The Future of Nitrous Oxide Analgesia: Advancements in Delivery Systems

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Summary

This white paper explores the evolving domain of Nitrous Oxide (N_2O) and Oxygen (O_2) administration. It highlights the importance of innovative gas mixing and delivery systems in improving medical applications, optimizing patient care, and ensuring economic sustainability and environmental responsibility. Among various systems, the O-Two eAdvantage[®] System stands out for its precision in gas delivery tailored to individual respiratory needs, minimizing wastage and environmental impact. By exploring technological advancements like the proportional valve and the electronic pressure sensor technologies, this paper provides insights into how this system can transform the use of inhaled analgesia across different clinical settings.

Introduction:

In today's rapidly advancing medical field, achieving the best patient outcomes is crucial. This drive pushes medical professionals to constantly refine and improve therapeutic methods. Nitrous oxide (N_2O), a cornerstone in anesthetic and analgesic regimens, has been at the forefront of such medical innovations for over a century. Its importance in diverse medical procedures is significant, offering pain relief and sedation with a high safety profile.

Historically, the application and benefits of nitrous oxide have been closely linked to the capabilities of its delivery systems. The efficiency, safety, and precision of these systems play a crucial role in harnessing the full therapeutic potential of N_2O . As medical practices have evolved and patient care standards have risen, more refined and advanced nitrous oxide delivery systems have emerged.

Conventional systems have had their challenges, especially in terms of inconsistent dosage and wasted resources. To overcome these issues, modern systems have been developed. Among the forefront of these innovations is the eAdvantage[®] System. Its ability to adjust gas flow in real-time to adapt to patient's respiratory patterns ensures efficient use of N₂O and significantly reduces wastage. This innovation marks significant progress in patient-centric care and environmental responsibility.

Historical Developments of Nitrous Oxide in Clinical Practice

The journey of nitrous oxide (N_2O) in clinical practice began in the 18th century with Joseph Priestley's discovery in 1772. His work, documented in "Experiments and Observations on Different Kinds of Air," laid the foundation for further research into N₂O's applications. This progress increased in 1794 when James Watt and Thomas Beddoes introduced a mechanism to administer N₂O, predicting a new era in its therapeutic use.

By the 19th century, Humphry Davy's work, "Researches, Chemical and Philosophical: Chiefly Concerning Nitrous Oxide," positioned N₂O as a promising surgical pain reliever. Its use in dentistry became evident in the mid-19th century through Gardner Quincy Colton's success with dental extractions. By the 1930s, N₂O was established for dental anesthesia and gaining traction in childbirth analgesia, as documented in Duncum's "The Development of Inhalation Anaesthesia" (Lew et al., 2018).

Mechanism, Pharmacokinetics, and Clinical Implication.

Nitrous oxide operates on several neural targets in both supraspinal and spinal regions. Its primary mechanism as an anesthetic is its ability to inhibit NMDA receptors in the central nervous system non-competitively. The analgesic effects of nitrous oxide are due to its stimulation of endogenous opioid release, similar to the effects of morphine. Additionally, its anxiolytic properties stem from its interaction with GABA-A receptors (Knuf & Maani, 2022). Nitrous oxide's influence on central sympathetic stimulating activity is crucial for maintaining blood pressure, systemic vascular resistance, and cardiac output. Its interaction with cerebral blood flow, potentially increasing intracranial pressure, is also noteworthy (Emmanouil & Quock, 2007).

From a pharmacokinetic standpoint, showing effects in 2 to 5 minutes (Khinda et al., 2021). Its swift diffusion across alveolar membranes causes the "second-gas effect," enhancing anesthesia onset. Despite being a weak inhalational anesthetic agent with a MAC of 105%, its analgesic strength is significant (Knuf & Maani, 2022). Most inhaled nitrous oxide remains unchanged in the body and is primarily excreted through the lungs. When nitrous oxide administration stops, it is quickly exhaled, which is a crucial advantage in clinical settings (Khinda et al., 2021).

Diverse Medical Applications of Nitrous Oxide

Nitrous oxide (N_2O) is widely recognized for its foundational role in anesthesia and its broader applications due to its unique pharmacological properties. Its quick onset and ability to alleviate stress and pain have made it favourable in various medical fields. Additionally, being odorless and non-irritating further underscores its versatility in clinical settings (Lew et al., 2018).

The Operating Room:

Nitrous oxide's pivotal role in anesthesia is due to its high FA/FI ratio (the ratio of alveolar concentration to inspired concentration), which facilitates rapid induction and recovery from anesthesia. Before the advent of low-solubility volatile anesthetics like Sevoflurane and Desflurane, the "second gas effect" of N₂O was indispensable (Peyton et al., 2011). The ENIGMA-II trial found no increased cardiovascular risk for high-risk patients during non-cardiac surgeries (Chan et al., 2016).

One of the significant findings of N₂O is its ability to provide a profound depth of anesthesia. This depth ensures that patients remain unaware of their surroundings during surgical procedures, reducing the risk of intra-operative sensations or memories. The use of BIS (bispectral index) monitoring further enhances this assurance. BIS monitoring measures brain activity to measure the depth of anesthesia, ensuring patients remain optimally unconscious throughout the procedure (Lew et al., 2018). Its non-irritating nature and absence of a strong odor make it valuable during mask inductions, especially for pediatric and developmentally delayed patients (Lew et al., 2018).

Pediatric Use:

The increasing use of N₂O for minor procedural sedation in children is notable. One key advantage is avoiding intravenous access, making it more child-friendly. Annequin and colleagues conducted a significant study highlighting the effectiveness and safety of a 50% N₂O mixture for managing pain and anxiety in various pediatric procedures (Lew et al., 2018). Remarkably, 93% of children who provided feedback expressed a willingness to use N₂O analgesia again. The observed side effects were generally mild and temporary. Similar safety outcomes were observed in other studies, even with N₂O concentrations beyond 50% (Zier & Liu, 2011).

Venipuncture: This procedure can often cause significant anxiety for children. Research has indicated that 70% N_2O is more effective than local anesthetics like EMLA cream for venipuncture (Furuya et al., 2009). Additionally, combining 50% N_2O with EMLA cream provides a better experience than combinations such as oral midazolam with EMLA cream (Trottier et al., 2019).

Laceration Repair: Combining a local anesthetic with 50% N_2O significantly lowers pain scores in children. The efficacy of N_2O seems to be agedependent, with better outcomes in children older than 3 years (Lew et al., 2018).

Lumbar Puncture: Several studies show that N_2O effectively reduces pain during lumbar punctures. An observational study reported reduced pain levels when N_2O was used, either alone or in combination with a topical anesthetic (Germán et al., 2011).

Nitrous Oxide in Pediatric Emergency:

Effective pain management for pediatric patients in emergency settings remains a critical area of ongoing research and development, as 60% of pediatric admissions to emergency departments are due to painful conditions.

A recent comprehensive study led by Professor Samina Ali from the University of Alberta explored the potential of inhaled nitrous oxide (N_2O) for pain relief. The research team reviewed 30 clinical trials involving N₂O, focusing on its use during procedures like IV insertion and laceration repairs with stitches (Sweetman, 2023). Their analysis found that combining N₂O with numbing creams is highly effective and safe, especially for IV-related procedures.

Proper pain management not only provides immediate relief but also helps prevent longterm psychological issues, such as needle phobia. Up to 10% of the adult population suffers from needle phobia, a statistic highlighted during discussions about vaccine hesitancy in the COVID-19 pandemic (Sweetman, 2023).

Despite compelling evidence supporting N_2O 's efficacy in pediatric emergency settings, its use in clinical practice remains limited. A PERC survey revealed that less than 50% of Canadian pediatric emergency physicians currently use N_2O for pain management. A 2021 survey found that out of 15 Canadian pediatric emergency hospitals, only six actively used N_2O (Sweetman, 2023).

Based on these findings, there is an urgent need to broaden the implementation of nitrous oxide in pediatric emergency departments. Dr. Ali's ongoing research and advocacy should drive this expansion, establishing nitrous oxide as a standard practice in pediatric pain management. The widespread use of nitrous oxide could significantly enhance the emergency care experience for children, aligning medical practices with the latest evidence and expert recommendations. This shift is not merely a clinical preference but a crucial step toward improving pediatric healthcare outcomes.

Age-Based Guidelines for Nitrous Oxide Administration in Pediatrics

The application of nitrous oxide for pediatric patients follows guidelines set by regional health authorities and hospital policies. It is commonly recommended for children aged 2 years and older, aligning with their ability to interact with the administration method. In some cases, nitrous oxide can be used for younger children, including those under two years, with certain policies extending usage to infants as young as six months. These variations in guidelines reflect the balance between clinical need and safety, tailored to the developmental capabilities of pediatric patients and the capabilities of the inhaled analgesia systems used (16), (18).

Nitrous Oxide in Aesthetic Medicine

Aesthetic medicine has seen a rise in the popularity of non-invasive procedures, particularly micro-focused ultrasound with visualization (MFU-V). While these treatments are appealing for their non-invasive nature, they often cause patient discomfort. Addressing this, a study explored the use of a balanced nitrous oxide (N₂O) and oxygen mixture for pain management during MFU-V treatments. The findings were promising, showing that N_2O reduced pain and allowed for immediate posttreatment recovery. This suggests that N₂O can significantly enhance patient comfort and satisfaction in aesthetic procedures (Tran et al., 2022).

Dermatology Procedures

Dermatology has harnessed the potential of nitrous oxide to manage pain and anxiety across a spectrum of procedures. Its efficacy has been demonstrated in treatments ranging from photodynamic therapy, botulinum toxin therapy for hyperhidrosis, and aesthetic laser procedures to more specialized applications like hair transplants and dermabrasion. Its versatility extends to managing bed sores, leg ulcers, excisions, repairs, and pediatric dermatological procedures (Brotzman et al., 2018).

Nitrous Oxide in Obstetrics

The role of nitrous oxide (N_2O) in labor analgesia has shown promising results. A study of 753 women who used N_2O as their primary pain relief during vaginal deliveries revealed more than just pain relief benefits. Satisfaction with N_2O was linked to enhanced relaxation, distraction, and a focus on breathing. Many women felt it aligned with their birth plans and provided an experience close to natural childbirth. These findings highlight the multifaceted benefits of N_2O in labor, confirming its value in obstetric care (Richardson et al., 2018).

Nitrous Oxide in Gastrointestinal Endoscopies

A prospective, randomized, controlled clinical study evaluated the safety and efficacy of nitrous oxide sedation during endoscopic ultrasoundguided fine needle aspiration (EUS-FNA). Fortyone patients were divided into two groups: one received nitrous oxide, and the other received pure oxygen. The inspiratory flow of nitrous oxide was adjusted based on the required depth of sedation, with concentrations ranging from 30% to 70%. Patients sedated with nitrous oxide experienced quick recovery with no significant complications. Surveys and visual analog scale (VAS) scores showed higher satisfaction in the nitrous oxide group, with better patient tolerance, positive physician evaluations, and a greater willingness to repeat the procedure compared to the control group. There were no significant changes in heart rate, oxygen saturation, or ECG, highlighting the safety of nitrous oxide. This study supports nitrous oxide as a safe and effective sedation option for enhancing the endoscopic experience in gastrointestinal procedures, particularly EUS-FNA (Wang et al., 2016).

Colonoscopy is a crucial diagnostic method for large bowel diseases, but its discomfort and pain often necessitate better sedation methods. Conventional sedation can lead to prolonged recovery and increased cardio-respiratory risks. Nitrous oxide/oxygen (N_2O/O_2) offers а compelling alternative due to its effective analgesic impact and short half-life. Clinical trials, comprising seven studies involving 547 patients, focused on N₂O/O₂'s efficacy and safety. The findings show that N_2O/O_2 is as effective as conventional methods in managing pain and discomfort, with added benefits of quicker recovery times, shorter hospital stays, and fewer side effects (Aboumarzouk et al., 2011).

A survey among colonoscopists within the English Bowel Cancer Screening Programme (BCSP) showed widespread favorable views. Most colonoscopists found nitrous oxide effective in reducing pain and inconvenience during colonoscopy and would choose to use it for themselves if they needed a colonoscopy. This highlights the acceptance of nitrous oxide within the medical community and its potential to improve procedural efficiency, leading to a better overall colonoscopy experience (Ball et al., 2014).

Integrating N₂O as a routine sedation method in colonoscopies holds significant promise, supported by various clinical trials and evidence. This has the potential to revolutionize sedation practices in gastroenterology.

Applications in Urology:

In urology, nitrous oxide (N₂O) is recognized as an effective analgesic for short-term pain relief during cystoscopies (CS). Its rapid onset and quick relief enhance patient comfort during the procedure. Recent research shows N₂O significantly reduces pain during CS and other outpatient urological procedures, such as prostate biopsies, ureteral stent placements, and extracorporeal shockwave lithotripsy (ESWL) (Łaszkiewicz et al., 2021).

Modern Advancements in Nitrous Oxide Administration

The analgesic gas mixing and delivery systems have seen significant advancements, to enhance precision, efficiency, and safety. One notable innovation in this field is the eAdvantage[®] System, which optimizes patient care through clinical, economic, and environmental considerations.

Optimizing Patient Care with Advanced Sensor Technology:

The eAdvantage[®] System uses Electronic Pressure Sensor technology, which is highly sensitive and promptly reacts to patients' inhalations. It triggers valves to accurately control the delivery of the required gas volume, tailored to match individual respiratory patterns. This technology adjusts to changes in breathing during uncomfortable or painful procedures, ensuring each inhalation is effective and safe.

Advancements in Precise Nitrous Oxide/Oxygen Delivery:

Modern advances in analgesic gas delivery aim to enhance precision, improving patient outcomes and provider efficiency. The eAdvantage[®] System stands out in this field by making real-time adjustments to the flow to match a patient's respiratory demands, unlike conventional continuous-flow N_2O/O_2 systems. This precision ensures optimal delivery of the inhaled analgesia and frees healthcare providers from manual adjustments. Instead of constantly monitoring the Minute Respiratory Volume (MRV), healthcare providers can focus on the procedure and the patient's immediate needs. Such technological innovations streamline operations and promote better patient care and procedural outcomes.

Trigger Sensitivity:

The concept of trigger sensitivity is crucial in analgesic gas delivery. It determines how quickly the system recognizes and responds to a patient's inhalation. Conventional delivery systems with demand valves have trigger sensitivities ranging from -2 to -5 cmH₂O. while generally effective, these systems can sometimes delay in responsiveness, affecting patient comfort and experience.

In contrast, the eAdvantage[®] System uses an innovative electronic pressure sensor with a trigger sensitivity of less than -1.0 cmH2O. This high sensitivity allows for rapid and accurate detection of pressure changes, enhancing the system's responsiveness and clinical efficacy.

This advanced feature ensures a swift, accurate response to a patient's inhalation effort, reducing

the additional work of breathing (WOB) and significantly improving patient comfort.

Studies have shown that lower trigger thresholds can lead to reduced work of breathing and decreased delay in triggering mechanical ventilators (Dargaville & Keszler, 2013). This concept matches the mechanism of inhaled analgesia systems. These findings highlight the clinical value of lower trigger thresholds, emphasizing their role in improving patient outcomes and experiences in various clinical settings.

Enhancing Patient Experience through Optimized Breathing Mechanics in Analgesic Gas Delivery:

Understanding the Work of Breathing:

Breathing is more than just inhaling and exhaling the air. As detailed by Yartsev (2022), the "work of breathing is the product of pressure and volume." Further, this work consists of two main elements: "elastic work," connected to the natural recoil of the lungs and chest, and "resistive work," related to overcoming tissue, chest wall, and airway resistance. (Yartsev, 2022)

Challenges with Conventional Systems:

Conventional continuous-flow analgesia delivery systems, are designed to maintain a steady flow during both inhalation and exhalation, which can sometimes conflict with a patient's natural breathing. These mismatches can strain patients, especially during exhalation, as they may need to exert additional effort due to the expiratory flow resistance. This is particularly challenging during procedures. painful medical Moreover. conventional demand valves, similar to those used in oxygen delivery, require patients to exert a specific inspiratory effort to initiate and adjust the flow. These mechanical valves can lead to patient-device asynchrony, resulting in misaligned breathing patterns due to trigger delays and errors. This asynchrony, especially from trigger errors, can significantly increase the Work of Breathing (WOB) (Blokpoel et al., 2020).

Advancing Respiratory Synchronization and Comfort:

In response to synchronization and comfort challenges observed in conventional systems, the eAdvantage[®] System integrates advanced Electronic Pressure Sensor technology. This technology ensures prompt and accurate responses to a patient's inhalation, thereby decreasing the Work of Breathing (WOB). Furthermore, its ability to dynamically modify gas flow to match a patient's respiratory rhythm reduces resistive work, improving patient comfort during procedures without compromising efficacy.

The Potential for Expanded Use of Nitrous Oxide in Pediatric Patients:

The Clinical Practice Guidelines for Nitrous Oxide-Oxygen Mixtures from The Royal Children's Hospital Melbourne (2021), along with the Pediatric Nitrous Oxide Administration policy at Providence Saint Joseph Medical Center in California (2020), highlight challenges in administering nitrous oxide to younger pediatric patients. The premixed method for delivering a 50:50 Nitrous Oxide and Oxygen mixture, as outlined by the Melbourne guidelines, requires active patient cooperation to generate sufficient negative pressure on inspiration to trigger the valve. This necessity limits its use to school-aged children and older.

Furthermore, the policy from Providence Saint Joseph Health notes that the demand-valve mask used in N2O administration, while requiring patient cooperation, can be challenging for more minor children to trigger. As a result, N2O is typically used in patients older than four years. The policy also acknowledges that continuous delivery systems, though used in younger children, have achieved variable success and are often more associated with emesis. The eAdvantage[®] System addresses these challenges with advanced technologies. Its highsensitivity sensor operates effectively at pressures below -1 cmH2O, significantly reducing the effort required from the patient for effective gas delivery. This innovation is crucial in expanding research opportunities to broaden nitrous oxide administration among younger pediatric patients, overcoming the limitations of both demand-valve and continuous delivery systems.

Environmental Implications of the eAdvantage[®] System in Nitrous Oxide Emissions

While discussions about greenhouse gas emissions often focus on major contributors like carbon dioxide and methane, nitrous oxide (N_2O) also plays a role in greenhouse gas emissions, albeit on a smaller scale. According to the U.S. Environmental Protection Agency (EPA, 2022), nitrous oxide accounted for 6.2% of the nation's greenhouse gas emissions in 2021, compared to carbon dioxide's 79.4% and methane's 11.5%.

Understanding Nitrous Oxide Emissions:

Nitrous oxide emissions originate from both natural and anthropogenic. In the natural nitrogen cycle, nitrogen transitions through various environmental components, often ending as nitrous oxide through bacterial activity in soils and oceans. However, human activities contribute approximately 40% of global nitrous oxide emissions (EPA, 2022).

Breakdown of U.S. Anthropogenic Nitrous Oxide Emissions:

- Agriculture: 73%
- Fuel combustion: 5%
- Wastewater treatment: 5%
- Manure management: 4%
- Transportation: 4%

• Land Use, Land-Use Change, and Forestry (LULUCF) emissions: 3%

• Other activities: 5% (EPA, 2022)

The EPA's 2021 report on greenhouse gas emissions does not specifically mention the contribution of nitrous oxide emissions from the healthcare sector. It suggests that these emissions are categorized under the "Other Activities" category, which covers various minor contributors.

The broad categorization and the absence of a direct mention of the healthcare sector in the report indicate that the healthcare sector's nitrous oxide emissions are relatively modest.

Given the global emphasis on sustainable healthcare practices, the healthcare sector's nitrous oxide emissions, both in the U.S. and globally, are likely to remain insubstantial.

Healthcare's Minimal Nitrous Oxide Contribution: An Analysis:

Due to the absence of precise data on the healthcare sector's nitrous oxide emissions, we can make an illustrative assumption that the healthcare sector contributes 20% to the "other activities" category of anthropogenic N_2O emissions.

Based on this assumption:

- Healthcare's share of U.S. anthropogenic nitrous oxide emissions: 0.2 x 5% = 1%.
- Its share in the total U.S. nitrous oxide emissions: 1% of 6.2% = 0.062%.
- Its contribution to the total U.S. greenhouse gas emissions: 1% of 5% = 0.05%.

Extending this analysis globally, assuming a similar contribution rate, the healthcare sector's impact on nitrous oxide emissions remains minor.

Comparative Analysis with Agriculture:

Agriculture is the leading source of U.S. anthropogenic nitrous oxide emissions, making up 73% of the total, while the healthcare sector, based on estimates, contributes around 1%. This indicates that agriculture's contribution is approximately 73 times greater than that of the healthcare sector. Such a stark difference highlights the minimal environmental footprint of healthcare within the broader context of nitrous oxide emissions. Given nitrous oxide's significant benefits in medical applications, its limited environmental impact in healthcare is even more justifiable.

To further minimize this already fractional contribution, systems like eAdvantage® optimize the delivery and usage of nitrous oxide by ensuring efficient and controlled gas delivery. This reduces potential wastage and environmental impact, improving patient care and aligning with broader environmental sustainability objectives.

Economic Implications in Nitrous Oxide and Oxygen Delivery:

In healthcare, particularly in analgesia-related procedures, efficient resource utilization is essential for economic sustainability. Conventional analgesia gas delivery systems with continuous flow have been used for many years, but they often face challenges with gas wastage, leading to increased operational costs. This issue is especially pronounced in high-volume settings like dental clinics that conduct multiple sedation procedures daily.

A key challenge with conventional systems is their fixed delivery mechanism, which may not always align with patients' fluctuating respiratory needs, resulting in potential over- or underdelivery of gases. In this context, the eAdvantage[®] System, with its dynamic gas flow adjustment capabilities, provides a refined approach to optimizing gas delivery, ensuring patient-centred care and economic efficiency.

Economic Efficiency through Improved Gas Delivery: A Hypothetical Analysis:

Consider a network of dental clinics performing an average of 50 sedation procedures daily, each lasting about 45 minutes. This scenario examines the potential financial and operational advantages of using the eAdvantage[®] System.

Baseline Assumptions:

• <u>Average Minute Respiratory Volume (MRV)</u>: MRV, which reflects the volume of air inhaled or exhaled by a patient per minute, is calculated by multiplying tidal volume (air volume per breath) by respiratory rate. For our adult patient demographic, we estimate an MRV of 6.5 L/min, within the 4.8 to 8.1 L/min range reported by Jayaraman & Schwartz (2021).

• <u>Procedure Duration</u>: The average procedure time is 45 minutes, representing a mean value between the typical duration range of 30 minutes to 1 hour.

• <u>Flow Rate Adjustment</u>: conventional systems might require a 10% increase in volume to ensure adequate gas delivery and reservoir bag inflation. Additionally, to accommodate irregular breathing patterns—especially during stressful or painful moments—an extra 10% may be added based on the patient's intra-procedural respiratory needs. These adjustments can raise the flow rate to 7.8 L/min from the base 6.5 L/min.

Addressing Variability in Breathing Responses Due to Pain:

Jafari et al. (2017) highlighted the significant variability in breathing patterns when patients experience pain, with many healthy participants showing increased respiratory depth and moderate increases in minute respiratory volume. This emphasizes the need for a modern analgesic delivery system capable of real-time adaptability.

Dissecting Conventional System Utilization:

Conventional systems with fixed MRV settings may struggle to address respiratory variability, potentially resulting in suboptimal patient experiences and excessive analgesic gas use.

• Daily Volume Utilization:

7.8 L/min × 45 min × 50 procedures = 17,550 L/day.

• Annual Volume Accumulation:

17,550 L/day × 365 days = 6,405,750 L/year

The eAdvantage® System's Approach:

The eAdvantage[®] System, featuring innovative electronic pressure sensor technology, eliminates the need for additional flow rate adjustments seen in conventional systems by dynamically adjusting gas flow in real time to match the patient's respiratory demands.

• Daily Volume Utilization:

6.5 L/min × 45min × 50 procedures = 14,625 liters

• Annual Volume Utilization:

14,625 L/day × 365 days = 5,338,125 liters/year.

Waste Dissection and Analysis:

Comparing the two systems reveals significant volume disparities:

• <u>Daily Wastage</u>: The additional flow rate due to the fixed MRV is about 1.3 L/min, resulting in a daily excess of 2,925 litres.

Calculation: Daily Wastage = $(7.8 \text{ L/min} - 6.5 \text{ L/min}) \times 45 \text{ min} \times 50 \text{ procedures}.$

• Annual Wastage:

2,925 L/day × 365days = 1,067,625 liters yearly.

Conclusively, this comparative analysis underscores the potential economic benefits of the eAdvantage[®] System. By significantly reducing gas wastage per procedure, it offers substantial cost savings. The cumulative annual waste reduction is considerable, reflecting the financial burden that can be mitigated with this system.

Conclusion:

Nitrous oxide has long been a preferred agent for inhaled analgesia due to its well-documented therapeutic benefits. However, the conventional delivery systems that have been in use for a long time have faced several challenges. These range from ensuring efficient gas delivery, maintaining patient comfort, and addressing clinical, economic, and environmental concerns. The O-Two eAdvantage® System, with its innovative Electronic Pressure Sensor technology and proportional valve technology, ensures swift and accurate gas delivery. This enhanced precision not only elevates patient comfort but also permits healthcare professionals to concentrate more effectively on the procedure. Additionally, its capacity for real-time adjustment minimizes gas wastage, showcasing a commitment to both efficiency economic and environmental responsibility. This innovative integration marks a progressive stride in the future of inhaled analgesia within modern medical practices.

References

 Aboumarzouk, O. M., Agarwal, T., Syed Nong Chek, S. A., Milewski, P. J., & Nelson, R. L. (2011). Nitrous oxide for colonoscopy. *The Cochrane database of systematic reviews*, (8), CD008506. https://doi.org/10.1002/14651858.CD0 08506.pub2

- Ball, A. J., Campbell, J. A., & Riley, S. A. (2014). Nitrous oxide use during colonoscopy: A national survey of english screening colonoscopists. Frontline Gastroenterology. <u>http://dx.doi.org/10.1136/flgastro-2014-100446</u>
- Blokpoel, R.G.T., Koopman, A.A., van Dijk, J. et al. (2020). Additional work of breathing from trigger errors in mechanically ventilated children. Respir Res, 21, 296. <u>https://doi.org/10.1186/s12931-020-</u> 01561-3
- Brotzman, E. A., Sandoval, L. F., & Crane, J. (2018). Use of Nitrous Oxide in Dermatology: A Systematic Review. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al.], 44(5), 661–669. https://doi.org/10.1097/DSS.00000000 0001464
- 5. Chan, M. T., Peyton, P. J., Myles, P. S., Leslie, K., Buckley, N., Kasza, J., Paech, M. J., Beattie, W. S., Sessler, D. I., Forbes, A., Wallace, S., Chen, Y., Tian, Y., Wu, W. K., & and the Australian and New Zealand College of Anaesthetists Clinical Trials Network for the ENIGMA-II investigators (2016). Chronic postsurgical pain in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial. British journal of anaesthesia, 117(6), 801–811. https://doi.org/10.1093/bja/aew338
- Dargaville, P. A., & Keszler, M. (2013). Setting the Ventilator in the NICU. Pediatric and Neonatal Mechanical Ventilation: From Basics to Clinical Practice, 1101–1125. <u>https://doi.org/10.1007/978-3-642-01219-8_42</u>

- 7. Emmanouil, D. E., & Quock, R. M. (2007). Advances in understanding the actions of nitrous oxide. Anesthesia progress, 54(1), 9–18. <u>https://doi.org/10.2344/0003-</u> 3006(2007)54[9:AIUTAO]2.0.CO;2
- Furuya, A., Ito, M., Fukao, T., Suwa, M., Nishi, M., Horimoto, Y., Sato, H., Okuyama, K., Ishiyama, T., & Matsukawa, T. (2009). The effective time and concentration of nitrous oxide to reduce venipuncture pain in children. Journal of clinical anesthesia, 21(3), 190–193.

https://doi.org/10.1016/j.jclinane.2008. 07.005

- 9. Germán, M., Pavo, M. R., Palacios, A., & Ordoñez, O. (2011). Use of fixed 50% nitrous oxide-oxygen mixture for lumbar punctures in pediatric patients. Pediatric emergency care, 27(3), 244–245. <u>https://doi.org/10.1097/PEC.0b013e318</u> 20db922
- 10. Gillman M. A. (2022). What is better for psychiatry: Titrated or fixed concentrations of nitrous oxide?.
 Frontiers in psychiatry, 13, 773190. <u>https://doi.org/10.3389/fpsyt.2022.773</u> <u>190</u>
- 11. Jafari, H., Courtois, I., Van den Bergh, O., Vlaeyen, J. W. S., & Van Diest, I. (2017). Pain and respiration: a systematic review. Pain, 158(6), 995–1006. <u>https://doi.org/10.1097/j.pain.0000000</u> 000000865
- 12. Jayaraman, J., & Schwartz, S. (2021). Effective nitrous oxide/oxygen administration for children. Dentalcare. <u>https://www.dentalcare.com/en-us/cecourses/ce92</u>
- Khinda, V., Rao, D., Sodhi, S. P., Brar, G. S., & Marwah, N. (2021). Physiological Effects, Psychomotor Analysis, Cognition, and Recovery Pattern in

Children Undergoing Primary Molar Extractions under Nitrous Oxide Sedation Using Two Different Induction Techniques: A Split-mouth Randomized Controlled Clinical Trial. International journal of clinical pediatric dentistry, 14(Suppl 2), S131–S137. https://doi.org/10.5005/jp-journals-10005-2090

- 14. Knuf, K., & Maani, C. V. (2022, September 7). Nitrous Oxide. In StatPearls. StatPearls Publishing. <u>https://www.ncbi.nlm.nih.gov/books/NB</u> <u>K532922/</u>
- Lew, V., McKay, E., Maze, M. (2018).
 Past, present, and future of nitrous oxide. British Medical Bulletin, 125(1), 103–119.

https://doi.org/10.1093/bmb/ldx050

 Nitrous Oxide - oxygen mix. The Royal Children's Hospital Melbourne. (2021, December).

https://www.rch.org.au/clinicalguide/gu ideline_index/Nitrous_Oxide_Oxygen_M ix/#:~:text=,use%20to%20school%20age d%20children

Overview of greenhouse gases | US EPA.
 U.S. Environmental Protection Agency.
 (2022).

https://www.epa.gov/ghgemissions/ove rview-greenhouse-gases

 Pediatric Nitrous Oxide Administration Policy. Providence St Joseph Health. (2020).

https://www.oregon.gov/oha/PH/PROVI DERPARTNERRESOURCES/EMSTRAUMA SYSTEMS/EMSFORCHILDREN/Document s/Pediatric-Nitrous-Oxide-Administration-Policy-Providence.pdf

 Peyton, P. J., Chao, I., Weinberg, L., Robinson, G. J., & Thompson, B. R. (2011). Nitrous oxide diffusion and the second gas effect on emergence from anesthesia. Anesthesiology, 114(3), 596-602.

https://doi.org/10.1097/ALN.0b013e318 209367b

20. Princess Margaret Hospital for Children, Emergency Department. (2020). Nitrous Oxide Sedation Guideline. Retrieved from

https://kidshealthwa.com/api/pdf/737

- 21. Richardson, M. G., Raymond, B. L., Baysinger, C. L., Kook, B. T., & Chestnut, D. H. (2018). A qualitative analysis of parturients' experiences using nitrous oxide for labor analgesia: It is not just about pain relief. Birth, 97–104. https://doi.org/10.1111/birt.12374
- 22. Sweetman, K. (2023, September 18). 'Laughing gas' helps relieve kids' pain and distress in emergency rooms, study shows. University of Alberta. Retrieved from

https://www.ualberta.ca/folio/2023/09/ laughing-gas-helps-relieve-kids-pain-inemergency-rooms.html

 Tran, J., Lultschik, S., Sapra, S., & Dong, K. (2022). Prospective, Single-arm, Splitface Pain Management Evaluation of Nitrous Oxide System During Micro-Focused Ultrasound With Visualization. Journal of drugs in dermatology : JDD, 21(11), 1228–1234. https://doi.org/10.36849/JDD.7030

 Trottier, E. D., Doré-Bergeron, M. J., Chauvin-Kimoff, L., Baerg, K., & Ali, S. (2019). Managing pain and distress in children undergoing brief diagnostic and therapeutic procedures. Paediatrics & child health, 24(8), 509–535. https://doi.org/10.1093/pch/pxz026

25. Wang, C.-X., Wang, J., Chen, Y.-Y., Wang, J.-N., Yu, X., Yang, F., & amp; Sun, S.-Y. (2016). Randomized controlled study of the safety and efficacy of nitrous oxide-sedated endoscopic ultrasound-guided fine needle aspiration for digestive tract

diseases. World Journal of Gastroenterology. <u>http://dx.doi.org/10.3748/wjg.v22.i46.1</u> 0242

- 26. Yartsev, A. (2022, October 14). Work of breathing and its components. Deranged Physiology. https://derangedphysiology.com/main/c icm-primary-exam/required-reading/respiratory-system/Chapter%20041/work-breathing-and-its-components
- 27. Łaszkiewicz, J., Krajewski, W., Łuczak, M., Chorbińska, J., Nowak, Ł., Bardowska, K., & Zdrojowy, R. (2021). Pain reduction methods during transurethral cystoscopy. Contemporary Oncology (Poznan, Poland), 25(2), 80– 87.

https://doi.org/10.5114/wo.2021.10665 2 28. Zier, J. L., & Liu, M. (2011). Safety of high-concentration nitrous oxide by nasal mask for pediatric procedural sedation: experience with 7802 cases. *Pediatric emergency care*, 27(12), 1107–1112. <u>https://doi.org/10.1097/PEC.0b013e318</u> 23aff6d

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