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RISK FACTORS LINKED TO IATROGENIC WITHDRAWAL AND ITS MANAGEMENT IN PEDIATRIC CRITICAL CARE PATIENTS

Beny Margrat, Suwitha, Aswathy Gopi, A. Priya and K. Arun Chander Yadav *

Department of Clinical Pharmacology, Apollo Children's Hospital, Chennai - 600006, Tamil Nadu, India.

Keywords:

Iatrogenic withdrawal syndrome, Sedatives, Paediatrics, Risk factors, WAT-1, RASS

Correspondence to Author:
Dr. K. Arun Chander Yadav

DGM-HOD & Consultant, Department of Clinical Pharmacology, Apollo Children's Hospital, Chennai - 600006, Tamil Nadu, India.

E-mail: drarunchander_k@apollohospitals.com

ABSTRACT: In paediatric critical care settings, the use of sedatives is common for managing pain, agitation and anxiety. However, prolonged administration of sedatives can lead to iatrogenic withdrawal syndrome, posing significant challenges in patient care. This study investigates the risk factors associated with iatrogenic withdrawal syndrome in paediatric critical care patients and explores effective management strategies through analysis of clinical data, type of sedative used for underlying medical condition, exposure of sedation, number of sedatives used, RASS (Richmond Agitation Sedation Scale) and (withdrawal assessment tool) WAT-1 score. Our study reveals that infants and males are more prone to IWS. Most patient produced with tachycardia and gave clonidine as treatment plan. We also did comparison between patient produced with IWS and no IWS. By understanding the risk factors and implementing evidence-based management strategies, healthcare providers can optimize the care of paediatric critical care patients and minimize the occurrence and impact of iatrogenic withdrawal syndrome.

INTRODUCTION: Ensuring quality care for critically ill patients requires appropriate drug therapy. The complex nature of these patients often leads to off-label drug use and individualized regimens. This can increase the risk of Adverse Drug Events, dependence, and tolerance, especially with sedatives, which can prolong hospital stays [1]. In the ICU, analgesics and sedatives are the most commonly used drugs to manage pain and sedation. Sedation is crucial for critically ill children, who often receive opioids and sedatives in the ICU to manage pain, anxiety, and facilitate mechanical ventilation [2]. Analgosedation aims to minimize exposure to multiple drug classes and avoid polypharmacy side effects [3].

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Prolonged use of opioids and sedatives during mechanical ventilation can increase the risk of delirium, potentially due to iatrogenic withdrawal syndrome [4]. Iatrogenic withdrawal can occur when medications are abruptly discontinued or tapered in the hospital setting, especially in patients with altered mental status [5]. Withdrawal syndrome, also known as discontinuation syndrome, can happen when individuals dependent on a substance reduce the use of the substance or stops its use. This syndrome can occur with various substances, including alcohol, illicit drugs, and prescription medications [6].

Limited suggestions exist regarding the medications suitable for sedation and pain relief in paediatric patients in critical condition. In clinical practice of Paediatric ICUs, the most commonly used pharmacological agents are opioids and benzodiazepines, being fentanyl the analgesic of choice, followed by paracetamol and metamizole as sedative, midazolam, followed by lorazepam, ketamine, and propofol.

The advantages of both pharmacological classes of medications for critically ill patients are clear, however, they can also lead to tolerance and physical dependence, resulting in the need for increased doses and extended infusions to uphold the intended outcomes and prevent withdrawal symptoms [7].

Opioid withdrawal was first recognized in neonates secondary to maternal drug addiction in 1969 and was later defined as neonatal abstinence syndrome. Opioid withdrawal gives rise to a distinct syndrome that can bear similarities to viral illness. The syndrome is characterized by rhinorrhoea, sneezing, yawning, lacrimation, abdominal cramping, leg cramping, pilo-erection, nausea, vomiting, diarrhoea, mydriasis, myalgia's and arthralgias [2]. In 1989, benzodiazepine withdrawal was first identified in children who required prolonged midazolam sedation in order to tolerate mechanical ventilation [8].

Discontinuing benzodiazepines, barbiturates, and other sedatives or hypnotics after long-term use can lead to symptoms similar to alcohol withdrawal syndrome. Sedative-hypnotic withdrawal syndrome is characterized by significant psychomotor and autonomic dysfunctions [6]. The withdrawal syndrome consists of three main categories of symptoms: overstimulation of the central nervous system (CNS), autonomic dysregulation, and gastrointestinal symptoms. Understanding the pharmacology of sedatives helps in choosing the right medications to manage withdrawal symptoms. It's also important in considering that critical illness can affect the pharmacokinetics of sedatives and analgesics used. The absence of a validated diagnostic and assessment scale for IWS in paediatric patients complicates the evaluation of treatment effectiveness, potentially leading to incorrect conclusions [7].

Clonidine seems to be a safe and effective option for adjunctive sedation to aid in dexmedetomidine weaning and for treating DWS [9]. Clonidine has been used off-label in the paediatric intensive care unit (PICU) and neonatal intensive care unit (NICU) for various purposes, such as sedation, analgesia, drug withdrawal, and neonatal abstinence syndrome [10]. Clonidine has shown effectiveness in alleviating withdrawal symptoms from sedoanalgesia [7]. The primary approach to treating IWS involves gradual weaning, recognizing withdrawal symptoms, and providing rescue therapy [10]. Short-acting continuous infusions of sedative and/or analgesic drugs are switched to long-acting agents, preferably given orally [8].

Additional doses of the suspected drug causing symptoms may be needed, along with adjustments to the weaning plan [11]. Close monitoring of the child's vital signs, fluid balance, and nutritional status is essential during the treatment of iatrogenic withdrawal syndrome. Regular assessments and modifications to the treatment plan may be required to ensure optimal symptom management.

Aim: The aim of the study is to assess the risk factors associated with IWS& treatment plans

Objective: The primary objective of this study is to identify the key risk factors associated with withdrawal syndrome in paediatric patients due to sedatives. Additionally, we aim to explore the efficacy of various treatment strategies for alleviating withdrawal symptoms.

METHODS:

Study Design: We conducted a prospective observational study, enrolling paediatric patients admitted to the intensive care units of our esteemed children's hospital.

Study Location: The study was meticulously carried out at the Apollo Children Hospital Inpatient Department, situated in the vibrant city of Chennai, Tamil Nadu. This multi-specialty hospital boasts 80 luxurious beds and is nestled in the heart of urban South India.

Study Duration: The study spanned a period of six months, commencing in August 2023 and concluding in January 2024.

Study Population: We meticulously selected and included 100 consecutive paediatric patients who met the stringent inclusion criteria for this study.

Source of Data: To ensure accuracy and reliability, we meticulously collected the data pertaining to this study by thoroughly assessing the patients and their comprehensive case records during follow-up.

Subject Recruitment: Participants are chosen for the study based on specific criteria, including both inclusion and exclusion factors

Inclusion Criteria: All paediatric patients under the age of 17 who require invasive mechanical ventilation and continuous infusions of sedatives for more than 3 days.

Exclusion Criteria: Patients who have undergone dialysis and those with severe nervous system impairment.

Study Procedure: All critical patients requiring invasive mechanical ventilation were initially administered fentanyl in combination with dexmedetomidine or dexmedetomidine alone. However, depending on the sedation level of the patients, ketamine, midazolam, or morphine could be used as alternatives to fentanyl. To gather demographic information, a data collection form was utilized, which included details such as age, gender, any pre-existing medical conditions, all sedative and rescue medications administered, withdrawal symptoms, withdrawal score, and any adverse events experienced during the study. The target sedation level fixed initially was a score of 4, and the sedated patients were regularly assessed using the Richmond Agitation Scale to determine their level of sedation. Once patients were deemed clinically ready, the withdrawal assessment tool (WAT-1) was used to monitor their readiness for weaning off sedation. For patients ready to be weaned off who were on fentanyl, midazolam, ketamine, or morphine infusions are weaned to oral sedation based on physician decision. Switching to oral lorazepam from parenteral midazolam and oral morphine from parenteral fentanyl or morphine. The dosage of parenteral sedative medications was calculated to determine the total daily dose, and then converted to enteral medication based on a specific conversion ratio.

The WAT-1 score was recorded every 12 hours, with continuous monitoring until all sedative medications were discontinued. If the WAT-1 score exceeded 3, the patient was considered to have withdrawal symptoms and a rescue agent was administered.

The enteral sedatives were gradually reduced by 20% each day, while closely monitoring the WAT score. Clonidine was the primary drug therapy used to treat withdrawal symptoms, along with other supportive medications based on the specific symptoms experienced by the patient. The total duration of treatment was documented for each patient.

Statistical Method: We conducted a thorough analysis of the samples, focusing on various aspects such as sedation score, duration of sedation, the number of sedatives administered to patients, and the score of the withdrawal assessment tool. To compare the two groups - patients who developed IWS and those who did not - we expressed the proportion in percentage using a simple calculation method. The outcome measures were reported using median and IQR (Interquartile Range). Microsoft Excel 2010 was utilized to create tables, figures, and graphs for a comprehensive presentation of the data.

RESULT: We carefully evaluated a total of 390 patients who were admitted to the intensive care unit between August 2023 and January 2024. Out of these, 100 patients were selected for the study based on specific eligibility criteria, while the remaining 290 patients were excluded due to various factors. Our focus was primarily on patients who received multiple sedations, as they were crucial for the comparative analysis. The eligible 100 patients were categorized according to their gender, age, duration of sedation, and the number of sedatives they were exposed to.

TABLE 1: AGE AND GENDER WISE CATEGORIZATION

Age Wise	IWS Patient		Non IWS Patient	
	Male	Female	Male	Female
Neonate	2	2	1	0
Infant	16	13	9	8
Toddler (1 To 2yrs)	5	4	5	4
Yearly Childhood (2 To 5 Yrs)	7	3	7	5
Middle Childhood (6 To 11 Yrs)	1	1	1	1
Early Adolescence (12 To 17 Yrs)	1	0	0	4
Total	32	23	23	22

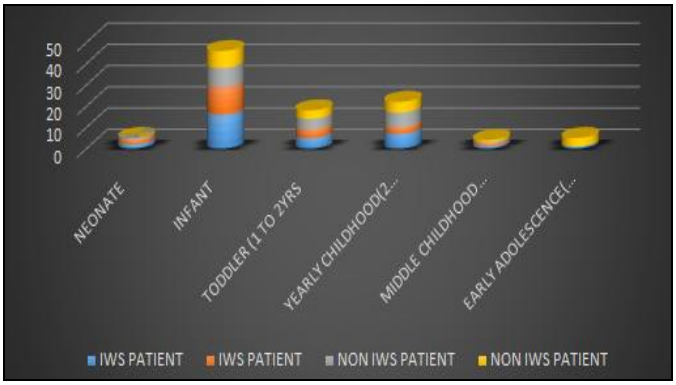

FIG. 1: AGE AND GENDER-WISE DISTRIBUTION OF IWS AND NON-IWS PEDIATRIC PATIENTS

Out of the 100 eligible patients who were screened, 55 (55%) were male children and 45 (45%) were female children. According to the age criteria, infants 29 {63.04%} were more likely to develop IWS syndrome compared to other age groups.

The age range for infants was from 1 to 12 months. When it comes to gender, more males developed IWS compared to females, with 32 (58.18%) male patients and 23 (41.82%) female patients.

TABLE 2: SEDATIVE DRUGS AND SEDATION SCORE

IV Drugs	IWS Patient					Non IWS Patient				
Rass Score	0	-1	-2	-3	-4	0	-1	-2	-3	-4
Dexmedetomidine + Ketamine	0	3	2	2	3	0	2	3	2	0
Dexmedetomidine + Fentanyl	0	4	3	0	0	0	3	4	4	0
Dexmedetomidine + Fentanyl+ Ketamine	0	0	4	10	6	0	6	3	5	0
Dexmedetomidine + Fentanyl+ Midazolam	0	0	0	1	6	0	2	3	2	0
Dexmedetomidine + Fentanyl+ Ketamine+Midazolam	0	0	5	5	1	0	0	0	0	0
Dexmedetomidine	0	0	0	0	0	0	0	2	0	0
Fentanyl	0	0	0	0	0	0	0	4	0	0
Total			55					45		

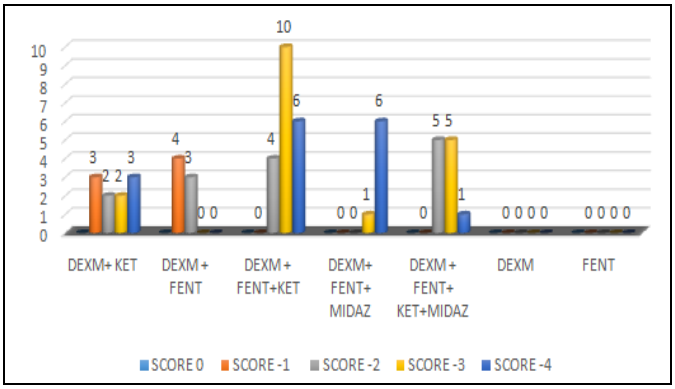

FIG. 2: SEDATIVE DRUGS AND SEDATION SCORE - FOR IWS PATIENT

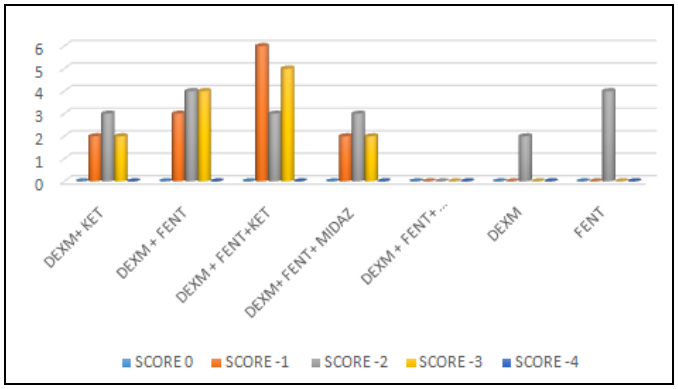

FIG. 3: SEDATIVE DRUGS AND SEDATION SCORE - FOR NON IWS PATIENT

55 out of 100 patients in the study developed IWS. They were all closely monitored for sedation levels using the Richmond Agitation Sedation Scale (RASS). The majority of these patients received sedation with Dexmedetomidine either alone or in combination with other sedatives. Among the 55 patients with IWS, 38 (69.09%) of them underwent more than 3 sedation sessions, with 61.81% (34) of them maintaining a median sedation score greater than -3 during their IV sedation.

TABLE 3: DURATION OF SEDATION

Duration of sedation		
Days	**IWS Patient**	**Non IWS Patient**
3 Days	3	10
4 - 5 Days	11	17
6 - 9 Days	23	12
10 - 20 Days	16	6
>20 Days	2	0
Total	55	45

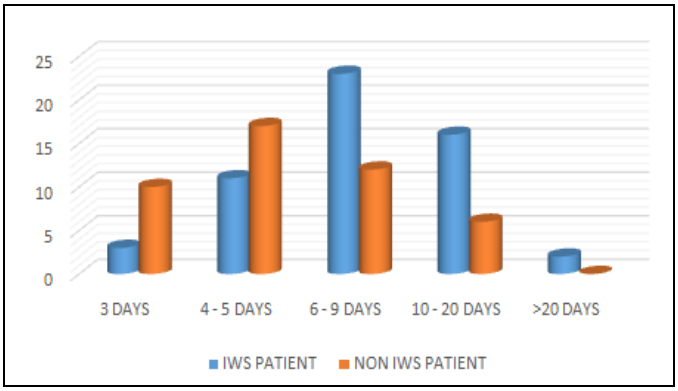

FIG. 4: DURATION OF SEDATON

The results of sedation duration in patients with and without IWS have been analysed. According to the data in **Table 3**, it is clear that patients who developed IWS were exposed to sedatives for a longer period of 6-9 days and above. Out of the 55 patients who developed IWS, 74.55% (41) underwent sedation for more than 5 days, while 25.45% (14) were sedated for less than 5 days. In contrast, in the non-IWS group, 18 patients were sedated for more than 5 days and 27 patients were sedated for less than 5 days.

TABLE 4: WAT SCORE VS NUMBER OF SEDATIVES

Drugs	No of Patients	Wat				
		3	4 To 5	6 To 8	9 To 10	>10
Dexmedetomidine + Fentanyl	7	4	3	0	0	0
Dexmedetomidine + Ketamine	10	6	4	0	0	0
Dexmedetomidine + Fentanyl+ Ketamine	20	3	15	2	0	0
Dexmedetomidine + Fentanyl+ Midazolam	7	0	0	6	1	0
Dexmedetomidine + Fentanyl+ Ketamine+ Midazolam	9	0	0	5	4	0
Dexmedetomidine + Fentanyl+ Ketamine+ Morphine	2	0	0	2	0	0

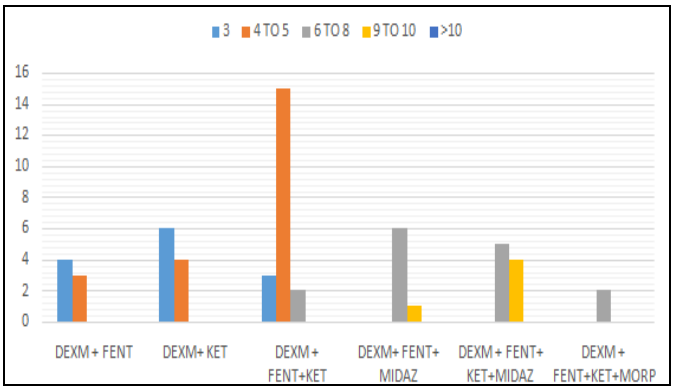

FIG. 5: CORRELATION BETWEEN THE NUMBER OF SEDATIVES

Table 4 provides information on type of sedatives exposed by individuals who developed IWS. It compares the number of sedatives used with the identified WAT Score. The sedative drugs included in the study were fentanyl, ketamine, midazolam, morphine and dexmedetomidine. Patients received either one drug (dexmeditomidine) alone or a combination of sedatives.

The sedatives were changed based on the level of sedation required, with 69% of patients receiving more than two sedative drugs. This means that they switched from fentanyl to ketamine or midazolam or morphine along with dexmeditomidine. Patients who received two sedationdid not have a WAT score above 5. However, patients who received more than two sedative drugs had a score of ≥5 in comparison.

On **Table 5**, it is evident that the number of sedatives exposed by patients with IWS has been compared to the duration of sedation they received. Out of the 55 patients, 74.54% (41) underwent a duration of more than 5 days. Additionally, 70.90% (39) received more than three sedations. The interquartile range indicates that IWS patients exposed to dexmedetomidine, fentanyl, ketamine, and midazolam showed a higher level compared to others.

TABLE 5: NUMBER OF SEDATIVES VS DURATION

Drugs	Duration					
	3 Days	4 - 5 Days	6 - 9 Days	10 - 20 Days	>20 Days	IQR
Dexmedetomidine + Fentanyl	3	4	0	0	0	2
Dexmedetomidine + Ketamine	0	2	8	0	0	3
Dexmedetomidine + Fentanyl+ Ketamine	0	5	6	8	1	5
Dexmedetomidine + Fentanyl+ Midazolam	0	0	2	5	0	3
Dexmedetomidine + Fentanyl+ Ketamine+ Midazolam	0	0	5	3	1	11
Dexmedetomidine + Fentanyl+ Ketamine+ Morphine	0	0	2	0	0	0

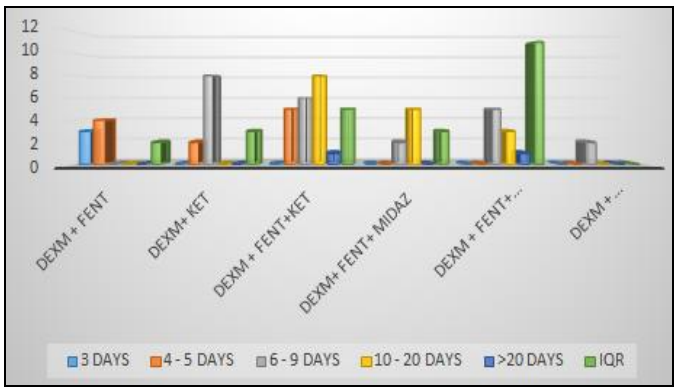

FIG. 6: NUMBER OF SEDATION VS DURATION

From parenteral to oral drug weaning, the oral drugs used were lorazepam, and morphine. The patients were weaned based on the WAT score, either with a combination of lorazepam and morphine or alone. All IWS patients received oral sedatives for weaning, while only a few non-IWS patients received oral weaning rather every other's oral weaned to the lowest doses of parenteral drugs and get stopped. All IWS patients were treated with tablet clonidine at a dose of 5mcg/kg/dose, along with other supportive treatments such as haloperidol and olanzapine, ondansetron, domperidone, acetaminophen *etc*.

DISCUSSION: Limited information is available regarding the incidence and risk factors for sedation withdrawal in paediatric ICU patients [12]. The duration and number of sedationsa patient need can be unpredictable due to various factors. However, achieving optimal sedation and analgesia in children can be challenging. In fact, only 60% of patients are able to achieve the needed sedations by the regular drug used and other patients require higher doses and additional boluses. Over-sedation can also lead to tolerance, withdrawal, and delirium. Prolonged use of sedatives and increased dosages can significantly increase the risk of withdrawal symptoms in children [13]. Commonly used sedatives in the ICU include benzodiazepines like midazolam and lorazepam, as well as propofol and dexmedetomidine [14].

In our study, we utilized fentanyl, midazolam, ketamine, morphine and dexmedetomidine as intravenous sedatives. Fentanyl and dexmedetomidine were our initial choices, as they have been found to be effective and safe in previous studies. We also used ketamine in situation of difficult analgesia or sedation, considering its safety profile. Which has been proved in the study of amigoni *et al.* Dexmedetomidine has gained popularity due to its ability to provide sedation without causing respiratory depression and due to its specific action in the locus coeruleus and avoidance of GABA activation [8]. For enteral substitutes of intravenous fentanyl and midazolam, we opted for morphine and lorazepam respectively based on recommendations from Habib E *et al.* RASS (Richmond agitation sedation scale) was the standard sedation scale used in our hospital, and we aimed for a target score of -4. Sedatives were adjusted according to the sedation score and monitored on an hourly basis. The Richmond agitation-sedation scale was also used, with more negative scores indicating deeper sedation and more positive scores indicating increasing agitation. A score of 0 represented a state of calm and normal alertness [14].

In the early part of 2017, two extensive studies were conducted to examine the risk factors for withdrawal using the WAT-1 (withdrawal assessment tool) [8]. The WAT-1 is an 11-item (12-point) assessment tool that includes various components such as reviewing the patient's record, observing the patient directly, assessing their level of consciousness, and evaluating their recovery after stimulation [15]. The scores on this assessment range from 0 to 12, with a score of ≥3 indicating the presence of signs or symptoms of IWS.

Interestingly, the incidence of IWS was found to be nearly 100% in patients who received sedative medication for more than 9 days as proved by Tiacharoen D *et al.*[16] On the other hand our study reported that, 75% of patients who received more than two sedatives experienced IWS and the remaining 25% who received less than two sedatives did not have any signs of IWS. As per the official definition of wat-1, the severity of IWS increases with higher scores [12]. Some reviews have suggested that drugs like clonidine, dexmedetomidine, or methadone could potentially reduce the severity of IWS in paediatric patients. However, Barbara Geven *et al* proposed that dexmedetomidine did not have a preventive effect on the development of IWS [17]. This finding aligns with similar studies conducted previously and proved parallel to our results.

Furthermore, it has been proposed that the lack of a standardized weaning protocol for withdrawal assessment may contribute to the variability in IWS treatment [12]. Fewer studies specifically analysed clonidine as a pharmacological treatment for IWS associated with continuous and prolonged infusion of benzodiazepines and opioids [7]. Overall, these studies shed light on the risk factors and potential treatments for IWS, providing valuable insights for healthcare professionals in managing this condition.

In the review of avila *et al* it is found that clonidine was effective in reducing withdrawal symptoms from sedoanalgesia [7]. Which was the main drug used in our study for treating IWS, along with other supportive medications based on symptoms and standardized practices. The more commonly experienced symptoms by our study participants are fever, vomiting, diarrhoea, tremor, tachycardia, agitation, delirium and restlessness. However, it is important to note that clear guidelines are crucial missing steps in weaning. Implementing a proper weaning protocol can significantly decrease the prevalence of IWS. It has also been suggested that a tapering rate of 10 to 20% per day is more promising. Tiacharoen *et al* proposed 20% daily tapering rate based on the WAT score that align parallel in our study [16]. Unlike other studies none of our patients were discharged home on opioids [13].

Duration of therapy and cumulative doses are the major risk factors of IWS suggested by kaitlin *et al*.[18] But according to our study no patients in our study group received cumulative doses, the target sedation is achieved through altering the drugs and administration of additional boluses. There is less evidence for relationships with age, criticality, sedation/weaning protocols, and sedation/IWS assessment. While our study reports that male patients are greater exposed and infants developed IWS majorly. We found that the major risk factor for IWS in our study was the longer duration of sedatives, especially when more than two sedatives were used which has also been proposed in other studies. Mette Dokken *et al* study stated that Symptoms such as agitation/restlessness and sleep disturbance were the most common reasons for additional doses of bolus medications, in which tachycardia was the most frequent sign. Our study participants also experienced symptoms like tremor, tachycardia and restlessness. The most commonly used bolus medications were fentanyl and ketamine [19]. To avoid the use of unnecessary opioid sedatives in discharge, melatonin and promethazine were used for patients experiencing sleeplessness upon discharge. Hallucinations were more frequently observed in benzodiazepine withdrawal [16]. We treated two patients with hallucinations using haloperidol and olanzapine for restlessness in three patients, other supporting drugs like domperidone and ondansetron for vomiting, loose stools and acetaminophen for fever where used. Clonidine was the major drug used in all IWS patients which seems effective in managing withdrawal symptoms as proved by Avilaalzate *et al* and few other studies.

CONCLUSION: Our research reveals that iatrogenic withdrawal can be impacted by a multitude of factors, including the complexity of surgical procedures, the gravity of the ailment, and the prolonged administration of multiple sedatives. Our findings demonstrate that infants are especially susceptible to IWS, additionally we also found that patient undergone moderate to deeper sedation developed greater number of IWS comparatively. Clonidine has exhibited remarkable efficacy in averting, mitigating, and diminishing the intensity of withdrawal symptoms induced by opioids, benzodiazepines, and dexmedetomidine. The symptoms of IWS are vague. In our investigation, we identified restlessness, tremor, agitation, delirium, vomiting, loose stools, and fever as the key indicators. We observed some symptoms overlapping. None of the patients were administered cumulative doses, which is a significant risk factor for IWS according to various studies. Our research also revealed that dexmedetomidine did not have a preventive effect on IWS development.

Limitations:

- Further prospective research studies are required to determine the appropriate treatment for IWS.
- Research on incorporating tapering protocols is essential.
- The literature on analgesia and sedation studies is limited.

- There is a need for research to develop guidelines on sedation.

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Ethical Committee Approval: Nil

CONFLICTS OF INTEREST: There are no Conflicts of Interest

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