Adjunctive Nitrous Oxide during ED propofol sedation in adults,

a pilot study.

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Objectives

To describe the safety and efficacy of adjunctive nitrous oxide pre-propofol administration for analgesia and pre-procedure anxiolysis during ED procedural sedation and analgesia in adults.

Background

Specific Aims

To measure the rates of hypoxia and respiratory depression requiring a physician intervention in adult patients receiving 50% demand valve nitrous oxide pre-propofol administration during ED procedural sedation and analgesia. Secondary aims include patient, nursing, and physician post procedure satisfaction scores, Ramsay sedation scores, total propofol dose given, length of time spent using nitrous oxide, patient recall of procedure.

Significance

Procedural sedation is the use of sedative, analgesic, and/or dissociative agents to relieve anxiety and pain associated with diagnostic and therapeutic procedures. Propofol has become one of the most commonly used agents for ED procedural sedation.[1,2] Propofol crosses the blood-brain barrier rapidly. The drug takes effect within approximately 40 seconds, and its

duration of action is approximately six minutes [2,3] Multiple randomized trials and prospective observational studies have found propofol to be safe and effective for PSA in the emergency department [3,4,5,] Propofol acts as a sedative and amnestic, but provides no analgesia.

A possible approach is pretreatment with short-acting opioids (eg, fentanyl). Unfortunately, the addition of opioids increases the likelihood of respiratory complications. As an example, fentanyl at a dose of 1.5 mcg/kg increases the risk of respiratory depression. In another study, patients given both alfentanil and propofol required stimulation to induce respiration more often than those given only propofol.[7] Another alternative to pretreatment with short-acting opioids is to use sub-dissociative doses of ketamine (0.3 mg/kg). Ketamine appears to provide comparable analgesia with less risk of respiratory depression. However, there is no literature that has shown that there is a decreased risk of respiratory depression than with propofol.[8]

The optimal agent for analgesia before procedural sedation would have effect that is short acting, easy to administer, and with minimal risk to the patient. Nitrous oxide may fit this profile. In pediatric emergency departments, inhaled nitrous oxide was found to be the most common agent for procedural sedation and analgesia.[8] There is a great deal of literature supporting the use of nitrous oxide in the pediatric population, and the safety and efficacy of its use as a single agent or in concert with a parenteral sedative and/or analgesic is excellent. However, there is a paucity of literature to support or refute the use of nitrous oxide in adults for ED procedural sedation and analgesia.

Nitrous oxide is a colorless gas that diffuses rapidly across the pulmonary alveoli providing analgesia and anxiolysis with minimal sedative effects, rapid induction, and emergence.[9] Nitrous oxide is a weak sedative agent with the potential for significant analgesic

effects. Noncompetitive antagonist activity at the NMDA receptor along with activation of opioidergic receptors contributes to its anesthetic mechanism.[10] In an RCT (ENIGMA 1) using anesthesia with and without nitrous oxide, there was a small increased risk of myocardial infarction in the nitrous oxide group.[11] However, there were patients getting general anesthesia for over two hours; our patients will be receiving 50/50 nitrous oxide for 5-10 minutes maximum, and there are no known cardiac side effects reported during short-term sedation in the literature.[11] There are rare adverse events, most often cited as case reports of chronic or acute toxicity causing myeloneuropathies and polyneuropathies.[12-15]

Nitrous oxide has been used in general anesthesia for over 2 centuries, but its use outside of the operating room began when Tunstall introduced the nitrous oxide/oxygen mixture as an analgesic agent during labor.[16] Since this inception, the nitrous oxygen/oxygen mixture has been used readily in the fields of dentistry, gastrointestinal procedures, and children's procedural sedation. Nitrous oxide is often administrated via continuous flow or on-demand at a concentration of 50-70%.

There is some early data describing a favorable adverse event profile with nitrous oxide as a single agent in adults. Hennequin et al. (2012) demonstrated support for the efficacy of nitrous oxide with no major adverse cardiorespiratory events. Although approximately 10% of participants received mild gastrointestinal and behavioral side effects (e.g. agitation). Greater than 90% of the study participants stated they would receive nitrous oxide again.[17] In a large prospective trial, Babl et al. (2008) found there to be only 2 patients out of 655 who suffered serious adverse events (i.e., chest pain and oxygen desaturation). Both patients had been administered 70% nitrous oxide compared to the more conservative 50% concentration. Additionally, there was an increased incidence of minor adverse events (i.e., emesis and

agitation) with the higher concentration of nitrous oxide.[18] Kariman et al. (2011) compared nitrous oxide versus parental fentanyl as an analgesic after long bone fracture and found similar pain scores and a more rapid decrease in the pain score in the nitrous oxide group when compared with the opiate group.[19]

Nitrous oxide has been shown to be a safe and effective agent for procedural sedation in children, including work that has combined opiates and benzodiazepines with nitrous oxide continuously. Burton et al. (1998) conducted a small, randomized controlled trial studying the effectiveness of nitrous oxide on anxiety scores in children during laceration repairs. They found a significant decrease in the group that used nitrous oxide compared to the placebo group.[20] This finding was further validated by Luhmann et al. (2001) with 50% continuous flow of nitrous oxide resulting in less distress and anxiety as well as increased patient satisfaction compared to midazolam or topical anesthetic agents [21]. The study also showed that the main adverse event associated with nitrous oxide was nausea and vomiting, whereas the midazolam group had significant ataxia and dizziness. There was no demonstrable advantage of the combination of midazolam and nitrous oxide in regard to patient satisfaction versus nitrous oxide alone, but there was an increase in adverse events when midazolam was included.[21] A study performed by Evans et al. (1995) demonstrated that the pain and memory of the procedure between children receiving either nitrous oxide versus children receiving intramuscular meperidine in combination with promethazine for fracture reduction was similar, but there was increased satisfaction and decreased length of stay in the nitrous oxide group.[22] Seith et al. (2012) demonstrated that the addition of intranasal fentanyl to nitrous oxide in children resulted in deeper levels of sedation when compared to nitrous oxide alone; however, there were no serious adverse events.[23]

Nitrous oxide as an adjunct to propofol may an ideal agent to decrease pre-procedure anxiety before deep sedation of adults in the ED. Nitrous oxide has some analgesic and anxiolytic qualities, with an excellent cardio-respiratory profile. The anxiety and pain surrounding procedural sedation is not limited to the procedure itself, but the elapsed time from the time the patient enters the ED to the time spent in preparation for the procedure can be significant and lead to increased anxiety. This may lead to increased time and difficulty in sedating a patient to an appropriate level for a procedure. These patients may require higher levels of propofol to appropriately sedate, which is associated with increased rates of adverse respiratory events.

We believe that pre procedure adjunctive nitrous oxide may provide a level of anxiolysis and analgesia before propofol is administered, leading to a smoother and more satisfactory sedation and procedure, with fewer adverse respiratory events and less overall propofol dose than propofol alone. Since this is a novel concept, we believe that a pilot study to evaluate the safety and efficacy of pre-procedure adjunctive 50/50 nitrous oxide administration with adult propofol administration is warranted.

Setting of the Research

Patients will be recruited from the Emergency Department of Einstein Medical Center Philadelphia. The Einstein Medical Center Philadelphia is an urban teaching hospital, level one trauma center with 500 beds and an annual ED census of 100,000 subjects.

Resources Available to Conduct this Research

The Einstein Medical Center Philadelphia ED sees approximately 300 patients a day, of which 5% are emergencies that require procedural sedation and analgesia, and thus will be available as potential subjects in this study. The Division of Clinical Research of the Department

of Emergency Medicine has extensive experience in both investigator led and pharmaceutical research. This will be the seventh trial we have conducted in our ED in procedural sedation and analgesia in the last 7 years, and each of these studies has recruited 100-200 patients. We have a research associate 7 days a week who will consent and enroll eligible patients. The division also has 2 full time coordinators and a full time division director, as well as biostatistician support. We have two well-equipped offices, one in the ED where the research associate is based and one in our department where our division director works. The lead investigator will lead 10% of their non-clinical time to this endeavor.

Study Design

This pilot study will be conducted in a prospective, non-randomized fashion using a convenience sample of 100 subjects undergoing sedation for ED procedures.

1. Recruitment Methods

The research associates as well as the heath care team (both residents and attending physicians) will screen patients who may need procedural sedation in the ED and may qualify for the study. Research associates will use the Cerner/AeCIS System for screening, and they will be in charge of informed consent, enrollment, placement of the capnography monitor, as well as data collection. The health care team will be in charge of the procedural sedation and all other management.

2. Inclusion and Exclusion Criteria

    i. Inclusion criteria: All spontaneously breathing subjects, 18 years of age and older, with an American Society of Anesthesiologists (ASA) Physical Status Classification 1 or 2, who will be receiving sedation for an ED procedure. Written informed consent will be obtained from all subjects.

ii. Exclusion criteria: Subjects with underlying conditions that could affect ventilation, perfusion, or metabolism including intubated subjects, subjects with clinical signs of cardiopulmonary instability, major trauma, shock, sepsis, ASA class 3, 4, and 5. Also those unable to provide informed consent, nursing home residents, age less than 18 years, non English speaking, pregnant women, subjects under police custody, or physician discretion.

3. Study Endpoints

i. Primary:

1. $ETCO_2$ measured q 20 miliseconds seconds
2. SpO_2 measured q 20 miliseconds seconds

ii. Secondary Endpoints

1. A baseline reading of the vital signs (heart rate, respiratory rate, peripheral SaO_2 and $ETCO_2$)
2. Physician interventions (verbal or physical stimulation, airway repositioning, additional oxygen, positive pressure ventilation, endotracheal intubation)
3. Level of sedation (Ramsay Score)
4. Patient Demographics
5. Patient recall of procedure
6. Total propofol dose
7. Total elapsed time of nitrous oxide use
8. Patient and physician procedure satisfaction score

4. Procedures Involved in the Research

Initial medical assessment will be made in accordance with established clinical procedures, including the history, physical examination, and vital signs. If by clinical assessment the patient meets eligibility criteria, then they will be approached by a research associate for enrollment in the study. After informed consent is obtained and prior to starting the sedation, standard vital sign monitoring will be placed on the patient (electrocardiogram, non-invasive blood pressure monitoring, pulse oximetry, and capnography). Level of consciousness will be determined using the modified Ramsay scale, which will be assessed at baseline. The Capnostream 20 $ETCO_2$ monitor will be used as the primary device to measure $ETCO_2$, with a nasal cannula capable of delivering supplemental oxygen and measuring $ETCO_2$ (Oridion Medical, Needham, MA).

The SEDARA gas mixer system [Linde Gas North America LLC] will be used as our primary nitrous oxide delivery device. It will mix and deliver nitrous oxide and oxygen in a 1:1 ratio, at a fixed concentration of 50%/50%. It uses a patient driven demand valve system that is hand held**.** This device provides a consistent, fixed 50%/50% blend of nitrous oxide (N_2O) and oxygen (O_2), eliminates the need to titrate, and provides fixed concentrations for controlled and consistent dosing. The device comparator detects dosing imbalance to protect against hypoxic mixtures, it cannot deliver nitrous gas without concurrent oxygen, and the device has an anti-asphyxia valve override. The on demand valve requires patient inspiration to trigger dosing. This portable device scavenges exhaled waste gases for environmental safety, as well as a key mechanism that renders the system inoperable without it for security.

After informed consent, the patient will fill out a pre procedure questionnaire and a 100 mm VAS baseline pain scale. The patient will be given the mask for delivery of nitrous oxide, and instructed on its use. The research associate will mark the time the patient began using the device electronically on the capnostream 20. Once IV access is established, and the team and

patient are ready to begin the procedure, the nitrous oxide mask will be removed, and a 100% NRB mask delivering 15 liters a minute of supplemental oxygen will be placed on the patients face. The loading dose of propofol will then be administered immediately. All sedations in this trial will use propofol 1.0 mg/Kg initial dose, with 0.5 mg/Kg doses titrated to deep sedation. Once the patient is deeply sedated, the procedure will begin.

The subject's clinical data and sedation information (refer to data management) will be entered into a standardized data collection form. The data will be continuously recorded throughout the sedation and recovery periods. Study will end when the subjects recovers back to baseline mental status.

Vital signs will be flagged electronically when a physician intervenes for clinical respiratory depression. Respiratory depression will be defined as peripheral SaO_2 below 92%, $ETCO_2$ level above 50, a rise or decrease of 10% above or below baseline, the loss of the $ETCO_2$ waveform for more than 15 seconds. Level of consciousness will be determined using the modified Ramsay scale, which will be recorded at baseline and at the point of deepest sedation. Once the procedure is complete, and the patient is deemed back to their mental status baseline, they will fill out a post procedure satisfaction questionnaire, and a 100mm VAS scale. They will be asked about procedure recall. The physician will also fill out a post procedure questionnaire.

5. Data Management

A standardized data collection form will be used to collect clinical data and a USB drive to collect electronic vital sign data. Initial data gathered will include age, gender, weight, and baseline vital signs (BP, HR, RR, peripheral SpO_2, and ETCO2). Other information collected will be the elapsed time of nitrous oxide use, start time (when protocol was given), time (when patient returns to baseline), elapsed time in seconds under sedation (from start time to end time),

medications administered, repeated doses and times for every administered medication, total dose of each medication administered, adverse events, and interventions aimed at correcting respiratory depression. Level of consciousness using the modified Ramsay scale will also be recorded at baseline and at set intervals during sedation.

The electronic monitoring data will be continuously recorded into the USB drive throughout the sedation and recovery periods. The Capnostream 20 $ETCO_2$ monitor (Oridian Medical, Needham, MA) is capable of sampling and recording $ETCO_2$ and pulse SaO_2 every 5 seconds. A patient identifier will be recorded to link the subject and the electronic monitoring data without compromising his/her confidentiality. At the completion of the sedation, all device data will be transmitted to a password-protected Excel/SPSS spreadsheet for analysis. The research associate is responsible for recollection and storage of the data. Only the primary investigators, the study coordinator, and the research associates will have access to such.

To assess these outcomes, we will download electronic data from each sedation into a Microsoft Excel database, checked and adjudicated any discrepancies with research associate notations, and generate a graph of the subject's sedation with the X-axis showing time and the Y-axis depicting $ETCO_2$, SpO_2, respiratory rate, and heart rate. Electronic time stamps noted propofol administration, procedure initiation and completion, adverse events, and physician interventions.

Before study blinding is broken, three investigators will evaluate each graph to code the presence or absence of cerebral hypoxia, peripheral hypoxia and respiratory depression. We will disqualify graphs if they had >35% data loss, unless all three evaluators agreed that there was unequivocal evidence of hypoxia (cerebral and or peripheral) and/or respiratory depression.

6. Withdrawal of Subjects

Participation is voluntary. Subjects may withdraw from this study at any time. If this is the case their data will be deleted. We will record the number of patients that withdraw. Subjects may be withdrawn without their consent if the electronic data cannot be recorded.

Statistical Plan

1. Sample Size Determination

As this is a pilot, prospective, observational trial, no power calculation will be used to measure a difference. In previous propofol studies, approximately 10-30% of patients develop hypoxia, and approximately 50% of patients meet criteria for respiratory depression. Thus, we believe enrolling 100 patients in this observational trial will allow for approximation of any correlations that are measured.

2. Statistical Methods

All clinical observations and demographic data will be summarized using medians with range or means with standard deviations as appropriate. Rate of detection of respiratory depression and hypoxia and timing of these events for each instrument (near-infrared spectroscopy, pulse oximetry, capnography) will be summarized descriptively. Associations among SaO2, and $ETCO_2$ will be estimated using spearman's rank correlation coefficient, using within-cluster resampling algorithm. This will allow for estimation of the marginal correlation in the presence of clustered data. Correlations not involving repeated measures data will be estimated with Spearman's rank correlation coefficient. All analysis will be conducted using SPSS software (IBM, Armonk, NY).

Risks to Subjects

There are no risks to the subjects other than the normal risks associated with the standard procedural sedation and analgesia, which may vary depending on the agent used, but in general include hypoxia, respiratory depression, hypotension, etc.

Potential Benefits to Subjects

There is no direct benefit for the subject. There will be no reimbursement to subjects for their participation in the study.

Provisions to Protect the Privacy Interests of Subjects

All data will be de-identified. Data that is loaded into the computer will be password protected and only available to the research associates and the investigators. Patients will be approached at their bedside by trained associates that will establish a private environment to disclose the information about this study and recollect the data. There will be no undue pressure placed to participate. All questions about the study may be answered by the research associates and the investigators prior, during and after informed consent is given.

Provisions to Maintain the Confidentiality of Data

Each subject will be given an identification number in the monitors and database in order to de-identify data for analysis. Study data will be stored for a minimum of 3 years in a secure and password protected file only accessible to study staff. Hard copy of data collection form will be kept in the research office under lock and only accessible to study staff.

Medical Care and Compensation for Injury

This is an observational study. No injuries can be consequence from participating in it. The procedural sedation and analgesia carries some risk that does not go beyond the standard ED protocol.

Cost to Subjects

There will be no cost to the subjects from participating in the study. Aspects that are part of standard clinical care will be responsibility of the subjects and their insurance companies.

Consent Process

Formal written consent will be completed by the patient with a trained research associate, who has extensive experience in research recruitment and consent. The consent discussion will be hold at the patient's bed side, and will last until the patient understand what is being told. Patient can ask any question related to the study and can take the time they consider necessary to consent. No coercion or undue influence will be placed to participate.

The signed documents will be stored in the study binder inside the research office and a copy will be given to each subject for their files.

Vulnerable Populations

Only eligible adult patients who can give informed consent in writing will be enrolled, no children, incarcerated, pregnant, or mentally incapacitated patients will be enrolled.

Sharing of Results with Subjects

Results will not be shared with subjects.

References

1. Gan TJ. Pharmacokinetic and pharmacodynamic characteristics of medications used for moderate sedation. Clin Pharmacokinet 2006; 45:855.

2. Swanson ER, Seaberg DC, Mathias S. The use of propofol for sedation in the emergency department. Acad Emerg Med 1996; 3:234.

3. Miner JR, Burton JH. Clinical practice advisory: Emergency department procedural sedation with propofol. Ann Emerg Med 2007; 50:182.

4. Newstead B, Bradburn S, Appelboam A, et al. Propofol for adult procedural sedation in a UK emergency department: safety profile in 1008 cases. Br J Anaesth 2013; 111:651.

5. Black E, Campbell SG, Magee K, Zed PJ. Propofol for procedural sedation in the emergency department: a qualitative systematic review. Ann Pharmacother 2013; 47:856

6. Miner JR1, Gray R, Delavari P, Patel S, Patel R, Plummer D. Alfentanil for procedural sedation in the emergency department. Ann Emerg Med. 2011 Feb;57(2):117-21. doi: 10.1016/j.annemergmed.2010.08.010. Epub 2010 Oct 13.

7. Willman EV1, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2007 Jan;49(1):23-30. Epub 2006 Oct 23.

8. Borland M, Esson A, Babl F, Krieser D. Procedural sedation in children in the emergency department: A PREDICT study. Emergency Medicine Australasia. 2009; 21: 71-79.

9. Patel PM, Patel HH, Roth DM. Chapter 19. General Anesthetics and Therapeutic Gases. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2011.

10. Fang F, Guo TZ, Davies MF, Maze M. Opiate receptors in the periaqueductal gray mediate analgesic effect of nitrous oxide in rats. Eur J Pharmacol. 1997; 336: 137–141.

11. Leslie K1, Myles PS, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Williamson E.Nitrous oxide and long-term morbidity and mortality in the

ENIGMA trial. Anesth Analg. 2011 Feb;112(2):387-93. doi: 10.1213/ANE.0b013e3181f7e2c4. Epub 2010 Sep 22.

12. Huang MY, Tsai W, Chang WH. Nitrous oxide-induced polyneuropathy in a teenager. Emerg Med J. 2009; 26(3): 186

13. Hsu CK, Chen Y, Lung V, His SC, Lo HC, Shyu HY. Myelopathy and polyneuropathy caused by nitrous oxide toxicity: a case report. American Journal of Emergency Medicine. 2012; 30: 1016.e3-1016.e6.

14.Alt RS, Morrissey RP, Gang MA, Hoffman RS, Schaumburg HH. Severe myeloneuropathy from acute high-dose nitrous oxide(N2O) abuse. J Emerg Med. 2011; 41(4): 378-380.

15.Richardson PG. Peripheral neuropathy following nitrous oxide abuse. Emergency Medicine Australasia. 2010; 22: 88-90.

16. Tunstall ME. The use of a fixed nitrous oxide and oxygen mixture from one cylinder. Lancet. 1961; 2: 964.

17. Hennequin M, Collado V, Faulks D, Koscielny S, Onody P, Nicolas E. A clinical trial of efficacy and safety of inhalation sedation with a 50% nitrous oxide/oxygen premix (kalinox) in general practice. Clin Oral Investig. 2012; 16(2): 633-42.

18. Babl FE, Oakley E, Seaman C, Barnett P, Sharwood LN. High-concentration nitrous oxide for procedural sedation in children: adverse events and depth of sedation. Pediatrics. 2008; 121: e528-32.

19. Kariman H, Majidi A, Amini A, Dolatabadi AA, Derakhshanfar H, Hatamabadi H, Shahrami A, Yaseri M, Sheibani K. Nitrous oxide/oxygen compared with fentanyl in reducing pain among adults with isolated extremity trauma: a randomized trial. Emerg Med Australes. 2011; 23(6): 761-8.

20. Burton JH, Auble TE, Fuchs SM. Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. Acad Emerg Med. 1998; 5(2): 112-7.

21. 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. Annals of Emerg Med. 2001; 37 (1): 20-27.

22. Evans JK, Buckley SL, Alexander AH, Gilpin AT. Analgesia for the reduction of fractures in children: a comparison of nitrous oxide with intramuscular sedation. J Pediatric Orthopedics. 1995; 15 (1): 73-77.

23 .Seith RW, Theophilos T, Franz BE. Intranasal Fentanyl and High-concentration Inhaled Nitrous Oxide for Procedural Sedation: A Prospective Observational Pilot Study of Adverse Events and Depth of Sedation. Academic Emergency Medicine. 2012 Feb; 19(2): 238.

Attachments

A) Sedara Gas Mixer System Quick Reference Guide

B) Data Collection Form

C) Ramsay Scale

D) Patient and physician procedure satisfaction score