

The Role of Nitrous Oxide in Pediatric Care

Moe Halawani, MD | O-Two Clinical Specialist

Abstract:

This white paper focuses on the advancements in pediatric pain management, particularly the expanded use of Nitrous Oxide (N₂O) in pediatric emergency departments. The paper presents evidence-based practices and research highlighting the critical role of N₂O in providing analgesic and anxiolytic effects to enhance procedural comfort and patient cooperation during painful pediatric procedures and its long-term consequences. It also underlines the recent innovation in N₂O delivery systems, represented by the eAdvantage® System, and how it applies the concepts of personalized medicine through precise and synchronized nitrous oxide delivery. It highlights the global advocacy of pediatric specialists and pain management experts for the broader use of N₂O as part of a comprehensive approach to pediatric pain management, along with the need for continuous research, training, and innovation to improve outcomes in pediatric healthcare.

Introduction:

Pain presents significant healthcare challenges across all ages, leading to financial, physical, and psychological consequences (Brown et al., 2017).

According to the International Association for the Study of Pain (IASP), pain is defined as an aversive sensory and emotional experience typically associated with actual or potential tissue damage. Pain is classified into two forms: acute and chronic. Acute pain is often linked to disease development, the exacerbation of a pre-existing condition, or invasive medical procedures. Chronic pain is characterized by its persistence, with recurrent pain occurring at least three times over three months or lasting beyond three months (Cunico et al., 2023).

A survey indicates that up to 60% of children and adolescents reported experiencing pain within the previous three months, and approximately 21% suffer from chronic pain conditions, emphasizing the need for effective pain management strategies in pediatric care (Cunico et al., 2023). The transition from acute to chronic pain can exacerbate distress, anxiety and fear, intensifying the pain experience and leading to hyperalgesia. Over time, this can alter pain pathways, resulting in central sensitization and impaired central nervous system mechanisms. This transition underlines the importance of a comprehensive approach to pediatric pain management to reduce the physical and

psychological impacts, including sleep disturbances, cognitive impairments, and reduced quality of life (Cunico et al., 2023).

Despite the known benefits of timely and adequate analgesic therapy, pain management in pediatric patients is often inadequate, with many children not receiving necessary pain relief during emergency room visits. Variability in guidelines and insufficient focus on pediatric pain treatment further complicate efforts to provide optimal care. Additionally, assessing pain in children who cannot effectively express their discomfort poses a significant challenge. To address this, various scales and measures have been developed to evaluate pain in these patients. Tools such as the Neonatal Infant Pain Scale (NIPS), the Face, Legs, Activity, Cry, Consolability (FLACC) scale, and the Wong-Baker Faces Pain Rating Scale are essential for assessing pain severity and guiding treatment decisions.

Given the complexities of pediatric pain and the challenges in its management, there is a critical need for standardized, evidence-based guidelines tailored to pediatric patients. Such guidelines would facilitate the recognition and treatment of pain in children, ensuring that all patients receive timely, effective, and compassionate care (Cunico et al., 2023).

Nitrous Oxide in Pediatric Pain Management.

In pediatric healthcare, Nitrous Oxide (N₂O) is distinguished not only by its analgesic and anxiolytic capabilities but also by its targeted effects on the neuro-psychological components of patient care. Its effectiveness is defined by its complex interactions with the central nervous system (CNS), which help modify these aspects of pediatric care.

- **Mechanism of Analgesia:** The analgesic effects of nitrous oxide primarily occur from stimulating the neuronal release of endogenous opioids, such as enkephalins, which interact with opioid receptors to modulate pain perception. It also affects the descending gamma-aminobutyric acid type A (GABA_A) receptors and noradrenergic pathways, modifying nociceptive processing at the spinal level and thus reducing pain sensations (AAPD, 2023).
- **Anxiolytic Properties:** The anxiolytic effect of N₂O is achieved through its action on the GABA_A receptor either directly or indirectly through the benzodiazepine binding site, leading to CNS depression and a significant anxiety reduction (AAPD, 2023).
- **NMDA Receptor Antagonism:** Furthermore, N₂O's antagonism of N-Methyl-D-aspartate (NMDA) receptors contributes to its anesthetic, analgesic, and amnesic properties, representing a comprehensive approach to pain and anxiety management (AAPD, 2023).
- **Pharmacokinetics and Safety:** N₂O is characterized by its low tissue solubility, a minimal alveolar concentration (MAC) of 105%, quick onset, and recovery time of approximately 2-3 minutes. It circulates as free gas within the body, does not bind to hemoglobin, and does not undergo biotransformation, ensuring a safety profile that preserves vital reflexes and maintains stable cardiovascular function (AAPD, 2023).

Efficacy and Safety of Nitrous Oxide in Pediatric Procedural Sedation

Effective pain management for pediatric patients undergoing minor but painful procedures is essential to prevent long-term adverse effects and ensure procedural success. Nitrous Oxide (N₂O), as a needle-free option for pain management, has been studied for its efficacy and

safety. A systematic review was conducted to evaluate the analgesic effectiveness of N₂O in pediatric patients undergoing laceration repair, IV cannulation, venipuncture, and other minor surgical interventions (Veger et al., 2024).

The study included seven controlled trials with 371 patients of a broad pediatric age spectrum, analyzing N₂O's effectiveness against local anesthesia alone and when combined with local anesthesia for these specific procedures. The results revealed that N₂O was as effective as local anesthesia in two studies. In contrast, five studies found that N₂O, when combined with local anesthesia, was more effective in reducing pain than local anesthesia alone for these procedures. None of the studies reported significant adverse effects associated with N₂O use, underlining its safety profile even at elevated doses (Veger et al., 2024).

These findings suggest that N₂O is safe and effective in managing pain in pediatric patients within ED settings. This comprehensive review underscores the importance of incorporating N₂O into pediatric pain management strategies to provide effective and safe care, thereby minimizing pain and anxiety for young patients undergoing specific procedures in the emergency department.

Another pivotal study assessing the safety of high-concentration N₂O administered via a nasal mask for pediatric procedural sedation across a broad pediatric demographic was conducted over 5.5 years. It evaluated 7,802 cases involving 5,779 patients ranging in age from 33 days to 18 years. The study results confirmed N₂O's high safety profile, with 95.7% of cases reporting no adverse events. Additionally, it revealed no difference in the rates of adverse events between N₂O concentrations of ≤50% and >50%, suggesting that higher concentrations of N₂O do not necessarily increase risk. Notably, the lowest incidence of adverse events was observed in the 1-4-year age group, confirming N₂O's safety across various pediatric age groups (Zier & Liu, 2011). However, adhering to authorized medical guidelines and policies regarding the appropriate age for N₂O use and its recommended concentrations remains essential.

Addressing Needle Phobia in Pediatric Pain Management

Needle phobia is a significant problem in pediatric healthcare that can have long-term impacts on a child's health. Negative experiences with needles during

childhood can lead to avoiding necessary medical procedures, which can result in poor health outcomes. Professor Samina Ali, a respected professor of pediatrics and emergency medicine at the University of Alberta and a pediatric emergency physician at the Stollery Children's Hospital, emphasizes the importance of managing pain and distress in emergency departments.

Early intervention with effective pain management techniques is crucial to developing future cooperation mechanisms and potentially reducing needle phobia in adulthood. Despite Nitrous Oxide (N₂O) being established in dental practices, labor and delivery, and paramedic services, its application in Canadian emergency departments is not as widespread (Sweetman, 2023).

A recent survey conducted by researchers from Pediatric Emergency Research Canada (PERC) found that less than half of Canadian pediatric emergency physicians currently use N₂O due to its unavailability. In 2021, only six out of 15 Canadian pediatric emergency hospitals used N₂O, including two in Alberta (Sweetman, 2023). This underutilization contributes to unnecessary pain for children and may lead to needle phobia. A systematic review and meta-analysis, led by Naveen Poonai and other researchers and published in the Canadian Journal of Emergency Medicine, analyzed 30 clinical trials focusing on N₂O's effectiveness, primarily during IV insertions and laceration repairs. The review revealed sufficient evidence to recommend using N₂O with topical anesthetic for these procedures (Poonai et al., 2023).

The benefits of using N₂O in painful pediatric interventions go beyond providing immediate pain relief. It can help minimize stress for pediatric patients, essential for their psychological well-being and future healthcare interactions. This approach also aims to decrease the prevalence of needle phobia, which affects approximately 10% of adults and often originates from childhood experiences. This condition has significant implications, as seen during the COVID-19 pandemic, where needle phobia contributed to vaccine rejection among adults (Sweetman, 2023).

The Role of Nitrous Oxide in Enhancing Pediatric Patient Cooperation.

Patient cooperation, mainly young children who experience anxiety or have undergone traumatic medical experiences, is crucial for successful medical and dental procedures. The American Academy of Pediatric Dentistry

endorses using nitrous oxide (N₂O) to enhance cooperation during dental interventions. This support is evidenced by research, including a retrospective study which investigated 371 children aged 4–10 years who showed dental anxiety or had previously refused treatment (Memè et al., 2022).

This study demonstrated the effectiveness of N₂O/O₂ sedation in improving cooperation, where children were initially administered 100% oxygen, gradually increasing the N₂O concentration up to 35%. The outcome showed a significant increase in cooperation levels as measured by the Venham score, compared to their baseline cooperation levels.

Notably, this research found that younger children (4–6 years) achieved optimal cooperation levels under N₂O/O₂ sedation more rapidly. This finding is critical, suggesting that N₂O/O₂ sedation can be safely and effectively applied in younger patients across various medical settings beyond dentistry, especially for those more susceptible to anxiety related to procedures. Consequently, nitrous oxide improves patient cooperation, reduces anxiety, and maintains continuous communication between the healthcare provider and the child. This communication empowers the child, helping them overcome fear and comfortably engage with necessary medical treatments (Memè et al., 2022).

Optimizing Pediatric IV Cannulation and Venipuncture

Peripheral intravenous (PIV) cannulation and venipuncture are critical but challenging due to the associated procedural pain and anxiety, especially in children aged 5 to 10 years, who often exhibit needle phobia (McCollum et al., 2017). Effective management of these challenges is required for the technical success of these invasive procedures and for improving the overall patient experience. Within this context, research has highlighted the role of Nitrous Oxide (N₂O) as a valuable tool in this procedure, offering clear evidence of its use. The study involving 393 pediatric patients requiring N₂O sedation for apprehension or prior unsuccessful cannulation attempts revealed a remarkable 96.2% success rate in achieving PIV cannulation. It also reported high satisfaction levels among healthcare providers, caregivers, and patients, with 89.3% of physicians, 92.1% of nurses, 90.6% of parents, and 87.8% of pediatric patients. The patient-parent agreement on satisfaction

reached 94.1%, highlighting the N₂O's role in reducing PIV cannulation distress (McCollum et al., 2017).

Moreover, a randomized control trial conducted at Shizuoka Prefectural Children's Hospital in Japan assessed N₂O's analgesic efficacy in pediatric venipuncture. The trial investigated the administration of varying concentrations of N₂O (50% and 70%) for different durations (three and five minutes) before venipuncture. A 70% concentration for three minutes notably decreased venipuncture-related pain, mainly in children older than five years, without increasing adverse effects. This demonstrates N₂O's capability for safe, rapid, and effective analgesia in a procedure feared by many children (Furuya et al., 2009).

Enhancing Comfort in Pediatric Facial Laceration Repair.

Managing pain and anxiety is crucial in emergency room settings, especially when performing delicate procedures such as pediatric facial laceration repair. A study conducted in the emergency room of a tertiary care, university-affiliated hospital in 2006 offered insightful evidence on the benefits of incorporating Nitrous Oxide (N₂O) into the care regimen for such cases. This study aimed to explore an effective method for pain relief during the repair of facial lacerations in children. It involved sixty patients aged 1 to 16 years who required facial laceration repair. The participants were divided into two groups: one receiving standard care with lidocaine infiltration and another receiving both lidocaine and N₂O. Pain scores were assessed by both the surgeon and a monitoring nurse using the FLACC scale, designed to measure pain based on observations of the child's face, legs, activity, cry, and consolability (Bar-Meir et al., 2006).

The children who were administered N₂O, in addition to lidocaine, exhibited significantly lower pain scores during both the infiltration and suturing phases compared to those receiving lidocaine alone. Notably, the average duration for N₂O administration was approximately 11.9 minutes, with most children returning to pre-procedure activities within one minute post-procedure. The study highlighted the minimal need for restraining in the N₂O group and reported a 70% absence of side effects. Vomiting and nausea were noted as transient side effects in 17% of cases receiving N₂O, with no respiratory or cardiovascular adverse events recorded (Bar-Meir et al., 2006). N₂O is a safe and effective option for plastic surgeons treating facial lacerations in pediatric patients in

emergency room settings. Its rapid onset and recovery times make it ideal for short surgical procedures, providing pain relief and reducing anxiety. This study supports the expanded use of N₂O in ambulatory procedures for pediatric patients, enhancing patient comfort and procedural efficiency.

Efficacy of Nitrous Oxide in Pediatric Lumbar Puncture Pain Management

Lumbar puncture (LP) is an essential diagnostic and therapeutic procedure in pediatric medicine, crucial for diagnosing, evaluating, and managing various medical conditions. Despite its importance, LP often causes significant pain and anxiety among pediatric patients, creating challenges in procedural pain management.

A randomized, double-blind controlled trial conducted at the General Hospital of Ningxia Medical University has provided valuable insights into addressing this issue by evaluating the analgesic efficacy of a Nitrous Oxide (N₂O) and Oxygen (O₂) mixture compared to oxygen alone in pediatric lumbar puncture (Liu et al., 2019).

The study included children aged five to 14 years diagnosed with leukemia and undergoing LP for diagnostic or therapeutic reasons. The participants were randomly assigned to receive either the N₂O/O₂ mixture or oxygen alone, with the primary outcome being the maximum pain level reported during LP, measured on a numerical rating scale (0–10). Results demonstrated a significant reduction in pain scores for patients receiving the N₂O/O₂ mixture, with median pain scores significantly lower in the study group compared to the control group. Specifically, pain scores decreased to a median of 2 for the N₂O/O₂ mixture-treated patients. Conversely, the control group, receiving oxygen alone, reported a median pain score of 5, indicating higher pain levels, highlighting the effectiveness of the N₂O/O₂ mixture as an analgesic option for pediatric LP procedures. The trial also confirmed the safety of the N₂O/O₂ mixture, with no severe adverse effects reported, and obtained positive feedback from medical staff, further supporting its use for pediatric procedural pain management (Liu et al., 2019).

Inhaled Nitrous Oxide and Intranasal Fentanyl for Pediatric Orthopedic Pain Management.

The use of Nitrous Oxide (N₂O), in combination with Intranasal Fentanyl (IN FENT), has been getting significant attention for its effectiveness in managing pain and

anxiety during pediatric orthopedic procedures. Recent studies, including the FAN Observational Study published in May 2017 and subsequent research outlined in *The Journal of Pediatric Pharmacology and Therapeutics* in 2022, have provided compelling evidence supporting the efficacy and patient satisfaction associated with this sedation method.

The FAN Observational Study observed children aged 4 to 18 years with mildly or moderately displaced fracture or dislocation reductions. The study assessed pain and anxiety using the Facial Pain Scale-Revised (FPS-R) and Face, Leg, Activity, Cry, Consolability (FLACC) scores. The results indicated that a combination of IN FENT with N2O was effective in managing pain and anxiety, with high satisfaction rates among parents (97%), patients (89%), and physicians (96%). This study highlighted the potential use of N2O and IN FENT in enhancing procedural experiences for pediatric patients in orthopedic settings (Hoeffe et al., 2017).

In 2022, another study explored the effectiveness of combining IN FENT with N2O 50%. This research covered a wide range of procedures and evaluated the satisfaction of patients and caregivers with this sedation approach. The study found that 94% of respondents preferred using the same sedation method for future procedures, reinforcing this combination's positive reception in pediatric care (Hoeffe et al., 2022).

These studies highlight the significant advantages of using N2O and IN FENT in pediatric orthopedic procedures. The high satisfaction rates among patients, parents, and medical professionals, along with effective pain and anxiety management, support the broader adoption of this sedation approach in pediatric emergency and orthopedic settings to improve the procedural experience for young patients, thereby enhancing the quality of pediatric orthopedic care.

Enhancing Pediatric Pain Management in Canadian Emergency Departments.

Effective pain management is crucial in pediatric healthcare, significantly impacting children's experiences and outcomes in hospital settings. Canadian pediatric emergency departments (PEDs) adopt an integrated approach to managing pain and anxiety, incorporating both physical and psychological care strategies (Trottier et al., 2019). These efforts have evolved alongside significant research contributions, such as the "Treating

and Reducing Anxiety and Pain in the Pediatric Emergency Department" (TRAPPED) series of studies, which have played a key role in improving understanding and guiding evidence-based practices in this area.

The TRAPPED Series Insights:

- **TRAPPED-1:** Conducted across Pediatric Emergency Research Canada (PERC) centers from October 2013 to January 2014, TRAPPED-1 revealed substantial variability in pain and anxiety management strategies across facilities. This study highlighted the disparities in resource availability and pain management approaches, underscoring inconsistencies in pediatric care practices across Canada (Trottier et al., 2015).
- **TRAPPED-2:** Building on the findings of TRAPPED-1, TRAPPED-2, initiated in 2015, focused on enhancing procedural pain management through a Quality Improvement Collaborative (QIC). This approach included patient engagement, distraction techniques, educational initiatives, and adopting less painful medication delivery routes. TRAPPED-2 marked a significant step toward improving pediatric pain management practices across Canadian emergency departments (Trottier et al., 2018).

However, the TRAPPED series identified a critical area for enhancement: the underutilization of Nitrous Oxide (N2O) for managing pain and anxiety. Despite its well-known safety and effectiveness as both an analgesic and anxiolytic, N2O was not widely available, highlighting the need for its broader use in pediatric emergency settings.

These findings from the TRAPPED series highlight the need for further advancements in pediatric pain management. By advocating for non-invasive, child-friendly strategies—such as the expanded use of N2O—these studies underscore the importance of adopting innovative and progressive approaches to managing pain and anxiety in children. The ongoing effort to improve pediatric care in Canada aims to ensure that every child's hospital experience is as comfortable and stress-free as possible.

The role of Nitrous Oxide (N₂O) in Canadian pediatric emergency departments.

The growing focus on Nitrous Oxide (N₂O) in Canadian pediatric emergency departments marks a significant shift toward improved pain management strategies. The introduction of a comprehensive research review in the Canadian Journal of Emergency Medicine in 2023, along with other recent studies, aims to gather evidence for guiding the safe and effective use of N₂O in children. These efforts are in response to the challenging reality that six out of ten children admitted to pediatric emergency departments experience painful conditions, highlighting the need for effective pain management solutions (Sweetman, 2023).

These studies have explained N₂O's ability to significantly reduce pain in various emergency procedures, including IV insertions and laceration repairs. The effectiveness of N₂O, mainly when used alongside topical anesthetics, has been consistently demonstrated through measurement of subjective or behavioural experience, like the Visual Analog Scale (VAS), proving its role in relieving pain (Poonai et al., 2023). Specifically, for pain during IV insertion, a 70% N₂O mixture provided a significant reduction in pain scores compared to topical anesthetics alone. Moreover, N₂O used in laceration repairs was favourably compared to subcutaneous lidocaine, oxygen, and oral midazolam, determining N₂O's broad utility and effectiveness in managing procedural distress in pediatric patients (Poonai et al., 2023).

Despite its proven benefits, the use of N₂O in Canadian pediatric emergency departments has been limited due to the limited accessibility. The Pediatric Emergency Research Canada (PERC) survey revealed that less than half of the pediatric emergency physicians in Canada use nitrous oxide to treat pain and distress in children in the emergency department.

Therefore, the pain management expert advocacy for the widespread use of N₂O in pediatric emergency departments arises from the concept of how quick, non-invasive and effective pain management can significantly affect a child's overall healthcare experience, potentially preventing long-term psychological trauma. As modern medical practices adopt evidence-based, child-centric approaches, the broader integration of N₂O in emergency settings becomes a critical strategy for

improving pediatric pain management, aligning with current research and expert recommendations.

Global Enhancement of Procedural Sedation in Pediatric Emergency Care: A Call for Nitrous Oxide Utilization

The use of procedural sedation and analgesia (PSA) for managing pain and anxiety in young patients during emergency care is becoming more prevalent worldwide. However, recent studies from Italy and Canada have shown that N₂O is not fully utilized in pediatric emergency departments (EDs), highlighting a global issue within emergency care practices.

In Italy, a study of pediatric emergency departments revealed concerning statistics: 27% of pediatric patients received inadequate sedation, and only 41% had access to N₂O. This underutilization is due to several systemic barriers, including the absence of N₂O among available medications, a lack of trained staff, and resource constraints such as inadequate space and personnel. Despite the proven benefits of N₂O in relieving procedural pain and anxiety, it remains unused in many pediatric EDs across Italy (Bevacqua et al., 2023) and in many other countries worldwide. Therefore, the researchers firmly encourage the urgent need for systematic implementation and use of N₂O in Italian pediatric EDs.

These findings call for improvements in pediatric pain management by improving the availability of N₂O in pediatric emergency departments. These improvements can be made by developing and implementing comprehensive PSA guidelines, expanding educational training for healthcare professionals, and promoting awareness among healthcare providers and patient families.

Innovations in Nitrous Oxide Delivery through Precision and Individualized Care in Pediatrics.

Advancements in pediatric healthcare have greatly benefited from innovations aimed at enhancing treatment precision and emphasizing personalized care. These developments reflect a commitment to improving clinical outcomes and enriching the patient experience through technological innovation. A leading example of this is the eAdvantage® System, which embodies the modern approach to precision and patient-centred care, driving the evolution of precise nitrous oxide delivery technologies.

The eAdvantage® System incorporates an Electronic Pressure Sensor with exceptional sensitivity, capable of detecting inhalation efforts as small as $-1.0 \text{ cmH}_2\text{O}$, ensuring that the $\text{N}_2\text{O}/\text{O}_2$ mixture is delivered in prompt synchronization with the patient's respiratory pattern. This precision aligns with the natural dynamics of inhalation, which is driven by diaphragm contraction, generating a negative pressure in the thoracic cavity that facilitates gas intake. By optimizing the delivery mechanism to align with the physiological breathing process, the system enhances the comfort and efficacy of analgesia for pediatric patients.

Inspired by the principles of mechanical ventilation for spontaneously breathing patients, which prioritize maintaining the lowest possible trigger threshold to reduce the work of breathing and avoid asynchrony (Dargaville & Keszler, 2013), the eAdvantage® System's advanced trigger sensitivity ensures a quick, precise, and smooth coordination of gas delivery across various pediatric age groups. This represents a significant improvement over conventional pneumatic demand valves, which require a higher inspiratory effort to activate gas flow, potentially increasing the patient's work of breathing (Luhmann et al., 1999).

The system's ability to synchronize with the child's respiratory efforts and maintain a minimal trigger threshold reduces the work of breathing and facilitates a smooth transition between inhalation and exhalation phases. This not only improves patient comfort during nitrous oxide administration but also allows for dynamic adjustments of gas flow, responding in real-time to changes in tidal volume and respiratory rate, particularly during procedures that induce stress or pain, which are known to alter respiratory patterns (Jafari et al., 2017).

By tailoring the delivery of the gas mixture to each patient's specific respiratory needs, the eAdvantage® System eliminates the need for constant manual adjustments and ongoing monitoring of gas reservoir levels required in conventional continuous flow systems. This technological advancement simplifies clinical workflows and significantly enhances patient care, enabling healthcare providers to concentrate more on the procedure rather than the operation of the nitrous oxide delivery system.

In addition to advancing patient care, the eAdvantage® System also addresses environmental concerns by significantly reducing N_2O wastage, aligning with sustainability and economic efficiency goals that are highly prioritized in modern healthcare. Through these comprehensive improvements, the eAdvantage® System exemplifies the seamless integration of personalized care through precision and environmental responsibility, setting a new standard in pediatric healthcare.

Conclusion:

Expanding the use of Nitrous Oxide (N_2O) in pediatric care, particularly in emergency departments and for mild to moderate procedural pain, is supported by evidence demonstrating its analgesic and anxiolytic properties and strong safety profile. Globally advocated by pediatric and pain management specialists and backed by evidence-based practices, N_2O is recognized as a critical element in pediatric pain management strategies, essential for improving procedural outcomes.

Multiple studies have shown that N_2O maintains a high safety profile in pediatric settings, even at high concentrations, without increasing the risk of adverse effects. The introduction of the O-Two eAdvantage® System, featuring a highly sensitive Electronic Pressure Sensor, marks a significant advancement in inhaled N_2O analgesia. The sensor's sensitivity allows children to easily trigger the valve, ensuring the required amount of gas mixture is delivered with minimal effort. This improves patient comfort and enables healthcare professionals to focus more effectively on clinical procedures.

Moreover, the system's real-time gas flow adjustment capabilities reduce wastage, aligning with economic efficiency and environmental sustainability goals. This innovation exemplifies the ongoing development of inhaled analgesia delivery systems, supporting the modern standards of medical practice.

References:

1. American Academy of Pediatric Dentistry. (2023). Use of nitrous oxide for pediatric dental patients. *The Reference Manual of Pediatric Dentistry*, 393-400. <https://www.aapd.org/research/oral-health-policies--recommendations/use-of-nitrous-oxide-for-pediatric-dental-patients/>
2. Bar-Meir, E., Zaslansky, R., Regev, E., Keidan, I., Orenstein, A., & Winkler, E. (2006). Nitrous oxide administered by the plastic surgeon for repair of facial lacerations in children in the emergency room. *Plastic and reconstructive surgery*, 117(5), 1571–1575. <https://doi.org/10.1097/01.prs.0000206298.71083.df>
3. Bevacqua, M., Sforzi, I., Bressan, S., Barbi, E., & Sahyoun, C. (2023). "Procedural sedation and analgesia in Italian pediatric emergency departments: a subgroup analysis in Italian hospitals." *Italian journal of pediatrics*, 49(1), 23. <https://doi.org/10.1186/s13052-023-01426-7>
4. Brown, M. L., Rojas, E., & Gouda, S. (2017). A mind–body approach to pediatric pain management. *Children*, 4(6), 50. <https://doi.org/10.3390/children4060050>
5. Cunico, D., Rossi, A., Verdesca, M., Principi, N., & Esposito, S. (2023). Pain management in children admitted to the emergency room: A narrative review. *Pharmaceuticals*, 16(8), 1178. <https://doi.org/10.3390/ph16081178>
6. 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>
7. Hoeffe, J., Doyon Trottier, E., Bailey, B., Shellshear, D., Lagacé, M., Sutter, C., Grimard, G., Cook, R., & Babl, F. E. (2017). Intranasal fentanyl and inhaled nitrous oxide for fracture reduction: The FAN observational study. *The American Journal of Emergency Medicine*, 35(5), 710–715. <https://doi.org/10.1016/j.ajem.2017.01.004>
8. Hoeffe, J., Vogel, R. G., & Ammann, R. A. (2022). Pediatric sedation and analgesia outside the operating room: Combining intranasal fentanyl and inhaled nitrous oxide. *The Journal of Pediatric Pharmacology and Therapeutics*, 27(5), 436–442. <https://doi.org/10.5863/1551-6776-27.5.436>
9. 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>
10. Liu, Q., Chai, X. M., Zhang, J. J., Wang, Y. L., Wang, Y., Gao, L. L., Dai, Y. L., Gao, H. X., Zhang, T. T., Yu, J. Q., & Li, Y. X. (2019). A Fixed Nitrous Oxide and Oxygen Mixture for Analgesia in Children With Leukemia With Lumbar Puncture-induced Pain: A Randomized, Double-blind Controlled Trial. *Journal of pain and symptom management*, 57(6), 1043–1050. <https://doi.org/10.1016/j.jpainsymman.2019.02.029>
11. Luhmann, J. D., Kennedy, R. M., Jaffe, D. M., & McAllister, J. D. (1999). Continuous-flow delivery of nitrous oxide and oxygen: A safe and cost-effective technique for inhalation analgesia and sedation of pediatric patients. *Pediatric Emergency Care*, 15(6), 388–392. <https://doi.org/10.1097/00006565-199912000-00004>
12. McCollum, N. L., Kamat, P. P., Stockwell, J. A., Travers, C., McCracken, C., Thompson, B., & Pettignano, R. (2017). Improving stakeholder satisfaction: Nitrous oxide for peripheral intravenous cannulation for pediatric procedural sedation. *Journal of Radiology Nursing*, 36, 1–4. <https://doi.org/10.1016/j.jradnu.2017.07.007>
13. Memè, L., Gallusi, G., Strappa, E., Bambini, F., & Sampalmieri, F. (2022). Conscious inhalation sedation with nitrous oxide and oxygen in children: A retrospective study. *Applied Sciences*, 12(22), 11852. <https://doi.org/10.3390/app122211852>
14. Poonai, N., Greene, C., Dobrolowski, A., Geda, R., Hartling, L., Ali, S., Bhatt, M., Trottier, E. D., Sabhaney, V., O'Hearn, K., Jain, R., & Osmond, M. H. (2023). Inhaled nitrous oxide for painful procedures in children and youth: A systematic review and meta-analysis. *CJEM*, 25(6), 508–528. <https://doi.org/10.1007/s43678-023-00507-0>
15. Sweetman, K. (2023). '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-in-emergency-rooms.html](#)

16. Trottier, E. D., Ali, S., Le May, S., & Gravel, J. (2015). Treating and reducing anxiety and pain in the paediatric emergency department: The TRAPPED survey. *Paediatrics & Child Health*, 20(5), 239–244. <https://doi.org/10.1093/pch/20.5.239>
17. Trottier, E. D., Ali, S., Thull-Freedman, J., Meckler, G., Stang, A., Porter, R., Blanchet, M., Dubrovsky, A. S., Kam, A., Jain, R., Principi, T., Joubert, G., Le May, S., Chan, M., Neto, G., Lagacé, M., Gravel, J., & Pediatric Emergency Research Canada Pain Interest Group. (2018). Treating and reducing anxiety and pain in the paediatric emergency department-TIME FOR ACTION-the TRAPPED quality improvement collaborative. *Paediatrics & Child Health*, 23(5), e85–e94. <https://doi.org/10.1093/pch/pxx186>
18. 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>
19. Veger, M. L., van Iterson, J., Bakx, R., & Ridderikhof, M. L. (2024). The Role of Nitrous Oxide in Minor Pediatric Procedures in the Emergency Department: A Systematic Review. *Journal of pediatric surgery*, S0022-3468(24)00011-3. Advance online publication. <https://doi.org/10.1016/j.jpedsurg.2023.12.026>
20. 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. <https://doi.org/10.1097/PEC.0b013e31823aff6d>

O-Two Medical Technologies Inc.

45A Armthorpe Road,
 Brampton, ON, Canada L6T 5M4
 Toll Free: (800) 387 3405
 Tel: (905) 792 OTWO (6896)
 Fax: (905) 799 1339
 Emails: resuscitation@otwo.com
 clinical@otwo.com
 Website: www.otwo.com