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Use of Nitrous Oxide in the Emergency Department: A Review of the Literature

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Introduction

Nitrous oxide (N_2O) was first discovered in 1771 and was initially used as a recreational drug. It was not until American dentist Horace Wells administered "laughing gas" to numb patients' pain while pulling teeth in 1884 that nitrous oxide was used as an anesthetic. Since then, it has been used in a myriad of clinical situations, ranging from the dentist's chair to the delivery room. Nitrous oxide has been used to treat many types of injuries in the emergency department in both pediatric and adult patients. In children, studies have shown N_2O to be superior to both oral midazolam [1] and lidocaine [2] for treatment of lacerations and better than intramuscular morphine for forearm fracture treatment [3]. In adults, N_2O has been shown to be effective in the Emergency Department (ED) for treatment for a variety of ailments including myocardial pain [4], migraines, [5] joint dislocations [6] and fractures [7]. Alternative options have replaced nitrous oxide as the preferred sedative and anxiolytic in the ED in the US, however this simple gas still has much to offer and is commonly used in other countries such as Australia and the UK [8]. Further study is needed to evaluate its effect on pain control in adults, cost, and ease of use in an ED setting compared to other agents.

Properties and Mechanism of Action

Nitrous oxide is sweet-smelling gas that is colorless and does not bind to body tissue or to hemoglobin. The low solubility of N_2O allows its effects to be felt quickly. There are varying theories on N_2O's precise mechanism of action, from targeting the endogenous opioid system [9] to causing general depression of the central nervous system. Studies have shown that nitrous oxide works on areas of the brain and spinal cord that are high in cells reactive to morphine [10]. Other studies suggest nitrous oxide may be a partial opioid receptor agonist [11].

Nitrous oxide, administered in concentrations of 50% or less, effects sensorium without causing decrease in respiration and meets American Society for Anesthesiologists (ASA) criteria for minimal sedation. Given in the proper doses, N_2O has no substantial effects on the respiratory system of healthy individuals. Time to onset and duration of effect is less than a few minutes, making it an ideal agent for brief procedures [12].

Adverse Affects and Contraindications

Nitrous oxide has relatively few side effects, but there are some patients in which it is not recommended or contraindicated. Several studies have shown N_2O can have a deleterious effect on the cardiovascular system, as patients with pulmonary hypertension have displayed increases in pulmonary vascular resistance after being treated with nitrous oxide. Therefore, it is recommended that patients with pulmonary edema, hypertension and mitral stenosis not be treated with nitrous oxide. Nitrous oxide is contraindicated in patients with pneumothoraxes, COPD, otitis media, bowel obstructions, or hyerbarism. This is due to the fact that| nitrous oxide diffuses into air pockets and forces them to expand. Because of how it is usually administered, nitrous oxide use is also contraindicated in those with head injuries and people with altered mental status. Nitrous oxide may cause nausea and vomiting. Due to its effects on DNA production, nitrous oxide should not be given to women during the first two trimesters of pregnancy [12].

Chronic nitrous oxide exposure can lead to diffuse neurological deficits and sensory loss. Although N_2O toxicity usually manifests only after prolonged exposure or abuse [13], one study showed that neuropathy could result from severely high dose of nitrous oxide given in an acute setting [14]. The risks of nitrous oxide to patients are relatively low, but healthcare workers can suffer from long-term exposure. Care should be given to make sure Enotox is given in a large, well-ventilated environment to prevent the unwanted accumulation.

Methods of Administration

Nitrous oxide can be administered in the Emergency Department by the Enotoxsystem. Enotox is a mixture of 50% nitrous oxide and 50% oxygen pressurized in a single cylinder. The patient receives the gas mixture through a mask, which they hold closely to their face and gas is delivered by a demand valve, which opens with inhalation. The negative-pressure dependent system makes it nearly impossible for an excessive dose to be administered and allows the patient to control his own level of anesthesia. There is one rare, but concerning risk with Enotox. If the cylinder drops below the "pseudo-critical" temperature of -5.5 degrees Celsius, the nitrous oxide can separate out as a liquid, depleting oxygen content of cylinder and eventually delivering pure nitrous oxide. This can result in the patient inhaling a hypoxic gas mixture.

Nitrous oxide can also be given using an apparatus that mixes nitrous oxide and oxygen from separate sources, eliminating the pseudo-critical temperature risk. This second method can be used to give different ratios of N_2O when more or less than a 50:50 mixture is needed. The device should have a failsafe that prevents inadvertent administration of nitrous without sufficient oxygen source pressure.

Clinical Research

Most of the research performed evaluating nitrous oxide has been directed toward the pediatric population. The first study compared nitrous oxide/lidocaine to placebo/lidocaine in pediatric laceration repair. The author used a lower concentration of 30% N_2O/70% O_2 and found that no difference exists in children under 8 years of age but was significantly reduced in children over 8 years old [15]. Another older prospective randomized study showed no significant difference in perceived pain in forearm fractures comparing nitrous oxide to intravenous regional anesthesia in pediatric patients, but did not specify the concentration of nitrous oxide used or standardize the alternative [3].

A randomized controlled trial of nitrous oxide vs. intravenous

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ketamine in pediatric patients demonstrated the N_2O was preferred but was limited by a sample size of only 32 patients. The authors found that sedation levels were deeper in ketamine, recovery times were shorter in the group randomized to nitrous oxide (0 vs. 21.5 minutes), and that no difference exists in observed satisfaction scores by physicians, patients, or nurses [16]. Another randomized controlled trial compared regimens using nitrous oxide to oral midazolam in children 2-6 years old. This larger study of 204 subjects found regimens including continuous flow nitrous oxide to be more effective, fewer adverse effects, and shorter recovery times [1]. A randomized comparison of nitrous oxide plus hematoma block vs. ketamine plus midazolam for ED forearm fracture reductions in children demonstrated less reported pain with the nitrous oxide/hematoma block and shorter recovery times [17]. A more recent study compared pain control with nitrous oxide/transmucosal fentanyl/hematoma block compared to nitrous oxide and hematoma block alone. The authors found the combination of 3 agents reduced pain control compared to the regimen of nitrous oxide and hematoma block alone, however this study was limited by its retrospective observational design and lack of randomization [18].

A review of a prospective single center procedural sedation registry with over 2000 patients found that almost all procedures performed in Australia were undertaken with nitrous oxide and ketamine; the serious adverse event rate was low [19]. A recent prospective observational pilot study combined intranasal fentanyl and high concentration (up to 70%) nitrous oxide in 41 children. They found no serious adverse events but reported a 19.5% incidence of vomiting and deep sedation in only 2 patients [20].

A cost effectiveness analysis was performed in 2008 demonstrated that nitrous oxide was half the cost of EMLA cream but more expensive than intradermal injection of buffered lidocaine. The estimated cost of buffered lidocaine was $1.60 compared to inhaled nitrous oxide, $27.80 [21].

There are a limited amount of randomized controlled trials looking at nitrous oxide efficacy in adults. A randomized prospective trial compared intra-articular lidocaine vs. Enotox for reduction of acute anterior shoulder dislocation. A statistically significant reduction in pain scores was achieved with both agents, the effect with Enotox was greater than lidocaine, however the study was not powered adequately to detect whether the differences between agents were statistically significant [6]. Another study attempted to perform a randomized controlled trial in 10 volunteers comparing nitrous oxide to oxygen (placebo), but was limited by small sample size and inability to blind patients due to the effect of nitrous oxide on the patients [22]. A prospective, randomized, double blind study queried the treatment of acute migraine headaches comparing nitrous oxide to oxygen in 22 patients. Nitrous oxide showed a reduction in percentage of patients requiring rescue medication (60% vs. 8%) [5]. A randomized controlled trial in adults in Iran compared 50% nitrous oxide to 2 mcg/kg of fentanyl in patients with isolated extremity fracture. There was no difference between groups, with mean visual analogue scores, 2.2 vs. 3.1 for nitrous oxide vs. fentanyl respectively [23]. A 50% nitrous oxide and oxygen mixture was compared to oxygen in a prehospital setting and was found to be safe in 60 patients and demonstrated efficacy of N_2O for treatment of pain from acute trauma [24]. Enotox was shown to decrease time in the ED compared to opiates with midazolam in adult patients with acutely dislocated shoulders [25].

Conclusion

Nitrous oxide is one of the oldest anesthetics and has been used for a variety of uses. It is simple to use, relatively cost effective and has very few adverse effects for the patient. Although there have been several studies on nitrous oxide, many of them are limited by small sample sizes, flaws in the study design and methods, or lack of randomization. There is much more to be learned about how it compares to other commonly used anesthetics in an ED setting.

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