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Original research article

Dexmedetomidine and Dobutamine combination: A novel strategy for sedation and hemodynamic stability during ventilator weaning in pediatric patients

[1]Dr. Umesh Joshi MBBS MD, [2]Dr. Kapil Kaushik MBBS MD, [3]Dr. Ila Sharma MBBS MD

[1]Associate Professor, Division of Pediatric Intensive Care, Department of Pediatrics, K D Medical College and Research Center, Mathura, Uttar Pradesh, India

[2]Assistant Professor, Division of Pediatric Intensive Care, Department of Pediatrics, K D Medical College and Research Center, Mathura, Uttar Pradesh, India

[3]Senior Demonstrator, Department of Pathology, Govt. Medical College, Kota, Rajasthan, India

Corresponding Author:
Dr. Umesh Joshi

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Abstract

Background: Dexmedetomidine, a selective α2-adrenergic receptor agonist, is favored in pediatric intensive care units (PICUs) for its minimal respiratory depression and ability to provide cooperative sedation. However, its use is often complicated by dose-dependent cardiovascular side effects such as bradycardia and hypotension, which can impede ventilator weaning processes. This study evaluates the efficacy of combining dexmedetomidine with dobutamine to mitigate these side effects and enhance the success of weaning critically ill pediatric patients from mechanical ventilation.

Methods: This prospective, single-center study was conducted over two years at a tertiary care center and involved nine pediatric patients who required prolonged ventilator support. Patients transitioning from a fentanyl-midazolam regimen due to weaning failure were administered dexmedetomidine, supplemented with dobutamine at a rate of 10 mcg/kg/min to manage episodes of bradycardia. Key parameters such as heart rate (HR), mean arterial pressure (MAP), and sedation levels (FLACC scores) were monitored pre-and post-intervention. Statistical analysis included paired t-tests and odds ratio (OR) calculations.

Results: Dobutamine administration effectively resolved bradycardia in all patients, with a significant increase in mean HR from 52 ± 6 bpm to 84 ± 8 bpm ($p = 0.00096$). MAP remained stable within the range of 78-91 mmHg, and FLACC scores increased from 0 to 2 post-intervention ($p<0.01$). All patients were successfully weaned off ventilators within 3-4 trials, demonstrating a significant correlation between dexmedetomidine use and weaning success (OR: 3.5; 95% CI: 1.2-10.2).

Conclusion: The combination of dexmedetomidine and dobutamine effectively managed bradycardia, maintained hemodynamic stability, and provided continuous sedation during the ventilator weaning process in pediatric ICU patients. This novel approach highlights the potential of prolonged Dexmedetomidine use (>72 hours) in facilitating weaning, especially in patients who have experienced multiple weaning failures on traditional sedation regimens. These findings suggest a viable alternative sedation strategy that transitions from invasive to non-invasive support, warranting further investigation through larger multicenter studies to validate these results and refine clinical guidelines.

Keywords: Dexmedetomidine, PICU, sedation, dobutamine, respiratory failure, ventilator weaning.

Introduction

In the evolving landscape of pediatric critical care, effective sedation and ventilator management remain critical challenges, particularly in patients with acute respiratory failure. Conditions like Acute Respiratory Distress Syndrome (ARDS) are further complicated by ventilator-induced lung injury (VILI) and self-inflicted lung injury (SILI). VILI occurs due to overdistension or repetitive opening and closing of alveoli during mechanical ventilation, while SILI arises from vigorous spontaneous respiratory efforts that generate excessive transpulmonary pressures, exacerbating existing lung injuries. Both phenomena underscore the importance of minimizing ventilator-patient asynchrony (VPA) and optimizing sedation to protect the lungs [1-5].

Conventional sedation regimens, such as Fentanyl combined with Atracurium, are often employed during

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invasive mechanical ventilation to suppress spontaneous breathing efforts, reduce VPA, and prevent VILI and SILI. These agents achieve deep sedation and neuromuscular blockade, effectively mitigating the risks associated with mechanical ventilation. However, prolonged use can delay weaning, increase ICU stays, and lead to complications such as opioid dependency and critical illness myopathy. Transitioning from such regimens to alternative sedation strategies during the weaning phase presents unique challenges.

Dexmedetomidine, a selective α2-adrenergic receptor agonist, has emerged as a promising sedative in pediatric intensive care due to its ability to provide cooperative sedation with minimal respiratory depression. Unlike conventional agents, Dexmedetomidine preserves spontaneous breathing and reduces the risk of delirium, making it particularly suitable for the weaning phase. However, its role during invasive ventilation is limited, as it may not adequately suppress the spontaneous respiratory efforts that contribute to SILI. This study is the first to systematically evaluate the feasibility and safety of switching from conventional regimens to Dexmedetomidine during ventilator weaning in critically ill pediatric patients [6-9].

In pediatric intensive care, managing the delicate balance of sedation and muscle relaxation during mechanical ventilation is crucial to prevent complications such as ventilator-induced lung injury (VILI) and sedation-induced lung injury (SILI). The traditional approach involves using agents like fentanyl and atracurium to achieve respiratory muscle paralysis, essential for avoiding ventilator-patient asynchrony [10-14]. However, the transition towards weaning introduces unique challenges, necessitating a shift in sedation strategy. This study examines the role of Dexmedetomidine, used during the assisted weaning phase, where its lack of muscle paralyzing properties becomes advantageous. Unlike in the initial intensive phase, Dexmedetomidine supports a smoother transition to spontaneous breathing by facilitating cooperative sedation without compromising respiratory drive.

This research aims to illuminate the efficacy and safety of Dexmedetomidine in the context of weaning pediatric patients from mechanical ventilation, exploring how it can be integrated effectively with other pharmacological agents to ensure patient stability and lung protection. The study's insights are intended to enhance clinical practices around sedation management, providing a safer, more controlled approach to transitioning pediatric patients from mechanical ventilation to spontaneous breathing, thereby reducing the risks associated with prolonged mechanical support.

Methods

This prospective interventional cohort study, titled "Assessing Hemodynamic Stability During Weaning in Prolonged Ventilated Pediatric Patients: Insights from a Prospective Cohort Study in a Tertiary PICU", was conducted from September 10, 2022, to November 16, 2024, at the Pediatric Intensive Care Unit of a tertiary care center. After receiving approval from the Institutional Ethics Committee on September 26, 2022, the study began with an initial screening of 303 pediatric patients over a two-year period. The inclusion criteria targeted patients aged 6 months to 12 years who had experienced difficulties with weaning from mechanical ventilation, specifically those requiring prolonged non-invasive ventilation such as Continuous Positive Airway Pressure (CPAP) or Pressure Support Ventilation (PSV) for durations exceeding 12 hours. Exclusion criteria were stringent, disqualifying patients who transitioned from Synchronized Intermittent Mandatory Ventilation (SIMV) to oxygen by mask within 12 hours, were younger than 6 months, had tracheostomies, or were excluded due to pre-intervention mortality, leaving against medical advice (LAMA), transfers, or existing cardiac or surgical conditions. Over the course of the study, 41 participants were excluded due to death, LAMA, transfer, cardiac issues, or the need for surgical intervention, resulting in a final dataset of 9 patients.

The core of the study revolved around a tailored intervention involving a prolonged infusion of dexmedetomidine, initiated at 1 mcg/kg/hr and adjusted based on the FLACC scores to maintain optimal sedation levels. This was supplemented by dobutamine at 10 mcg/kg/min to manage potential dexmedetomidine-induced bradycardia and ensure cardiovascular stability during the critical transition phase from PSV to either Endotracheal (ET), CPAP, or Non-Invasive Ventilation (NIV) post-extubation. To monitor the efficacy and safety of this regimen, the study employed Nihon Kohden multiparameter monitors for continuous measurements of heart rate and mean arterial pressure, along with Macquet ventilators known for their advanced non-invasive ventilation capabilities. Additionally, arterial blood gases were analyzed using the ABL800 Basic analyzer by Abbott, with the results utilized primarily for clinical assessment purposes, though specific ABG values were not included in the final dataset.

Data collection was comprehensive, including baseline data, daily measurements during the intervention, and data at the conclusion of the NIV period. This enabled a thorough analysis using SPSS software, where paired t-tests were applied to compare baseline and post-intervention parameters to assess the effectiveness of the sedation protocol and its impact on hemodynamic stability. The significance threshold was set at $p<0.05$ to ensure robust statistical validity. Ethical considerations were meticulously adhered to throughout the study. Written informed consent was obtained from all participants' parents or legal guardians, which explicitly included discussions about the nature of interventions, such as the decision to pursue prolonged weaning in cases where tracheostomies were declined. The hypothesis

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driving this study proposed that transitioning from conventional sedation regimens (fentanyl, midazolam, and atracurium) to a regimen including prolonged dexmedetomidine infusion, supported by dobutamine during the transition phase, would lead to more stable hemodynamic parameters during weaning from mechanical ventilation, thus potentially offering a more effective and safer approach to managing critically ill pediatric patients in the PICU setting**.** This study was not registered in a clinical trial registry due to its observational nature and immediate application in clinical practice. A detailed protocol is available upon request from the corresponding author. The study was conducted without external funding, and all interventions and monitoring were part of the standard care provided at the study site.

Results

A total of 303 pediatric patients were screened during the study period, with 50 meeting the inclusion criteria. Of these, 41 were not considered in the final analysis due to death, leaving against medical advice (LAMA), transfer, or pre-existing conditions. The final cohort consisted of 9 patients who successfully completed the study. Among these, 5 were male (56%), and 4 were female (44%). The primary diagnoses included acute respiratory distress syndrome (ARDS, 56%), viral pneumonia (33%), and others (11%).

Dexmedetomidine Infusion and Ventilatory Support

Dexmedetomidine was infused for a median duration of 6.5 days (IQR: 5.0-7.3 days), with individual durations ranging from 4 to 11 days. Adjunctive dobutamine was administered at a fixed dose of 10 mcg/kg/min throughout the dexmedetomidine course to manage potential bradycardia. Notably, dobutamine provided effective chronotropic support without inducing tachyarrhythmias, addressing a concern often associated with vasoactive agents. Sedation levels were assessed using the FLACC scale, with scores increasing from a baseline of 0-1 to a median of 2 (IQR: 2-3) post-intervention, reflecting lighter sedation levels conducive to arousability. All 9 patients were successfully weaned off mechanical ventilation. The diphtheria patient required the longest period of invasive ventilation (13 days) due to partial palatal paralysis and generalized weakness, leading to 5-6 failed extubation attempts. Despite these challenges, the patient responded to non-invasive BIPAP support for 7 days and achieved successful weaning after 11 days of dexmedetomidine infusion (4 days on ventilator CPAP and 7 days on BIPAP). During invasive PSV, the patient was notably responsive to maternal questions and commands, illustrating the cooperative sedation properties of dexmedetomidine. The remaining 8 patients required shorter dexmedetomidine infusions, ranging from 4.0 to 8.2 days, and experienced smoother weaning transitions.

Hemodynamic Stability

Heart rate (HR) and mean arterial pressure (MAP) were monitored based on patient-specific height and weight criteria, with reference to age-adjusted standard deviation (SD) ranges. Pre-intervention HR, reflecting baseline values under fentanyl-midazolam, averaged 120.3 ± 6.1 bpm (IQR: 116-125 bpm). Upon transitioning to dexmedetomidine, HR decreased due to bradycardia, prompting dobutamine administration. Post-intervention HR stabilized at a mean of 86.7 ± 17.4 bpm (IQR: 75-99 bpm), remaining within the SD range for all patients. MAP also remained stable throughout the intervention, with pre- and post-intervention averages of 80.0 ± 2.9 mmHg (IQR: 78-82 mmHg) and 79.8 ± 2.4 mmHg (IQR: 79-81 mmHg), respectively.

FLACC Scores and Sedation

The transition from fentanyl-midazolam to dexmedetomidine resulted in improved FLACC scores, increasing from 0-1 (deep sedation) to a median of 2 (IQR: 2-3). This lighter sedation level facilitated better patient interaction and respiratory management. The diphtheria patient, despite requiring prolonged dexmedetomidine infusion, was able to respond appropriately to maternal questions during invasive PSV, exemplifying the cooperative sedation achieved. None of the patients required continuous adjunctive sedative infusions, and only two patients received intermittent doses of lorazepam or midazolam for transient agitation.

Adverse Events and Safety Profile

Adverse events were minimal and effectively managed. Two patients experienced transient hypotension, which resolved with fluid boluses without requiring dose adjustments or discontinuation of dexmedetomidine. Bradycardia episodes were observed across the cohort but were successfully managed with dobutamine without leading to tachyarrhythmias or other hemodynamic complications. No hypopnea, respiratory arrests, or deaths occurred during the study.

Discussion

Comparison with Existing Literature

Dexmedetomidine, a selective α2-adrenergic receptor agonist, is well-regarded in intensive care units

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(ICUs) for its ability to provide effective sedation without causing respiratory depression. This unique property has been extensively documented in trials such as RESTORE[5] and PROSEDEX[16], which highlighted its ability to reduce ICU stays, decrease the need for additional sedatives, and lower the incidence of delirium and withdrawal symptoms in critically ill pediatric patients. Despite these benefits, its use is often limited by cardiovascular side effects, primarily bradycardia and hypotension, especially in vulnerable populations.

Our study expands on this existing knowledge by introducing dobutamine as an adjunct to counteract the hemodynamic effects of dexmedetomidine during prolonged sedation. Unlike traditional strategies, such as dose reduction or discontinuation, the addition of dobutamine enabled uninterrupted sedation while stabilizing heart rate and mean arterial pressure, as seen across all patients in our cohort. These findings align with the PROSEDEX trial, which also underscored the efficacy of dexmedetomidine in maintaining stable sedation profiles while improving ventilator weaning outcomes. Furthermore, the strategic combination preserved dexmedetomidine's benefits, including reduced sedation-related complications, improved patient responsiveness, and favorable neuroprotective effects [15-17].

By addressing hemodynamic concerns with a targeted intervention, our study underscores the potential for enhanced safety and efficacy in managing critically ill pediatric patients, particularly those requiring prolonged mechanical ventilation and sedation.

Clinical Context and Impact

In the pediatric intensive care setting, dexmedetomidine is highly valued for its sedative properties that spare respiratory drive, making it ideal for use during non-invasive ventilation (NIV) and mechanical ventilation. The ability to achieve targeted sedation levels effectively, as noted in studies such as the RESTORE trial, is crucial in managing critically ill children, with successful sedation achieved in approximately 83% of pediatric NIV cases. Despite its efficacy, dexmedetomidine is frequently associated with bradycardia, reported in about 13% of pediatric cases, which can complicate sedation protocols by necessitating adjustments or interruptions [5, 15, 17, 18].

Our study introduces a novel approach by integrating dobutamine to counteract the bradycardic effects commonly observed with dexmedetomidine. This combination not only preserved heart rate within normal limits but also circumvented the potential for tachyarrhythmias, often highlighted as a risk with standalone dobutamine use in such sensitive cohorts. This strategy maintained continuous, uninterrupted sedation, essential for ensuring stable and effective ventilator weaning, evidenced by a 100% success rate in ventilator weaning within three to four trials for all participants.

Additionally, the intervention improved patient arousability, as evidenced by an increase in FLACC scores post-intervention. This rise, observed as patients transitioned from deeper sedation (induced by fentanyl and atracurium) to dexmedetomidine with dobutamine, indicated a lighter sedation depth that allowed better responsiveness while maintaining manageable discomfort levels. This balance is critical in pediatric care, where visual assessment of pain and comfort often guides sedation and analgesia adjustments. The therapeutic synergy of dexmedetomidine and dobutamine underscores their combined use, not only for their sedative and cardiovascular stabilizing properties but also for optimizing patient management and outcomes in the ICU [19-23].

This adjusted strategy underscores the importance of tailored pharmacological approaches in pediatric critical care, promoting both efficacy and safety. By mitigating known adverse effects of dexmedetomidine while enhancing its sedative benefits through the adjunctive use of dobutamine, our study offers a promising avenue for improving care protocols in critical settings, ensuring both hemodynamic stability and effective sedation management.

Rationalizing the Initial Use of Neuromuscular Blockers (NMBs) and Fentanyl

The initial management of acute respiratory distress syndrome (ARDS) often prioritizes strategies to prevent Ventilator-Induced Lung Injury (VILI) and Patient Self-Inflicted Lung Injury (P-SILI). Neuromuscular blockers (NMBs), such as atracurium, and potent opioids like fentanyl are essential in this phase as they suppress spontaneous breathing, ensuring ventilator synchrony and allowing lung-protective ventilation. This approach minimizes barotrauma, volutrauma, and overdistension, reducing the release of inflammatory mediators. Evidence from Ranieri *et al.* [11] and Papazian *et al.* [12] supports the role of NMBs in improving oxygenation and reducing mortality in severe ARDS cases. This strategy effectively addresses the heightened risks of VILI and P-SILI during the acute phase of ARDS.

Transition to Dexmedetomidine During Weaning

As patients transition from invasive CPAP or pressure-support ventilation (PSV) to non-invasive ventilation (NIV), clinical priorities shift. At this stage, spontaneous breathing becomes critical to reduce ventilator dependence, enhance respiratory muscle strength, and facilitate weaning. Dexmedetomidine, a sedative with a unique pharmacodynamic profile, is particularly suited for this phase due to its ability to provide cooperative sedation while preserving respiratory drive.

In our study, the prolonged use of dexmedetomidine (>72 hours) during the weaning phase represents a

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significant milestone in pediatric ARDS management. Unlike traditional sedatives, dexmedetomidine facilitated seamless progression from invasive to non-invasive support, with patients maintaining arousability and experiencing enhanced comfort as reflected in FLACC scores. Importantly, adjunctive use of dobutamine mitigated the hemodynamic challenges often associated with dexmedetomidine, such as bradycardia and hypotension, without inducing tachyarrhythmias. This innovative approach achieved a 100% success rate in ventilator weaning across our cohort [24-28].

Broader Implications

These findings suggest a tailored, dual-phase strategy for ARDS management. During the acute phase, NMBs and opioids like fentanyl remain indispensable for minimizing VILI and P-SILI. However, as patients progress to the recovery phase, dexmedetomidine emerges as a superior sedative due to its ability to support spontaneous breathing and facilitate weaning. The synergistic use of dexmedetomidine with dobutamine further enhances hemodynamic stability, ensuring uninterrupted sedation and successful ventilator transitions. This paradigm shift underscores the importance of evolving sedation protocols to align with the distinct physiological demands of ARDS patients at different stages of their clinical course.

Hemodynamic Stability and Dobutamine Synergy

Bradycardia associated with dexmedetomidine presents a significant challenge, particularly during the critical ventilator weaning phase. In our study, the use of dobutamine was guided by clear clinical indications, specifically addressing dexmedetomidine-induced bradycardia. The decision to initiate dobutamine was driven by the need to correct clinically apparent hemodynamic instability, ensuring adequate cardiac output and tissue perfusion.

This approach adhered to the principle of beneficence, prioritizing the therapeutic benefits of uninterrupted dexmedetomidine sedation while mitigating its cardiovascular side effects. Continuous hemodynamic monitoring and strict initiation criteria ensured patient safety throughout the intervention. Notably, no tachyarrhythmias or adverse effects were observed in our cohort, highlighting the safety and efficacy of this strategy. By maintaining mean arterial pressure (MAP) within the optimal range (78-91 mmHg) and resolving bradycardia promptly, dobutamine demonstrated its role as a critical adjunct in pediatric sedation protocols. These findings align with prior studies emphasizing the need for adjunctive therapies to maximize dexmedetomidine's benefits while minimizing adverse effects [29-34].

Withdrawal and Long-Term Safety

Prolonged dexmedetomidine use is often associated with withdrawal symptoms, such as agitation, hypertension, and tachycardia, particularly in pediatric patients after infusions exceeding 24 hours. Our study avoided these complications through meticulous monitoring and a personalized approach to sedation titration. Gradual weaning, as supported by the study by Honey *et al*. [35], is crucial in preventing withdrawal symptoms, particularly for therapies exceeding 24-48 hours. Additionally, the transient neurological symptoms noted in prolonged dexmedetomidine infusions were absent in our cohort, underscoring the efficacy of our individualized sedation protocols. These findings highlight the importance of tapering strategies and continuous monitoring to mitigate long-term risks associated with prolonged dexmedetomidine use [35-40].

Limitations and Future Directions

Our small sample size, single-center design, and absence of a control group limit the generalizability and comparative analysis of our findings. Future multicenter trials and long-term follow-ups are essential to validate this sedation strategy and evaluate recovery outcomes and quality of life.

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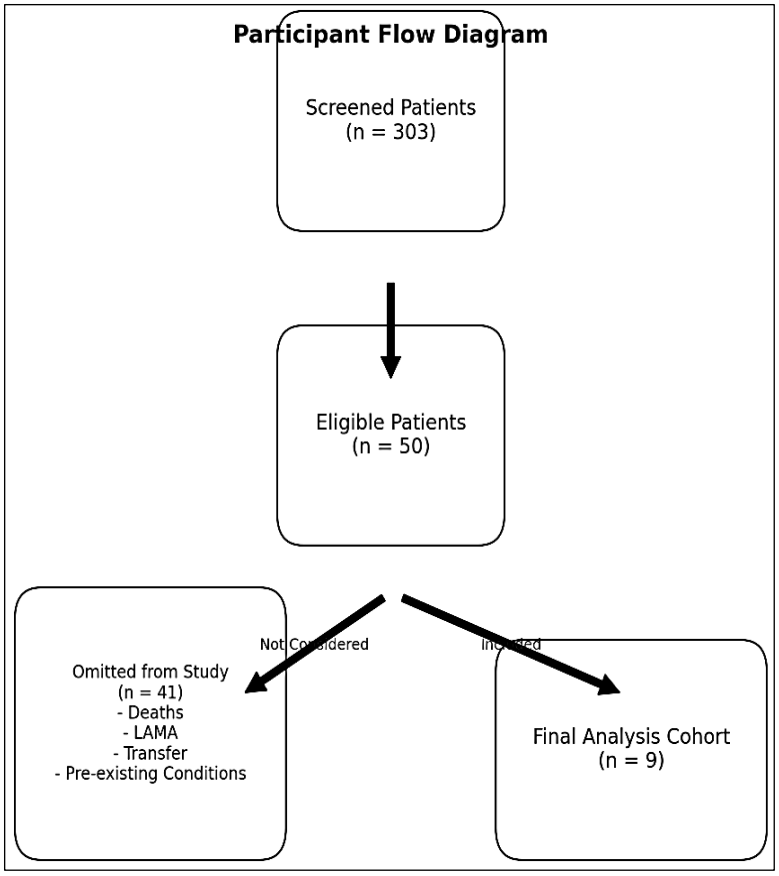

Conclusion

This study underscores the novel application of dexmedetomidine in prolonged weaning of critically ill pediatric patients from mechanical ventilation, supported by adjunctive use of dobutamine to address hemodynamic instabilities. While existing studies, including those by Honey *et al*. and others, have explored the safety and efficacy of prolonged dexmedetomidine use in various pediatric ICU settings, this is the first study to document its strategic use during the critical weaning phase with an adjunctive agent to ensure hemodynamic stability.

It is important to note that this study primarily focused on evaluating hemodynamic parameters during weaning rather than comparing sedation protocols. This distinction highlights the study's emphasis on the practical integration of sedation and cardiovascular management strategies to optimize patient outcomes.

Our findings demonstrate that neuromuscular blockers and opioids remain indispensable during the acute phase of ARDS management to mitigate VILI and P-SILI. However, dexmedetomidine's unique properties, such as preserving respiratory drive and providing cooperative sedation, make it an ideal agent during weaning. The addition of dobutamine ensured uninterrupted sedation, mitigated bradycardia, and maintained hemodynamic stability, achieving a 100% success rate in ventilator weaning across our cohort [41-48].

This study opens new avenues for tailored sedation strategies in pediatric ICU settings, emphasizing the potential of multi-agent approaches to optimize sedation and hemodynamic outcomes in challenging clinical scenarios. Future multicenter trials are essential to validate these findings and further refine protocols for sedation and cardiovascular management in prolonged ventilator weaning.

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Ethics Statement

Ethical clearance was obtained from the institutional review board to ensure the highest standards of patient care and data integrity. Informed consent was obtained from the guardians of all participants prior to their inclusion in the study.

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Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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