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ProNox in Performing Dermatologic Procedures: A Literature Review

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ABSTRACT

ProNox is an FDA-approved device used by patients during procedures to self-administer a mixture of nitrous oxide (N2O) and oxygen to manage stress and pain. Pain management is a crucial aspect of healthcare that helps alleviate patient discomfort. Effective pain management not only improves the patient experience but also permits dermatologists to perform procedures with greater precision and efficacy. The delivery of nitrous oxide helps relieve anxiety and pain by serving as an analgesic, and its administration through ProNox's unique delivery system allows patients to have complete control over their anesthetic experience. The most common side effects listed in the literature include mood lability, nausea, dizziness, anxiety, crying, hysteria, and delusions. Incorporating ProNox into dermatologic practice can bring significant improvements to patient comfort and overall experience, leading to higher patient satisfaction and potentially enhanced patient retention. Further research is required to explore the long-term effects and overall cost-effectiveness of using ProNox in dermatologic procedures.

Keywords: ProNox; Dermatological procedures; Dermatological surgeries; Anesthesia; Pain-free procedure

INTRODUCTION

The frequency of dermatological surgeries has perceived remarkable growth over the past decade. This growth is associated with increased accessibility, improved technologies, expanding indications, and greater acceptance of cosmetic treatments in society. Although there has been significant growth in dermatological procedures, many are still associated with periprocedural discomfort despite their effectiveness. To alleviate this discomfort, many modalities are being used, including local and topical anesthetics, opioids, benzodiazepines, and non-steroidal anti-inflammatory drugs (NSAIDs). However, inhalation of N2O is receiving attention due to its lower side effect profile, short half-life, ease of clinical integration, and rapid onset.[1]

ProNox is an FDA-approved on-demand valve device used for the self-administration of nitrous oxide (N2O) and oxygen.[2] N2O is a colorless, odorless, and nonflammable gas used for inducing general anesthesia and

procedural sedation.[3] It is widely used in dermatological medicine and exhibits anxiolytic and analgesic properties, which are mediated by its action on γ-aminobutyric acid receptor pathways and opioid receptors. The limitation of N2O is that it is a mild analgesic; therefore, it is often combined with some other systemic analgesics and nerve blockers. ProNox employment includes adjunction with medications — often with opioids (12.8%), benzodiazepines (22.1%), and NSAIDs (47.1%) — to provide adequate anesthesia to patients.[3] ProNox delivers a mixture of 50% inhaled nitrous oxide and 50% oxygen to produce analgesia in patients and is associated with a lower risk of loss of consciousness.[1] Some adverse effects associated with the use of N2O in ProNox include mood lability, nausea, dizziness, anxiety, crying, hysteria, and delusions.[4]

Pain and anxiety are frequently encountered problems in dermatological procedures, so dermatologists must know how to effectively manage and mitigate a patient's pain.[5] With devices like ProNox, physicians can ease patient discomfort and improve patient care. However, it is essential to discuss the benefits, risks, and costs associated with N2O as an adjunctive treatment with patients, as it is typically an uncovered service.[6]

Pain management is a crucial aspect of healthcare to alleviate patient discomfort. Effective pain management not only improves the patient experience but also permits dermatologists to perform procedures with greater precision and efficacy. By reviewing existing studies and research articles, we aim to deliver a comprehensive overview of the existing evidence surrounding the use of ProNox in dermatology. The purpose of this literature review is to examine the use and efficiency of ProNox in performing dermatologic processes. It will assist in identifying knowledge gaps, highlight the potential benefits and limitations of ProNox, and inform future research in this area.

ProNoX

Overview of ProNoX

ProNox is a management solution for stress and pain that consists of a 1:1 ratio of oxygen and nitrous oxide. It is a convenient solution for those undergoing dermatological procedures during which a completely unconscious state is not necessary. ProNox helps relieve anxiety and pain by serving as an analgesic through a unique delivery system that allows patients to have complete control over their anesthetic experience. Patient preference guides anesthetic use, especially in the case of patient anxiety, with some patients preferring to be under analgesics for specific procedures and others not. Either way, the patient can control their degree of analgesia, using only what they need to relieve their pain and anxiety.[7] Upon inhalation using the ProNox delivery system, patients typically experience a sensation of warmth, heaviness, tingling, and euphoria. They then experience a reduction in nervousness, pain, anxiety, and tension with use during the treatment process. This solution serves as a balanced medium between more serious anesthetics, offering patients the opportunity to manage their treatment by self-administering the dose they require (VALLEY).

Mechanism of Action

The nitrous oxide that is inhaled through ProNoX has multiple spinal and supraspinal targets. Its anesthetic effect is through non-competitive NMDA inhibition in the central nervous system. The analgesic effect is mediated through the release of endogenous opioids that act on opioid receptors, as well as through the activation of GABA-A receptors. N2O also exhibits central sympathetic-stimulating activity, which supports

systemic vascular resistance, cardiac output, and blood pressure. It stimulates cerebral blood flow and enhances intracranial pressure.[8]

After inhalation, N2O is rapidly absorbed through the alveoli. The onset of N2O action is within approximately 2 to 5 minutes.[9] It diffuses more rapidly than other gases across the alveolar basement membranes. It may produce the second gas effect, where there may be a simultaneous increase in the alveolar concentrations of other gases. The remaining alveolar gases become concentrated when N2O rapidly exits from the alveoli. This concentration of gases accelerates N2O uptake into the blood, speeding the onset of anesthesia. As N2O has a minimal alveolar concentration of 105%, it is a weak anesthetic inhalational agent but exhibits strong analgesic effects. At the end of anesthesia, N2O rapidly enters the alveoli, causing oxygen dilution and diffusion hypoxia in the alveoli.[10] Anaerobic bacteria metabolize the remaining trace amount of N2O through a reduction process, and N2O is primarily eliminated via the lungs.[8]

Safety Profiles

Before its use in cosmetic and aesthetic treatments, N2O was first utilized during dental procedures for several decades, beginning in the early 1900s.[1] Due to the increasing use of ProNox in dermatological practices, it is essential to evaluate the safety and efficacy of this delivery system. For this purpose, an online survey was distributed among physicians specializing in aesthetics, dermatology, and plastic surgery who use the novel N2O delivery system (ProNox, CAREstream America, Lake Merry, FL).

Of the respondents, 64.2% combined this N2O delivery system with other medications for better results. Respondents of this survey believed that ProNox was safe for patients. Overall, 99% of physicians acknowledged the effectiveness of this delivery system, and 100% of respondents found ProNox to be easy to use. Approximately 7.8% of physicians experienced adverse events during procedures due to ProNox.

To further assess the safety of this delivery system, supplemental databases and internal safety data from CAREstream America were reviewed. Among the 3,000 ProNox users over a 3-year period, no adverse events were reported. Furthermore, no formal incidents were reported by the FDA. At an urban cosmetic dermatology clinic, a retrospective review of the database was performed. In this review, 263 patients were involved, and no serious adverse complications were seen related to the ProNox system.[11]

To assess the safety and efficacy of inhaled N2O, oxygen saturation, and pulse oximetry were monitored in addition to vital signs, including blood pressure and heart rate.[4] In a study conducted by Drosner conducted in 2013, monitored patients maintained stable oxygen saturation, except for one patient whose saturation dropped to 87%. Another study that utilized N2O for the treatment of ulcers and bedsores recorded oxygen saturation at the start and end of the procedure. There was a significant difference in oxygen saturation before and after the treatment, but further details were not recorded. Vitals reported similar stable results in almost all patients, except in the study by Claeys et al., where there was a slight increase in diastolic and systolic blood pressure, as well as an increase in heart rate and partial oxygen pressure. This study also reported significant changes in arterial pressure at the start and end of the treatment.[12] Therefore, while the majority of our findings suggest that ProNox has a favorable safety profile, the isolated cases of adverse events in several studies raise questions regarding its overall safety. Thus, more investigation is imperative.

Effectiveness of ProNox in Dermatological Procedures

To examine the effectiveness of nitrous oxide in dermatological procedures, a systematic review was conducted in 2018. A total of 8 studies were identified and systematically reviewed. This review highlighted that the administration of a N2O/O2 mixture resulted in a significant decrease in pain when used in photodynamic therapy, aesthetic procedures such as laser processes, treatments for leg ulcers and bed sores, and botulinum toxin therapy for hyperhidrosis of the axillae and palms. However, pain scores remained high when this mixture was used for the debridement of chronic ulcers compared to the use of topical anesthesia. N2O was also effective in reducing pain in cases of hair transplant, excision, repair, dermabrasion, and pediatric processes.[4] This study suggests that N2O has numerous potential applications in dermatological processes; however, due to insufficient evidence, further randomized controlled trials are needed to support these findings. The studies found in the literature are listed in the table, along with their outcomes.

Table 1: Characteristics of the Studies present in the literature

Study	Design	No. of Participants	Dermatological procedure	Outcomes Related to Pain	Adverse effects	Findings
Otley et al. (Otley & Nguyen, 2000)	Observational and Prospective	8	Pediatric procedures such as biopsies, pulse dye lasers, and excisions.	Not Reported	Uncommon to mild	A low to moderate concentration of inhaled mixture of benzodiazepine and nitrous oxide is safe and effective in providing continuous sedation in pediatrics.
Paris et al. (Paris et al., 2008)	Open-label, randomized, cross-over pilot study	34		The pain was reduced in both N_2O arms (P <	Adverse events were reported in	There was a superiority in the N_2O/ O_2 mixture over morphine for

				0.01)	7 patients	analgesia in this pilot study. This mixture is easy to use and has a rapid effect. It also has limited contradictions when used during painful procedures in elderly patients
Claeys et al. (Claeys et al., 2011)	Multicenter, randomized, and open-label study	Varicose ulcers and care of bedsores	Debridement of leg ulcers	The pain was increased in the N_2O arm than topical anesthetic arm ($P < 0.01$)	Not available	It was demonstrated that nitrous oxide and oxygen mixture is superior to lidocaïne–prilocaïne cream in controlling pain during the painful procedure of mechanical debridement of chronic leg ulcers.
Drosner et al. (Drosner, 2013)	Observational. Open-label and prospective study	24	Multiple aesthetic laser procedure	A significant decrease in the treatment of pain	Mild	This easy self-administration and pronounced analgesia, fast onset of

				was observed with the N_2O/ O_2 mixture inhalation. t		anesthesia, and a complete fast recovery within a few minutes, low ratio of adverse effects make this inhalation an ideal addendum in the management of larger painful processes in dermatology.
Paracka et al. (Paracka, Kollewe, Dengler, & Dressler, 2015)	Intraindividual, open-label, and observational study	13	Botulinum toxin injections for hyperhidrosis	Significant reduction in pain at the site of injection with N_2O: axilla (P = .0002) and Palms (P = .0001)	Not identified	N_2O is a potent, non-sedative, safe, and quickly reversible inhalative analgesic that can considerably reduce the pain at the site of injection.
Fink et al. (Fink, Uhlmann, Enk, & Gholam, 2017)	Observational, controlled, single-center, and prospective study	71	Photodynamic therapy for actinic keratoses	The pain was reduced after inhalation of N_2O	Not available	Providing analgesia by inhalation of N_2O/ O_2 mixture is a very well-

						tolerated and effective method of achieving significant pain reduction during photodynamic therapy.
Lin et al. (Lin, Dubin, & Khorasani, 2019)	Observational study	400	Micrographic surgery	Nitrous oxide was the most successful agent in reducing pain than topical ice and vibrations (P < .01).	Not available	Vibration, ice, and nitrous oxide reduce pain at the injection sites mainly in younger males Undergoing ear, lip, eyelid, and nose surgery.

Adverse Events

Inhalation of the N2O/ O2 mixture is reported to have some mild to moderate adverse effects, mainly at the time of inhalation. However, when compared with morphine and benzodiazepines, these effects are less and persist for a shorter time. An adverse effect found from the pooled data is mood lability, associated with laughter, anxiety, hysteria, delusions, and crying. Dizziness, euphoria, and nausea are other adverse effects associated with inhalation of the mixture.[4] When nitrous oxide is used alone, it has limited respiratory effects, but when used in combination with other sedatives, it can potentiate their respiratory depressant effects.[8]

Additional reasons why healthcare providers avoid giving nitrous oxide to patients undergoing any dermatological procedures include:

- History of mental conditions
- The first trimester of pregnancy
- Having some enzymatic conditions
- History of respiratory illness
- Vitamin B12 Deficiency (Fletcher, 2019)

Nitrous oxide can irreversibly oxidize the cobalt atom of vitamin B12, leading to its inactivation and reducing the activity of dependent enzymes, such as methionine synthetase. This interaction can be detected by elevated homocysteine levels, which are associated with an increased risk of cardiovascular disease. Studies have been conducted to explore the effects of preoperative supplementation with Vitamin B12 and its impact on homocysteine levels after nitric oxide administration. Daily oral supplements containing Vitamin B12 for one week before surgery have shown promise and were correlated with decreased homocysteine levels. The option of single-dose IV administration of Vitamin B12 has also been explored but did not yield significant effects.[13] Nitrous oxide disorder can also cause potentially reversible myeloneuropathy characterized by axonal sensorimotor neuropathy.[14]

For pregnant patients undergoing dermatological procedures, nitrous oxide use through ProNox raises several concerns. The first trimester of pregnancy is a critical period when the fetus's organs are developing, and it is during this period of organogenesis when there is the most risk of adverse events from harmful substances and toxins as cellular differentiation and DNA synthesis are at their peak. Due to the rapid transfer of nitrous oxide to the placenta, its potential effects on the fetus must be considered. Vitamin B12 is critical in the development and function of the fetus's brain and spinal cord. It is an essential cofactor for methionine synthetase, a crucial methyl donor involved in the synthesis of DNA, RNA, and myelin, which is fundamental for proper gene expression and cell proliferation (Amsterdam, Brink, 2022). Inactivation of vitamin B12 by nitrous oxide, therefore, poses a serious concern, as use can increase the risk of neural tube defects as a result of impaired DNA synthesis. A low vitamin B12 status is associated with cleft palate, early recurrent abortion, low birth weight, and preterm birth. Furthermore, it is also important to note that a vitamin B12 deficiency can impact male fertility by disrupting testicular function, leading to impaired spermatogenesis (Amsterdam, Brink, 2022).

Another notable limitation of ProNox is that it does not have a built-in mechanism to scavenge the residual nitrous oxide from the air after use. Scavenging systems are essential in suctioning and eliminating the waste nitrous that the patient exhales during sedation procedures. Without such a system, healthcare workers, especially pregnant employees who are more often exposed to nitrous oxide, may be harmed. Chronic occupational exposure to nitrous oxide is associated with spontaneous abortion and reduced fertility rates. A study involving a mail survey of 30,650 dentists and 30,547 chairside assistants exposed to inhalation anesthetics and sedatives reported a 1.7-2.3 times increased risk for spontaneous abortion. The lack of a scavenging system with ProNox, therefore, presents both ethical and legal challenges for healthcare clinics, as employees who experience these adverse events may pursue litigation. To help address this issue, it is essential for clinics that utilize ProNox to consider installing ventilation systems that decrease the risk of chronic occupational exposure and ensure safety standards are met. [15-22]

Cost and Practical Considerations

The significant cost implications of integrating ProNox into a dermatological practice require careful consideration. A ProNox system initially costs between $5,000 and $7,000, depending on the specific manufacturer. Though this cost may be manageable for more affluent and high-volume clinics, this may not be the case for smaller practices. Beyond the initial investment of the system, disposable patient masks and mouthpieces, as well as nitrous oxide and oxygen canisters, also need to be factored into the cost. Furthermore,

the Pro-Nox manufacturer recommends preventative maintenance every six months to ensure optimal performance and safety. Preventative maintenance includes testing the individual features of the ProNox system, including oxygen and nitrous oxide concentration, low supply pressure alarms and shut-off functions, emergency air intake resistance, and vibration. The annual cost of this preventative maintenance is $690.

The per-procedure cost of using ProNox is estimated to be $75 to $100, depending on the duration of gas use and the type of procedure. Since many dermatologic procedures are not covered by insurance, including cosmetic procedures, ProNox becomes a self-pay service for patients, which may deter cost-sensitive individuals, especially in markets where less expensive sedation and pain management options are available.

Economically, ProNox should be compared to other alternative sedation and pain management options. Traditional methods, such as local anesthesia (lidocaine) and topical anesthesia (bupivacaine cream), are much more affordable. Furthermore, there are no maintenance costs associated with these modalities, and because they are widely used across a variety of procedures, this ensures their cost-effectiveness.

Despite the cost limitations of ProNox, ProNox still provides benefits that these traditional options do not. For example, its self-administration feature provides patients with control over their pain relief in real-time, which traditional modalities cannot provide. This benefit can significantly enhance patient experiences and may, therefore, be a worthwhile investment in dermatology practices. Future studies comparing the financial and clinical outcomes of ProNox versus more traditional alternative methods are therefore critical in providing more information and helping dermatology practices make more informed decisions about the adoption of ProNox.

Alternatives to ProNox

While ProNox is gaining significant attention for its impressive safety, ease of administration, and efficacy in serving as a moderate anesthetic, it also has some limitations. As discussed previously, its cost-effectiveness may limit its use, as well as a patient's history of certain predisposing conditions, causing professionals to consider alternatives.

Local anesthetics such as lidocaine and bupivacaine are commonly used forms of anesthesia for many procedures, including Moh's reconstruction and biopsies, due to their inexpensive nature. Local anesthetics are available in both topical and percutaneous forms, acting by disrupting action potentials to temporarily block nerve impulse transmission and inhibit the sensation of pain without causing loss of consciousness. Topical formulations are applied 10-15 minutes before the procedure, typically as a mixture of lidocaine and another amide. They are praised for their ease of application and non-invasive nature, although they have a shorter duration of action compared to other forms of treatment. Subcutaneous formulations, on the other hand, have a longer-lasting effect, although they are more invasive and typically contain a mixture of lidocaine and bupivacaine. Upon first administration, subcutaneous injections can be painful for the patient and lead to distortion of soft tissue at the injection site. Drawbacks to both forms of local anesthetic are the potential for systemic toxicity leading to depression of cardiac function and seizures (Bharadwaj & Dougherty, 2023).

Nitrous Oxide has also been used in many alternative forms prior to its administration as ProNox. Nitrous oxide can be administered as cartridges, known as whippets, in which a physician fills a balloon with nitrous oxide cartridges and has a patient breathe from it. While effective, this method of delivery is significantly less convenient than Pronox and is tied to a history of recreational abuse in this formulation.

Challenges and Future Directions

While the existing literature on the use and efficiency of ProNox in dermatologic procedures is encouraging, it is limited by several restrictions.

1. A majority of the studies in this area are limited by small sample sizes, which may not provide sufficient statistical power to draw definitive conclusions about the efficacy and safety of ProNox, so larger-scale studies with diverse patient populations are needed to authenticate the findings and generalize the results to a broader population.
2. Future research should focus on using validated scales for pain assessment, subjective patient-reported outcomes, and comparative studies with control groups to enhance the robustness of the findings.
3. Long-term follow-up data on the outcomes of ProNox use in dermatologic procedures are deficient in the current literature.
4. Exploration of optimal dosing regimens, including the concentration of nitrous oxide and oxygen mixture, as well as the timing and duration of administration, could help optimize the pain-relieving effects of ProNox and enhance patient comfort during various dermatologic procedures.
5. Investigation of the cost-effectiveness of incorporating ProNox into routine dermatologic practice and comparing it with other pain management modalities would be beneficial for assessing the economic implications and feasibility of widespread adoption.
6. The development of standardized protocols and guidelines for administering ProNox in dermatologic procedures would be necessary to ensure consistent, safe, and effective use in dermatologic practice.

CONCLUSION

ProNox, a mixture of nitrous oxide and oxygen commonly used for pain management during medical procedures, has been gaining popularity in dermatologic practice for its potential to improve patient comfort and reduce procedure-related anxiety. It has been shown to effectively reduce pain and discomfort during numerous dermatologic procedures, including laser treatments, injections, and minor surgeries. The use of ProNox is generally well-tolerated with negligible side effects, making it a safe option for pain management in dermatologic settings. With its ability to provide patients with more control of their pain management, this can meaningfully improve patient comfort and overall experience, leading to higher patient satisfaction and potentially improved patient retention. Despite its numerous benefits, further research is required to explore the long-term effects and overall cost-effectiveness of using ProNox in dermatologic procedures. Investigating optimal dosing regimens, occupational safety protocols, and standardized guidelines is crucial in advancing the widespread adoption of this innovative modality in dermatological procedures. With further research, ProNox shows promise and has the potential to become an essential tool for enhancing pain management and the quality of care for many patients in dermatological practice.

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