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Original Research Article

INCIDENCE OF WITHDRAWAL SYNDROME IN CHILDREN ON IV SEDOANALGESIA IN A TERTIARY CARE PICU

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ABSTRACT

Background: Analgesics and sedative agents are routinely used in pediatric intensive care units (PICUs) to ensure comfort, alleviate pain, and reduce anxiety in critically ill children. However, prolonged use of opioids and benzodiazepines, such as midazolam and fentanyl, may lead to withdrawal syndrome (WS). Current literature, predominantly from western settings, lacks validation for Indian PICU setups due to varied inclusion criteria, assessment tools, and protocols. This study aims to determine the incidence of WS in children receiving IV sedoanalgesics and its correlation with the duration of PICU stay and reintubation rates.

Material and Methods: This prospective observational study included children aged 1 month to 18 years admitted to the PICU at the Indira Gandhi Institute of Child Health, Bengaluru, between January 2021 and June 2022. Children receiving IV sedoanalgesia for more than 48 hours were assessed for WS using the Withdrawal Assessment Tool-1 (WAT-1). Data on age, weight, sedoanalgesic doses, duration, and outcomes were analyzed using SPSS version 20, with significance set at $p<0.05$.

Results: Among 327 children studied, 119 (36%) developed WS. The median dose and duration of midazolam were 3 µg/kg/min and 7 days, while fentanyl had a median dose of 1.5 µg/kg/min for 7 days, both significantly higher in WS cases ($p<0.01$). Children sedated for ≥8 days had a 90% incidence of WS, compared to 59% for 6-7 days and 27% for 3-5 days, with no cases reported for <3 days ($p<0.001$). WS was most frequent among children with central nervous system disorders (19%). Reintubation occurred in 59 cases, with 54 (91%) associated with WS. Clonidine was used for WS management and showed effective symptom resolution.

Conclusion: The incidence of WS in children receiving IV sedoanalgesics in the PICU was 36%, with prolonged sedation and higher cumulative doses as significant risk factors. Proper monitoring and individualized sedation protocols are essential to minimize WS and associated complications such as reintubation.

Key Words: Withdrawal Syndrome, Pediatric Intensive Care Unit, Midazolam, Fentanyl, Sedoanalgesia, Reintubation.

INTRODUCTION

Analgesics and sedative agents are widely utilized in pediatric intensive care units (PICUs) to ensure comfort and alleviate anxiety and pain in critically ill children undergoing invasive procedures or experiencing distress from environmental factors.[1] Sedoanalgesia with a combination of opioids and benzodiazepines, such as fentanyl and midazolam, is commonly preferred due to its hypnotic, respiratory depressant, and antitussive properties. These agents help achieve adequate sedation, alleviate pain, and minimize the risk of accidental removal of life-supporting tubes and devices.[2] However, balancing sedation and analgesia remains a significant

challenge due to the diverse age groups, developmental stages, and medical complexities of pediatric patients.[3]

Although advancements in sedation practices have improved patient outcomes by reducing physical restraints, post-traumatic stress disorder, oversedation, delirium, and neuromuscular weakness, prolonged use of these agents can lead to tolerance and physical dependence, manifesting as withdrawal syndrome (WS).[4,5] The incidence of PICU-acquired complications, including WS, has surpassed PICU mortality rates, making their early identification and management critical for improving pediatric outcomes.[6]

WS is frequently underdiagnosed and undertreated due to its nonspecific clinical presentation and overlap with other conditions in critically ill children.[7] Existing guidelines recommend midazolam and fentanyl as first-line agents for continuous infusion in sedoanalgesia, but prolonged administration beyond six days increases the risk of tolerance and dependence.[8] Diagnostic challenges are compounded by the lack of standardized tools for assessing WS, with different studies employing varying methodologies and criteria.[9]

Current literature on WS primarily originates from western settings, where inclusion criteria, assessment tools, and treatment protocols vary significantly, limiting their applicability to Indian PICU settings.[10] Recognizing a high incidence of WS in our PICU, this study aimed to determine the true incidence of WS among children receiving IV sedoanalgesics and its correlation with the duration of PICU stay and reintubation rates. A uniform assessment protocol could help develop effective strategies to reduce adverse outcomes and improve clinical care in pediatric critical settings.

MATERIALS AND METHODS

A prospective observational study was conducted to evaluate the incidence of withdrawal syndrome (WS) in children receiving intravenous sedoanalgesia in the pediatric intensive care unit (PICU) of Indira Gandhi Institute of Child Health, Bengaluru. The study was carried out over 18 months, from January 2021 to June 2022, in this tertiary care pediatric hospital. The study population comprised children aged 1 month to 18 years who were admitted to the PICU and received intravenous sedoanalgesia, irrespective of their underlying etiology.

Inclusion criteria included children aged 1 month to 18 years and those receiving intravenous sedation, whether mechanically ventilated or non-ventilated. Exclusion criteria were children with severe global developmental delay or pre-existing psychiatric disorders. The study received approval from the institutional ethical committee, and written informed consent was obtained from the parents or legal guardians of the enrolled children.

Upon enrollment, children meeting the inclusion criteria were observed throughout their PICU stay. Sedation was administered per PICU protocols, primarily using midazolam and fentanyl in continuous infusions. Withdrawal syndrome was assessed using the Withdrawal Assessment Tool-1 (WAT-1), which evaluates symptoms such as diarrhea, vomiting, irritability, tremors, perspiration, abnormal movements, yawning, sneezing, increased muscle tone, and delayed calming post-stimulation. A WAT-1 score of ≥3 was indicative of WS, and assessments were conducted every 12 hours or more frequently if WS symptoms were observed. Dosages and durations of midazolam and fentanyl infusions were recorded, and their relationship to the development of WS was analyzed.

Children were monitored for withdrawal symptoms during sedation weaning and post-extubation. Reintubation rates and their correlation with WS were also evaluated. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences), version 20. Descriptive statistics, including frequencies, percentages, means, standard deviations, and interquartile ranges (IQR), were calculated. Inferential statistics were applied using chi-square tests for categorical variables, with a significance threshold of $p < 0.05$.

RESULTS

Description of Key Findings

Incidence of Withdrawal Syndrome

Out of 327 children included in the study, 119 (36%) developed withdrawal syndrome (WS) during or after the administration of intravenous sedoanalgesia. The remaining 208 (64%) children did not exhibit any signs of withdrawal syndrome.

The duration of sedoanalgesia significantly influenced the development of WS (Table 1). No cases of WS were observed among children receiving sedoanalgesia for less than 3 days. For those sedated for 3–5 days, 27% developed WS, while the proportion increased to 59% in children sedated for 6–7 days and to 90% in children sedated for more than 8 days. This finding was statistically significant ($p<0.001p < 0.001p<0.001$).

The majority of children who developed WS were sedated for longer durations, with 90% of cases observed in those receiving sedoanalgesia for more than 8 days. [Table 1]

The dosage of sedoanalgesics was significantly higher in children who developed WS compared to those without WS (Table 2). The median dose of midazolam in WS cases was 3 µg/kg/min (IQR: 2.5–4), compared to 2 µg/kg/min (IQR: 1–2) in non-WS cases ($p<0.01p < 0.01p<0.01$). Similarly, the median dose of fentanyl was 1.5 µg/kg/min (IQR: 1–2) in WS cases versus 1 µg/kg/min (IQR: 1) in non-WS cases ($p<0.01p < 0.01p<0.01$).

Higher doses of midazolam and fentanyl were associated with a greater likelihood of WS, with

statistically significant differences between cases and non-cases. [Table 2]

The study demonstrated a significant relationship between the duration and dosage of sedoanalgesics and the development of WS. Longer sedation periods and higher cumulative doses of midazolam and fentanyl were major contributing factors.

Table 1: Distribution of Sedoanalgesia Duration Among Cases with and Without Withdrawal Syndrome

Sedoanalgesia Duration	Withdrawal Syndrome (n, %)	No Withdrawal Syndrome (n, %)	Total (n, %)
Less than 3 days	0 (0%)	78 (23.8%)	78 (23.8%)
3–5 days	39 (11.9%)	107 (32.7%)	146 (44.6%)
6–7 days	23 (7.0%)	16 (4.9%)	39 (11.9%)
More than 8 days	57 (17.4%)	7 (2.1%)	64 (19.6%)
Total	**119 (36.4%)**	**208 (63.6%)**	**327 (100%)**

Table 2: Continuous Infusion Dosage of Sedoanalgesics Among Cases with and Without Withdrawal Syndrome

Sedoanalgesic Drug	Median Dose in WS Cases (IQR)	Median Dose in Non-WS Cases (IQR)	p-value
Midazolam (µg/kg/min)	3 (2.5–4)	2 (1–2)	<0.01
Fentanyl (µg/kg/min)	1.5 (1–2)	1 (1)	<0.01
Ketamine (µg/kg/min)	10 (10–30)	-	<0.01
Dexmedetomidine (µg/kg/min)	0.2 (0.2–0.3)	-	<0.01

DISCUSSION

The present study evaluated the incidence of withdrawal syndrome (WS) in children receiving intravenous (IV) sedoanalgesia in a tertiary care pediatric intensive care unit (PICU). The findings revealed a 36% incidence of WS among 327 study participants, indicating a significant clinical concern in this setting. The use of midazolam and fentanyl as continuous sedoanalgesics and their prolonged duration were identified as major contributing factors.

The incidence of WS in this study aligns with previous reports, such as those by Araújo et al. and Fernández-Carrión et al., who reported 39% and 50% WS, respectively, in children receiving prolonged sedoanalgesics.[1,2] Variability in WS incidence across studies is attributable to differences in assessment tools, diagnostic criteria, and patient populations. The Withdrawal Assessment Tool-1 (WAT-1) used in the present study has been validated for both opioids and benzodiazepines, offering high sensitivity (87%) and specificity (88%).[3]

This study found that the risk of WS increased significantly with longer sedation durations and higher sedoanalgesic doses. Among children receiving sedation for more than seven days, 90% developed WS, compared to 59% for those sedated for six to seven days and no WS for sedation lasting less than three days. Similarly, Araújo et al. observed WS in 100% of children sedated for more than seven days.[1] The median doses of midazolam (3 µg/kg/min) and fentanyl (1.5 µg/kg/min) among WS cases were significantly higher than those in non-WS cases, corroborating previous findings.[4,5]

The majority of WS cases were observed in younger children, particularly those aged 1–12 months. This trend is consistent with reports suggesting that younger age groups may be more vulnerable to developing WS due to immature metabolic and neurological systems.[6] Additionally, most participants in the study weighed less than 10 kg, emphasizing the need for careful dosing in this population to minimize WS risk.

Central nervous system disorders were the leading indication for sedation in this study, accounting for 38% of cases, followed by respiratory system involvement (27%) and sepsis (12%). This differs from Fernández-Carrión et al., who reported respiratory system disorders as the most common indication.[2] Variations in PICU admission patterns and disease burden across regions may explain these differences.

The study identified a significant association between WS and reintubation rates, with 91.5% of reintubated children exhibiting WS. The primary causes of reintubation were poor sensorium (45.7%) and respiratory failure (15.3%). These findings underscore the adverse impact of WS on clinical outcomes, which aligns with studies highlighting the complications of WS in critical care settings.[7,8]

Clonidine was the primary treatment for WS in this study, showing symptomatic improvement in all affected children. Other studies have reported the effectiveness of methadone, lorazepam, and clonidine in managing WS, depending on the drug involved and patient characteristics.[9,10] A tailored approach to WS management, incorporating sedation weaning protocols, is essential to mitigate risks.

The findings of this study are comparable to those of international research. For example, Franck et al. reported an 85% incidence of WS in a pediatric cohort using the SBOWC tool.[11] However, differences in sedation protocols, monitoring practices, and healthcare infrastructure highlight the importance of regional data to guide local PICU protocols.[12]

This study has limitations, including the lack of quantification of intermittent sedation boluses and the inability to correlate WS with the length of PICU stay due to early transfers to step-down units. Future studies should address these gaps and explore preventive strategies, such as standardized sedation

protocols and early mobilization, to reduce WS incidence.[13-15]

CONCLUSION

The high incidence of WS in children receiving IV sedoanalgesia underscores the need for careful monitoring and individualized sedation practices in PICUs. Prolonged sedation and higher drug doses are significant risk factors. Early identification and intervention using tools like WAT-1 and evidence-based management strategies, including the use of clonidine, are critical for improving patient outcomes.

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