Inhaled Nitrous Oxide Versus Placebo as an Analgesic and Anxiolytic Adjunct to Peripheral Intravenous Cannulation

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The objective was to determine whether an inhaled 50:50 mixture of nitrous oxide and oxygen (N_2O/O_2) provides significant pain and anxiety relief during intravenous cannulation in healthy adults. The study was conducted at the ED of a military teaching hospital. Participants included adult volunteers aged 18 to 50 years. Excluded were those with allergy to N_2O, anemia, cardiac disease, pregnancy, asthma, or bone marrow disorder. A prospective, randomized, double-blind, placebo-controlled crossover design was used comparing a 50:50 mixture of N_2O/O_2 versus O_2. After recording baseline nonhatched 100mm visual analog scales (VAS) for pain and anxiety, subjects inhaled gas 1 for 120 seconds, followed by antecubital intravenous cannulation, discontinuance of gas and VAS rating of procedural pain and anxiety. After 15 minutes, the experiment was repeated with gas 2. Ten subjects would detect a 12mm difference in pain or anxiety with a standard deviation of 10 mm, an alpha error under 0.05 and a power over 80%. Differences between VAS were compared by matched 2-tailed t-test. Eleven subjects were enrolled. One withdrew because of dizziness while inhaling gas (N_2O). The 10 remaining subjects reported significantly less pain (N_2O/O_2 14.5mm, SD 18; O_2 34.3mm, SD 23.4; $P < .01$) and anxiety (N_2O/O_2 - 7.9mm, SD 7.8; O_2 6.0mm, SD 11.6; $P < .02$) when inhaling N_2O/O_2 than when inhaling O_2 alone. N_2O/O_2 provided significant pain and anxiety reductions during intravenous cannulation. Some patients may experience adverse perceptions while using N_2O, limiting its utility. Further studies defining the role of N_2O as an anxiolytic agent, efficacy in actual patients, and cost comparisons with intravenous conscious analgesia/sedation, are warranted. (Am J Emerg Med 2001;19:492-494. This is a US government work. There are no restrictions on its use.)

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There exists a multitude of bedside procedures performed in the emergency department (ED) that produce both pain and anxiety. Such procedures include dressing changes, incision and drainage of wounds, fracture reductions, pelvic examinations, and peripheral IV cannulation. Pain control, when considered at all, is often achieved by injection of local anesthetics or the application of systemic analgesic agents.[1] Both of these can be painful, and may produce lasting effects necessitating close monitoring for extended periods. In addition to pain, such procedures may produce significant anxiety,[2] generating unpleasant memories for the patient and making the performance of the procedure difficult for the health care provider.

Nitrous oxide (N_2O) is an inhaled anesthetic gas possessing analgesic properties at lower concentrations.[3] It has been used as an analgesic and surgical anesthetic for decades, including extensive use in Europe for peripartum analgesia.[4] Throughout the decade spanning the mid-1980s through 1990s, there was a surge of N_2O research in prehospital EMS systems across the United States.[5-8] This initial interest lost momentum, however, most likely because of adverse effects associated with higher concentrations of N_2O (a 70:30 admixture with O_2) as well as concerns over potential abuse and accountability.

Despite the attractive clinical and pharmacologic profiles, and extremely low abuse potential, N_2O is currently underused in the ED setting.[9] N_2O possesses several properties that make it ideal for bedside use in the ED.[1,3] It is easy to administer, requires no intravenous access before its administration, and the patient may control the level of analgesia by removing the gas. It possesses a rapid onset of clinical effect (less than 2 minutes), and after termination of administration, its effect disappears almost as quickly. It has very few side effects, all of which are self-limited and generally resolve with termination of exposure to the gas. N_2O is ubiquitous in facilities possessing anesthesia services. The apparatus to deliver the gas is inexpensive and portable, and staff resources for its use are essentially identical to those required by standard conscious analgesic protocols already in place in most EDs.

With the current emphasis upon efficiency maximization and cost-effective health care, it is evident that N_2O/O_2 warrants a critical "second-look" at efficacy, safety, and potential cost savings as an analgesic and possible anxiolytic agent for noxious procedures which may otherwise

require intravenous conscious analgesia / sedation (ICAS). This study was undertaken as an initial pilot to confirm or refute N_2O utility as an analgesic agent, and to determine whether it might possess a putative anxiolytic effect.

METHODS

This study was evaluated and approved by the Human Subjects Committee (Institutional Review Board) of the institution in which it was conducted. The specific question to be addressed was whether an inhaled 50:50 mixture of N_2O/O_2 (study agent) provides significantly greater pain relief and anxiety reduction than O_2 alone (placebo), using peripheral intravenous cannulation as a model for an elective bedside procedure producing a noxious stimulus in otherwise healthy adult subjects. The design was based on a prospective, randomized, double-blind placebo-controlled crossover format. Study gasses were administered using a NITRONOX 50:50 delivery system. A trial profile appears in Fig 1.

For this pilot study, it was determined that 10 subjects would detect a 12 mm difference in pain or anxiety perception with a standard deviation (SD) of 10 mm, an alpha error less than 0.05 and a power greater than 80%. Differences between baseline and treatment VAS would be compared by matched 2-tailed t-test. Initially, 5 enrollment packets with separately sealed instructions for the order of gas administration were prepared with N_2O/O_2 as the initial gas followed by O2, with the remaining 5 packets calling for O_2 as the initial gas followed by N_2O/O_2. All packets were randomly assigned a number and were used sequentially. In addition to an investigator who monitored each subject and administered the data collection, an additional investigator positioned behind a privacy screen with the N_2O/O_2 delivery system administered the study gasses sequentially as directed by each corresponding subject's sealed instruction packet. Both the subject and data collector/patient monitor were unaware of the order of gas administration.

Healthy adult volunteers aged 18 to 50 years were included as subjects. Potential subjects were excluded if they possessed a history of allergy to N_2O, anemia, cardiac disease, pregnancy, asthma or bone marrow disorders. After enrollment, vital signs were obtained and a cursory cardiopulmonary examination was performed. Then, subjects were asked to rate their baseline perceptions of pain and feelings of anxiety about the impending intravenous cannulation by placing a mark on a 100 mm non hatched visual analog scale (VAS) bounded by the numbers zero (minimum) and 10 (maximum).

Each subject inhaled the first study gas for 120 seconds, then IV cannulation was performed using an 18-guage over-the-needle

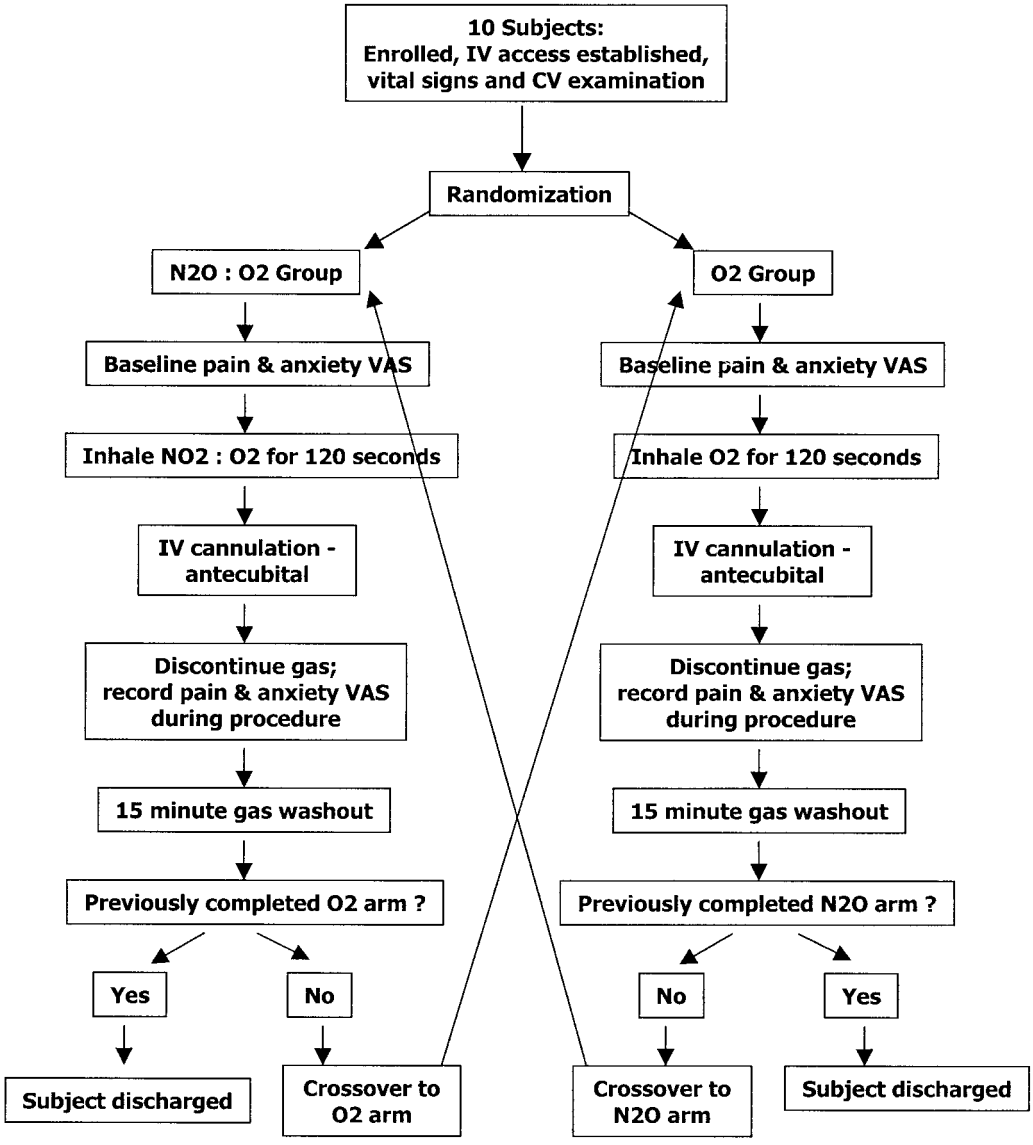

FIGURE 1. Nitrous oxide versus placebo study profile.

catheter in an antecubital vein. After cannulation was confirmed by the successful injection of 10mL of normal saline solution, the study gas was withdrawn and the catheter removed. Subjects then rated pain and anxiety perception during the intravenous cannulation on a VAS using the aforementioned method. After a 15 minute period to allow for washout of the study gas, subjects again recorded baseline pain and anxiety on a VAS, inhaled the second study gas for 120 seconds and underwent IV cannulation in the contralateral antecubital space. After confirmation of cannulation, the second gas was withdrawn and pain and anxiety perception during the procedure were rated on the VAS. Subjects were then observed for 30 minutes and discharged.

RESULTS

Initially, 10 subjects were enrolled. One subject withdrew because of subjective dizziness while inhaling gas (N_2O). One additional subject was enrolled to provide the aforementioned 10 completed datasets. The order of gas administration for the final subject was determined by coin flip. No other adverse effects were reported or observed by subjects or investigators. Median pain score during intravenous cannulation was 10 (SD 24.5) for the N_2O/O_2 group and 31 (SD 23.5) for the O_2 control group; median anxiety during cannulation was 0.5 (SD 13.0) for the N_2O/O_2 group and 15 (SD 9.4) for the O_2 group. Neither comparison of these raw average scores reached statistical significance. The average calculated difference in pain and anxiety perception measured between baseline and during IV cannulation of each subject are displayed in Table 1. Here, both pain and anxiety perception during cannulation were significantly lower in the N_2O/O_2 group than in the O_2 controls. Regarding anxiety, it is noteworthy that after subtracting baseline from procedural VAS, subjects receiving N_2O/O_2 actually perceived less anxiety on average awaiting IV cannulation than they did at baseline.

DISCUSSION

During the decade of the late 1980s and early 1990s, N_2O/O_2 enjoyed a period in which it was in vogue as an analgesic agent for both prehospital and ED use. This notoriety has waned in recent years. Despite its scattered adherents, N_2O use has not become widespread in emergency care. We believe, however, that with the increasing use of bedside analgesia and sedation for elective procedures in the ED setting, and with the shift of many elective procedures to the ambulatory patient setting, N_2O deserves a second look. This study sought to objectively confirm the efficacy of a 50:50 mixture of N_2O and O_2 as an analgesic agent for a mildly noxious stimulus in otherwise healthy subjects.

This study was conducted to provide a logical basis for an expanded reappraisal of N_2O in the setting of relatively brief elective procedures performed in the ED or similar ambulatory settings. Under such circumstances, ICAS has evolved into the primary method of pain and anxiety management. Despite its efficacy, it possesses several drawbacks in this setting. By definition, it requires intravenous access. Because most ICAS agents belong to the opioid or benzodiazepene pharmaceutical classes with their inherent side effects, ICAS requires hemodynamic and neurologic monitoring, which is both technology- and labor-intensive. Lastly, despite the advent of shorter-acting agents and antidotes, the recovery and observation period after ICAS may approach a duration in excess of 2 hours.

TABLE 1. Average Change in Pain and Anxiety Perception (VAS During Procedure Minus VAS Preprocedure)

	N_2O/O_2 (mm) (SD)	O_2 (MM) (SD)	*P*
Pain	14.5 (18)	34.3 (23.4)	.01
Anxiety	−7.9mm (7.8)	6.0 (11.6)	.02

An ideal alternative to ICAS would be an agent that could provide adequate analgesia and anxiolysis while minimizing side effects, avoiding intravenous access, and possessing a shorter recovery period. We propose that N_2O/O_2 may potentially fit those requirements for specific subsets of patients and procedures.

This study possesses several limitations. By design, it possesses a small study population. Larger numbers of subjects will be required to validate our preliminary findings and to further delineate the actual incidence rate of adverse perceptions while using N_2O. Children were excluded from the study, thus leaving unstudied an entire demographic group who might benefit from N_2O treatment. Although intuitively the VAS would appear to be an effective instrument for assessment of anxiety, it has not been validated specifically for this purpose. We studied the effect of N_2O on healthy adult volunteers; assessment its efficacy as both an analgesic and anxiolytic agent in actual patients undergoing specific procedures or experiencing specific types of pain awaits further study. In such a setting, N_2O would be ineffective in patients unable or unwilling to self-administer the gas.

In this study, a 50:50 inhaled mixture of N_2O/O_2 has been shown to effectively decrease the pain and anxiety associated with a mild noxious procedure in healthy adults. We hypothesize that it is also easier to administer, will require less time from onset of effect until recovery and discharge, and as a result, will cost less to employ than ICAS. N_2O/O_2 also may potentially decrease ED length-of-stay for selected procedures significantly in comparison to ICAS. The critical question to be answered, however, is whether the analgesic and anxiolytic effects of N_2O/O_2 are adequate and comparable to ICAS in the perception of actual patients in the ED setting. These issues await further investigation.

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