life and Social Research.

Additional Contributions: We thank Jan Kowalski, MSc, for his expert help with the statistics.

REFERENCES


Error in Abstract. In the Article titled “A Randomized Trial of Air Cleaners and a Health Coach to Improve Indoor Air Quality for Inner-City Children With Asthma and Secondhand Smoke Exposure” by Butz et al, published in the August issue of the Archives (2011;165[8]:741-748), an error occurred in the Abstract on page 741. The last sentence of the “Results” section should have read, “Symptom-free days were significantly increased in both air cleaner groups compared with the control group (P=.03).” The article was corrected online.