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Withdrawal syndrome to sedatives and analgesics in the pediatric ICU

Tassiana Bonifácio de Oliveira[1*], Paula Yuri Sugishita Kanikadan[2]

[1]Program "Emergencies and Intensivism in Neonatology and Pediatrics" of the Santo Amaro University - UNISA, São Paulo/SP, Brazil.
[2]Medicine of the Santo Amaro University - UNISA, São Paulo/SP, Brazil.

ABSTRACT

OBJECTIVE

This study aims to identify the prevalence of withdrawal syndrome in children after the use of sedatives and analgesics, the associated factors, and the role of the clinical pharmacist.

METHODS

An observational, cross-sectional, retrospective, descriptive study was conducted, with a quantitative approach, through convenience sampling and secondary data analysis. Through consultation in electronic medical records of children admitted to the pediatric intensive care unit of a teaching hospital in the south of São Paulo, between April 2022 and April 2023, who required sedative and analgesic therapy, hospitalized for a period longer than 24 hours.

RESULTS

The withdrawal syndrome occurred in 65% of the hospitalized patients, most of whom were in the age group between 0 and 12 months (69.23%), who used the opioid analgesic fentanyl (65.38%), and the association of midazolam, ketamine and dexmedetomidine (42.31%) as sedation drugs. All patients used methadone and lorazepam for weaning (57.69%). It was observed that patients diagnosed with withdrawal syndrome were those who used sedatives and analgesics for a longer period (mean of 13 days) and remained in the PICU for the longest number of days, mean of 18.3 days.

CONCLUSION

Discussions of monitoring and prevention strategies, constant reevaluation of the pharmacotherapy used for sedation and analgesia, and more active participation of the clinical pharmacist for the adequate management of the use of these drugs are necessary.

DESCRIPTORS

Withdrawal Syndrome, Pediatric Intensive Care Unit, Sedatives, Analgesics, Clinical Pharmacist.

Corresponding author:
Tassiana Bonifácio de Oliveira.
Multidisciplinary Residency Program at Santo Amaro University – UNISA/Campus Subway Adolfo Pinheiro - Rua Isabel Schmidt, 349 – ZIPCODE: 04743-030 - Santo Amaro - São Paulo - SP.
Email: tassioliver30@gmail.com
ORCID ID: http://orcid.org/0009-0004-5492-576X

INTRODUCTION

Sedative drugs and opioid analgesics are necessary during the care of patients admitted to the pediatric intensive care unit (PICU), due to the invasive and painful procedures inherent to the patient's state of severity to minimize discomfort, stress, anxiety, and agitation[1-3]. The combination of drugs from different pharmaceutical classes is justified by the synergistic effect that allows the reduction of the doses of both and, thus, a reduction in the damage caused by excessive sedation and[4].

Although essential, undesirable effects resulting from the continuous use of these drugs can be observed because of the cumulative effects they have. The excessive use of analgesic agents and sedatives, in addition to leading to an increase in the duration of mechanical ventilation in days, and a prolonged stay in the intensive care unit, can lead the patient to develop the withdrawal syndrome (WS)[5].

The WS consists of the set of signs and/or symptoms that manifest when administration of an opioid sedative and/or analgesic agent is discontinued or abruptly reduced in patients who have physical tolerance after prolonged exposure or high doses. The manifestations are variable, the most common being: tachypnea, nausea, vomiting, diarrhea, sweating, tachycardia, mydriasis, tremors, exalted reflexes, hypertonicity[6].

The importance of weaning off these drugs rather than abruptly stopping them is well defined. However, even in studies with established weaning protocols, reported cases of AS range from 5 to 87% of hospitalized children[7].

The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies published guidelines in 2022 recommending that patients undergoing sedatives and analgesics should be constantly monitored and assessed for pain, agitation, and withdrawal scales, and suggest strategies to minimize exposure to sedation whenever possible[5].

Health services must provide tools to accurately assess withdrawal symptoms in their patients, and professionals involved in care need to fully understand the management of sedation and analgesia, tolerance, and weaning[8].

Since the multidisciplinary team is essential for the management of sedation analgesia, the clinical pharmacist in a critical care unit plays a key role in optimizing drug therapy, identifying drug-related adverse events, daily monitoring of patients at risk, and interacting with the multidisciplinary team about potential problems involving drugs[9,10].

The present article aims to identify the prevalence of cases of withdrawal syndrome, as well as to describe the factors that may contribute to the development of this syndrome in children undergoing sedation and analgesia admitted to the pediatric intensive care unit, in addition to identifying the role of the clinical pharmacist in this context.

METHODS

The present study is cross-sectional, retrospective, descriptive, using convenience sampling, through the analysis of medical records of children admitted to the Pediatric Intensive Care Unit (PICU) of a general teaching hospital in the south of São Paulo, Brazil. For this, 40 medical records of children admitted to the PICU in the period from April 2022 to April 2023, aged between 1 (one) day and 12 (twelve) years, using sedative and analgesic drugs, for more than 24 hours, if they required orotracheal intubation, drugs used for sedation and analgesia, treatment time, and the use of drugs for treatment or prevention of withdrawal syndrome. In addition, the clinical pharmacist's records present in the electronic medical records were analyzed, indicating the need for some intervention on his part after the analysis of the prescriptions of the sedatives and analgesics drugs, such as: need for dose adjustment, monitoring of treatment time, adequacy of weaning drugs, etc.

After data collection, the data were organized in a Microsoft Excel® spreadsheet. We analyzed which drugs for sedation were used, if they were used in combination, as well as the drugs used for analgesia. The time of beginning and end of treatment was also considered, in addition to the use of weaning drugs. It was observed which scale for the analysis of sedation and abstinence was described by the responsible professional and, finally, if the patient was diagnosed with withdrawal syndrome. The date of admission to the PICU and the date of discharge were the factors considered for the calculation of the length of stay in the PICU.

This research followed the rules related to Resolutions No. 466/2012 and No. 510/2016 and was approved by the Ethics Committee on Research Involving Human Beings of the Santo Amaro University No. 356/2023 and the General Hospital of Grajaú No. 6,576,159.

RESULTS AND DISCUSSION

The use of sedative drugs and analgesics by continuous infusion has the advantage of titration of doses, i.e., ease of adjustment according to the observed need, providing physical and psychological comfort to patients. On the other hand, they increase the risk of excessive sedation that can compromise the effectiveness of therapy, prolonging recovery time, causing tolerance and promoting the development of withdrawal syndrome[11,12].

A total of 40 patients were included in this study. As shown in Table 1, admissions were characterized by a higher frequency of males, representing 62.50%. As far as we have researched, most of the patients in our sample fall into the age group of 0 to 12 months of age, which corresponds to 75%. And 52.5% were born full-term, i.e., born between 37 and 42 weeks. Respiratory disorders were the most common admission diagnosis (95%). All patients required orotracheal intubation (OTI).

Table 1. Demographic and clinical characteristics of the patients participating in the study (n= 40).

Admission Information	n	%
Sex		
Male	25	62,5
Female	15	37,5
Age		
0 to 12 months	28	75
> 1 to 5 years	11	22,5
> 5 years	1	2,5
Born		
Preterm	11	27,5
Term	21	52,5
N/D*	8	20
Reason for admission to the PICU		
Respiratory Disorders	38	95
Others	2	5
OTI*		
Yes	40	100

*OTI: orotracheal intubation; *N/D: no data. n: absolute frequency, %: frequency relative. Source: The author.

The main result of the present study is a prevalence of withdrawal syndrome of 65%. However, 30% of these patients received the diagnosis only after discharge from the ICU and admission to the ward. The highest concentration is present in the age group between 0 and 12 months (69.23%).

Analgesics

Patients diagnosed with withdrawal syndrome used exclusively the opioid fentanyl, representing 65.38% of our sample, as shown in Table 2.

Table 2. Drugs of choice for analgesia, patients with WS.

Analgesics	n	%
Opioids		
Fentanyl	17	65,38
Fentanyl and morphine	4	15,38
Others		
Dipyrone	5	19,24
	26	**100**

n: absolute frequency, %: frequency relative. Source: The author.

Sedatives

The drugs of choice for sedation, as described in Table 3, were the combination of the following drugs: midazolam, dexmedetomidine and ketamine, which was equivalent to 42.31%.

Table 3. Drugs of choice for sedation, cases diagnosed with WS.

Sedatives used in combination	n	%
Midazolam, dexmedetomidine e ketamine	11	42,31
Midazolam, dexmedetomidine, ketamine e rocuronium	5	19,23
Midazolam, dexmedetomidine e rocuronium	4	15,38
Midazolam e dexmedetomidine	3	11,53
Midazolam e ketamine	1	3,85
Midazolam, ketamine e rocuronium	1	3,85
Midazolam, dexmedetomidine, ketamine e propofol	1	3,85
	26	**100**

n: absolute frequency, %: frequency relative. Source: The author.

In our sample, none of the patients used monotherapy for sedation, i.e., none of the patients were sedated using only one drug. The association of two or more drugs can be useful because it is possible to use smaller doses of each drug and, thus, potentially reduce undesirable effects[13]. All patients used midazolam for sedation. Midazolam is similarly described in other studies as a first-line drug for sedation[14]. We noticed a considerable number of patients who also used dexmedetomidine (DEX), which allows reaching a state of conscious sedation, known as "awakening sedation", i.e., an easier transition between sleep and wakefulness, allowing the patient to be more collaborative and communicative when stimulated[15]. In addition, the sedative effect of DEX is significantly enhanced when a benzodiazepine is used in association with patients requiring intubation and mechanical ventilation[16]. It is considered an effective sedative agent without many side effects compared to benzodiazepines or opioids with the added advantage of reducing the dose of conventional sedatives when used together and of reducing mechanical ventilation time[17-19].

Similarly, we observed that most of the patients used ketamine. Ketamine has bronchodilator effects, so it is the drug of choice in asthmatic patients requiring mechanical ventilation. On the other hand, it is still stigmatized by some doctors due to concerns about psychological side effects, as well as the availability of other sedative and analgesic drugs. From 30 to 50% of patients have signs and symptoms upon awakening. Symptoms include discomfort, hallucinations, vivid dreams, floating sensations, and delirium[20]. On the other hand, rocuronium, a neuromuscular blocker, is used to improve the quality of intubation, avoid asynchrony with the ventilator, risk of psychomotor agitation and cough[21-23].

Weaning

In our study, all patients used weaning drugs. Table 4 shows that 57.69% used lorazepam and methadone. Lorazepam is used orally to replace intravenous midazolam and facilitate the gradual reduction of sedation, as long as the patient's condition allows[24]. Similarly, methadone is used to wean off the painkiller fentanyl. Fentanyl is a drug in the class of opioids and needs weaning. Thus, intravenous fentanyl is replaced by oral methadone as a prevention against opioid withdrawal[25-27]. Oral clonidine was used by 26.92% of the patients to wean themselves off intravenous dexmedetomidine.

Table 4. Drugs of choice for weaning.

Drugs	n	%
Lorazepam and Methadone	15	57,69
Clonidine, Lorazepam, Methadone	7	26,92
Lorazepam	2	7,69
Clorpromazina, Lorazepam and Methadone	1	3,85
Clonidine, Lorazepam	1	3,85
	26	**100**

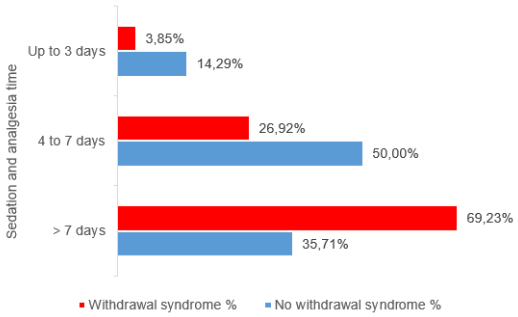
n: absolute frequency, %: frequency relative. Source: The author.

Although the pediatric literature suggests that the gradual reduction of sedative and analgesic drugs can prevent the onset of the withdrawal syndrome, in addition to maintaining the therapy in the ward after ICU discharge, there is no gold standard that recommends specific weaning strategies[28]. In a study published in 2017, the authors suggested a weaning scheme, where patients are classified for risk and abstinence, before weaning is initiated, based on the number of days of infusion[29].

Length of treatment and length of hospital stay

It was noted that the patients who developed the withdrawal syndrome were those who used sedatives and opioid analgesics for a longer period of days, as illustrated in Graph 1.

Graph 1. Comparison of treatment time of patients who developed withdrawal syndrome. Source: The author.



An American retrospective study evaluated the management of medications for sedation, analgesia, and neuromuscular blockade in 161 ICUs between 2009 and 2016 and concluded that the duration of use of opioid analgesics and sedatives may be associated with tolerance and withdrawal complications[30,31]. On the other hand, the length of stay in the PICU was longer, about 18.3 days compared to 6.6 days for patients who had a negative diagnosis for the withdrawal syndrome. In other studies, it has been observed that children who required sedatives or opioid analgesics demonstrated longer hospitalization, prolonged mechanical ventilation, and higher mortality[32].

Sedation and analgesia analysis scales

There are several published scales that assess pain or sedation. In this study, 73.08% of the cases diagnosed with withdrawal syndrome were evaluated using the Richmond Agitation-Sedation Scale (RASS). The RASS is a fast and intuitive scale that uses the duration of eye contact after verbal stimulation as the primary means of titration and sedation. It was developed for adult patients and, although it has not been validated for pediatric patients, many professionals use it[33,34].

In our sample, only one patient was evaluated based on the COMFORT-B scale, which is a scale derived from the COMFORT scale, but more simplified and the most recommended by international guidelines and validated for pediatric and neonatal use[35]. COMFORT-B uses six behavioral items of the patient based on direct observation and detects changes in pain or intensity of suffering[36,37].

Role of the pharmacist

In our study, we did not identify any records of pharmaceutical intervention related to the use of sedative or analgesic medications.

Several published studies indicate that the presence of a clinical pharmacist has a positive impact on patient treatment, including interventions by the clinical pharmacist that played a beneficial role in the management of sedation, in addition to other benefits related to drugs management in an ICU[38-40]. The participation of the clinical pharmacist in an intensive care unit aims to contribute to patient safety through the evaluation and monitoring of the drugs used. The role of the clinical pharmacist is to promote the rational use of drugs, identify and prevent drug-related risks, including analysis of interactions, doses, routes, and times of administration. The implementation of clinical pharmacy has stood out not only from an economic point of view, but also because it is attributed to the reduction of drug-related errors, optimization of use, and prevention of adverse events[41,42].

Thus, the pharmacist can contribute to an adequate management related to sedative and analgesic drugs together with the other members of the team.

Limitations

This study had some limitations. The worsening of the patient's clinical condition according to the length of hospital stay may be an influencing factor. The diversity of variables presents in the study, such as: the therapy chosen for sedation, the scale used to assess pain, and the concomitant use of other medications. Administration of extra doses of sedatives prescribed as "if necessary", and it is not always possible to confirm the administration via medical records. Medical records with scarce data. Interventions by the clinical pharmacist made verbally and not recorded in the medical records.

CONCLUSION

The use of analgesic and sedative drugs in the PICU proved to be a constant practice. The diagnosis of withdrawal syndrome is still a challenge because the signs and symptoms are like the conditions of a patient admitted to an intensive care unit. The lack of standardization in the use of tools to assess the level of sedation may impair the quality of care provided by facilitating the occurrence of adverse events.

Therefore, the use of sedation analgesia should be carefully analyzed to minimize the risks of developing the withdrawal syndrome. It is necessary to discuss monitoring and prevention strategies, standardization of processes, constant reevaluation of the pharmacotherapy used, and more active participation of the clinical pharmacist.

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