ISSN: 2977-6147

Research Article

Open Access Journal of Clinical Images

Clinical Characteristics of Patients with Iatrogenic Withdrawal Syndrome Aged 1 Month to 17 Years

Vallejos-Mita Gloria Martha[1*], Velasco-Pérez Georgina[2] and Duarte-Castro Angelica[2]

[1]*Pediatric Pain Medicine Resident Physician, National Institute of Pediatrics, Mexico City*

[2]*Pediatric Pain Specialist, Pain Clinic, National Institute of Pediatrics, Mexico City*

[*]**Corresponding author**

Vallejos-Mita Gloria Martha, Pediatric Pain Medicine Resident Physician, National Institute of Pediatrics, Mexico City.
ORCID: https://orcid.org/my-orcid?orcid=0009-0008-5556-9874

Received: November 24, 2025; **Accepted:** December 01, 2025; **Published:** December 09, 2025

ABSTRACT

Introduction: Sedoanalgesia aims to relieve anxiety, agitation, and pain, where prolonged use and high doses of opioids and benzodiazepines can cause dependence, tolerance, and withdrawal, thereby prolonging hospital stay and increasing costs for the healthcare system. The incidence of iatrogenic withdrawal síndrome (IWS) in pediatric patients is approximately 57%-64.6% (frequently associated with fentanyl and midazolam), so it is important to identify and adequately manage the clinical features associated with this syndrome. It can be identified and assessed using validated scales in the pediatric population. The question of how to prevent and treat it remains uncertain.

To date, there is no updated data on IWS in pediatrics in general, except in neonates. The findings of this research aim to establish a knowledge base that could facilitate the creation of clinical guidelines and promote continuous improvement in pediatric care.

Objective: To describe the clinical manifestations of iatrogenic withdrawal syndrome as well as the dose and administration time of fentanyl and midazolam in patients aged one month to 17 years at the National Institute of Pediatrics from January 2022 to December 2023.

Materials and Methods: An observational, cross-sectional, retrospective, and descriptive study with non-probabilistic, non-random, convenience sampling was conducted with patients aged 1 month to 17 years with iatrogenic withdrawal syndrome from January 2022 to December 2023. Data were collected in Excel 2020 and exported to SPSS version 21 for statistical analysis, using descriptive statistics to present demographic characteristics, drugs, dosages, administration time, and rating scale scores applied by the treating service and pain clinic that led to the diagnosis of iatrogenic withdrawal syndrome.

Results: There were 46 cases of iatrogenic withdrawal syndrome, 21 female patients (45.7%) and 25 male patients (54.3%), mostly aged 1 to 6 months (47.8%), assessed by pediatric pain specialists using the SOS scale with 27 patients (58.7%) and WAT-1 with 19 patients (41.3%). The most frequent clinical manifestations were irritability (100%), which occurred mostly with withdrawal or dose reduction of fentanyl (54.3%), followed by midazolam and buprenorphine (each 15.2%).

Keywords: Abstinence in Pediatrics, Iatrogenic Withdrawal, Clinical Characteristics of Pediatric Withdrawal Syndrome

Introduction

Sedoanalgesia aims to relieve the anxiety, agitation, and pain caused by illness and procedures, as well as to maintain invasive devices and mechanical ventilation [1,2]. Prolonged use and high doses of opioids and benzodiazepines can lead to dependence, tolerance, and withdrawal, resulting in longer hospital stays and higher costs for the healthcare system [3,4].

Pain should be recognized and treated due to the consequences of physiological and pathophysiological changes (increased endogenous catecholamines with vasoconstriction, impaired tissue perfusion, hypercatabolism, lipolysis, hyperglycemia, and higher risk of infections [4,5]. The intensity of the pain determines the choice of drug [6]. In the pediatric intensive care unit, major opioids are the first choice for managing moderate to severe pain [7]. Major opioids supported by minor analgesics (paracetamol and non-steroidal anti-inflammatory drugs) can facilitate recovery [8,9].

Citation: Vallejos-Mita Gloria Martha, Velasco-Pérez Georgina, Duarte-Castro Angelica. Clinical Characteristics of Patients with Iatrogenic Withdrawal Syndrome Aged 1 Month to 17 Years. Open Access J Clin Images. 2025. 2(4): 1-10. DOI: doi.org/10.61440/OAJCI.2025.v2.27

To avoid excessive sedation, the level of sedation should be frequently assessed. In 1992, Ambuel et al. developed the COMFORT Behaviour scale to evaluate sedation in ventilated patients, recommended for the assessment and management of sedation in pediatrics, applied every 4-8 hours (level of evidence A) [10].

Continuous use of sedoanalgesic drugs can cause: Tolerance, which is characterized by the need to progressively increase the dose of a drug to achieve the same effect. Physical dependence, a physiological condition with functional organic changes after prolonged use and abrupt discontinuation of its administration or administration of an antagonist. Withdrawal syndrome, a set of signs and symptoms resulting from physical dependence on a specific drug when it is abruptly stopped or reduced, which ceases when it is administered again [11,12].

Since 1990, iatrogenic withdrawal syndrome (IWS) has been identified as a complication of prolonged or high-dose sedoanalgesia, first described in newborns [13]. Especially in relation to opioids and benzodiazepines, abrupt or rapid discontinuation can cause signs and symptoms of dependence [14]. It is a multisystem disorder that is difficult to diagnose since it presents symptoms and signs that could be caused by other conditions (pain, inadequate sedation, delirium), making it a diagnosis of exclusión [15].

This syndrome can complicate medical treatment, cause distress to patients and their families, prolong recovery and hospital stay, which is why prevention becomes important to reduce healthcare costs [16].

The incidence of IWS in pediatric patients is high, approximately 57%-64.6%.8 Caused by benzodiazepines in 17%-35%, by opioids around 57%, and 77% when receiving both, >50% in patients who receive infusions for more than 24 hours, increasing to 80%-100% after 5 days [11].

Pediatric patients usually show symptoms within the first 24 hours after stopping the infusion; however, this time depends on the drug, taking into account its pharmacokinetics and pharmacodynamics [9].

The IWS is characterized by autonomic dysregulation and central nervous system excitation; at the respiratory level (tachycardia, nasal flaring), at the gastrointestinal level (nausea, vomiting, diarrhea, hyperphagia), at the nervous system level (irritability, fever, sweating, tachycardia, mydriasis, sleep disturbances), and at the motor level (tremors, abnormal movements, hyperreflexia, hypertonia) [15,16].

There is a higher risk with synthetic opioids or short half-life opioids, accumulated doses (midazolam ≥40 mg/kg or 300-400 mcg/kg/h and fentanyl ≥0.48 mg/kg or 5 mcg/kg/h), due to the duration of continuous infusion with low risk being <5 days, moderate ≥5-7 days, high >7 days, and very high risk >30 days [13,14]. The smaller the child, the greater the vulnerability; depending on the severity of the disease, neurological conditions such as brain damage, cognitive and functional impairment are also associated with a higher risk; in patients with renal failure, accumulation can occur, leading to a higher risk; other studies have identified markers associated with better responses to IWS treatment, such as COMT and 118A>G AG/GG [17,18]. Other risk factors are dependent on the healthcare system, including the lack of training and experience of healthcare personnel, the small number of protocols and sedation-analgesia withdrawal plans, the absence of an interdisciplinary team, and others, which increase the incidence of ICU-acquired infections [18,19].

For assessment and diagnosis, there are different validated scales in the pediatric population, where the Withdrawal Assessment Tool (WAT-1) and the Sophia Observation Scale (SOS) have high sensitivity and specificity [7,8].

The Finnegan scale, created in 1975 to assess withdrawal symptoms in newborns with prenatal exposure to drugs, has only been validated in this population. WAT-1, created in 2008, was specifically designed to evaluate this syndrome in pediatric patients [19,20]. Franck and colleagues suggest that WAT-1 better detects the clinical signs of opioid withdrawal, while SOS does so for benzodiazepines [21,22]. WAT-1 was created as a simple, reproducible, and validated tool consisting of 11 items and provides a diagnosis of withdrawal syndrome with a score of ≥ 3 points.23 SOS (sensitivity 83%, specificity 93%, and negative predictive value 98%) is composed of 15 items, and a score of ≥ 4 points guides the diagnosis of withdrawal síndrome [20-23].

The clinical characteristics mentioned originate from an increase in corticotropin, which causes increased stress and hyperphagia; a decrease in dopamine leading to hyperirritability and anxiety; an increase in acetylcholine causing diarrhea, vomiting, yawning, and sneezing; an increase in excitatory receptors resulting in hyperalgesia and allodynia; an increase in norepinephrine leading to hyperthermia, hypertension, tachycardia, and tremor; and a decrease in serotonin causing insomnia and fragmented sleep [24].

There is no consensus on the method of tapering opioids or benzodiazepines, but a gradual reduction has been shown to be safe. If the infusion lasts between 5-8 days, the daily dose can be reduced by 20%; if more than 8 days, reduce by 10%; and in special cases where the patient's condition does not allow for reduction, it could be 5% daily or every other day. On the other hand, if the duration is less than 3 days, it could be discontinued without tapering [14-21].

There is no gold standard for the treatment of IWS; however, currently the basis of management is gradual tapering, which can be supported by replacement with long-acting medications such as lorazepam, methadone, morphine, buprenorphine, or alpha-2 agonists [7-25].

The answer to the question of how to prevent and treat IWS remains uncertain. Several studies suggest the implementation of protocols that include timely recognition of risk factors, use of validated scales, standardized prescriptions, checklists, reminders and care measures, as well as the availability of experts for weaning consultation, which may help reduce morbidity and improve outcomes [17-21].

Existing studies are scarce in the pediatric population, so it is important to identify and properly manage the clinical characteristics associated with this syndrome, which will be

presented in this study. IWS is a health problem frequently associated with the administration of fentanyl and midazolam.

To date, there is no updated data on IWS in pediatric patients in general, other than in neonatal patients, which is why the findings of this research aim to establish a knowledge base that could facilitate the creation of clinical guidelines and promote continuous improvement in pediatric care.

Objective

To describe the clinical manifestations of iatrogenic withdrawal syndrome as well as the dose and administration time of fentanyl and midazolam in patients aged one month to 17 years at the National Institute of Pediatrics from January 2022 to December 2023.

Materials and Methods

An observational, cross-sectional, retrospective, and descriptive study was conducted. Non-probabilistic, non-random, convenience sampling was used, considering patients aged 1 month to 17 years seen in the pain clinic with iatrogenic withdrawal syndrome from January 2022 to December 2023 who met the selection criteria. Medical records were reviewed, data were collected in Excel 2020, and exported to SPSS version 21 for analysis. Both qualitative and quantitative values were measured and analyzed using descriptive statistics, which present the demographic characteristics, medications, doses, duration of administration, and assessment scale scores by the treating service and pain clinic that led to the diagnosis of IWS.

Results

There were 46 cases that met the selection criteria, 21 patients were female (45.7%) and 25 male (54.3%) with ages ranging from 1 month to 17 years, with a predominance in the age group of 1 to 6 months (47.8%), followed by 1 to 3 years (21.7%) and 7 to 11 months (15.2%) (Table 1).

Table 1: Patient's sex

Sex		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Female	21	45.7	45.7	45.7
	Male	25	54.3	54.3	100.0
	Total	46	100.0	100.0	

The assessment scales used by pediatric pain specialists were the SOS scale with 27 patients (58.7%) and WAT-1 with 19 patients (41.3%) (Table 2).

Table 2: Evaluation Scale by algology

Sex		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	SOS	27	58.7	58.7	58.7
	WAT-1	19	41.3	41.3	100.0
	Total	46	100.0	100.0	

The patients who tested positive on the WAT-1 scale mostly had scores of 3 (13 out of 19 patients, 68.4%), with the highest score being 8 for a single patient (Table 3).

Table 3: WAT-1 Score by algology

Sex		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	3 points.	13	28.3	68.4	68.4
	4 points.	4	8.7	21.1	89.5
	6 points.	1	2.2	5.3	94.7
	8 points.	1	2.2	5.3	100.0
	Total	19	41.3	100.0	
Lost	Assessed by SOS	27	58.7		
Total	46	100.0			

In contrast, the patients who tested positive on the SOS scale (score ≥4), totaling 27 patients, had a most frequent score of 4 (14 patients, 51.9%) and a maximum score of 7 for one patient (Table 4).

Table 4: SOS Score by algology

SOS		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	4	14	30.4	51.9	51.9
	5	7	15.2	25.9	77.8

Valid	6	5	10.9	18.5	96.3
	7	1	2.2	3.7	100.0
	Total	27	58.7	100.0	
Lost	Assessed by WAT-1	19	41.3		
Total	46	100.0			

We were able to identify that the clinical manifestations according to the items of both scales that occurred most frequently were: for WAT-1, irritability in 19 patients (100%) and tremors in 12 patients (63.2%) (Table 5). Coinciding with the SOS patients where the most frequent item was irritability in 27 patients (100%), followed by tachycardia in 20 patients (74.1%) (Table 6).

Table 5: WAT-1 Items

Items		Count	Percentage
Diarrhea	Yes	4	21.1%
	No	15	78.9%
Vomiting	Yes	0	0.0%
	No	19	100.0%
Temperature >37.8°C	Yes	3	15.8%
	No	16	84.2%
Irritable	Yes	19	100.0%
	No	0	0.0%
Tremors	Yes	12	63.2%
	No	7	36.8%
Sweating	Yes	11	57.9%
	No	8	42.1%
Abnormal or repetitive movements	Yes	10	52.6%
	No	9	47.4%
Yawning or sneezing	Yes	1	5.3%
	No	18	94.7%
Startles to touch	Yes	4	21.1%
	No	15	78.9%
Increased muscle tone	Yes	4	21.1%
	No	15	78.9%
Recovery after stimulus in minutes	< A 2 minutes	18	94.7%
	2 A 5 minutes	1	5.3%
	> A 5 minutes	0	0.0%

Table 6: SOS items

Items		Count	Percentage
Tachycardia	Yes	20	74.1%
	No	7	25.9%
Tachypnea	Yes	15	55.6%
	No	12	44.4%
Fever 38.4°C	Yes	1	3.7%
	No	26	96.3%
Sweating	Yes	17	63.0%
	No	10	37.0%
Agitation/Irritability	Yes	27	100.0%
	No	0	0.0%
Anxiety	Yes	3	11.1%
	No	24	88.9%
Tremor	Yes	16	59.3%
	No	11	40.7%
Abnormal movements	Yes	6	22.2%
	No	21	77.8%
Hypertonia	Yes	2	7.4%
	No	25	92.6%
Inconsolable crying	Yes	4	14.8%
	No	23	85.2%
Making faces or signs of discomfort	Yes	12	44.4%
	No	15	55.6%
Insomnia	Yes	5	18.5%
	No	22	81.5%
Hallucinations	Yes	0	0.0%
	No	27	100.0%
Vomiting	Yes	0	0.0%
	No	27	100.0%
Diarrhea	Yes	0	0.0%
	No	27	100.0%

It was found that half of the services that consult pain management for IWS did not apply assessment scales, while the other half most frequently used the SOS scale (16 out of 23 patients) (Table 7).

Table 7: Scale used by treating physician

Scale		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Finnegan	2	4.3	4.3	4.3
	WAT-1	5	10.9	10.9	15.2
	SOS	16	34.8	34.8	50.0
	None	23	50.0	50.0	100.0
	Total	46	100.0	100.0	

The service that most frequently requested a consultation for IWS was infectious diseases (30%), followed by the emergency department (17%), the neonatal intensive care unit (10%), the cardiovascular intensive care unit (8%), and the pediatric intensive care unit (8%) (Table 8).

Table 8: Treating service

Treating service		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Infectology	14	30.4	30.4	30.4
	Emergency	8	17.4	17.4	47.8
	NICU*	5	10.9	10.9	58.7
	CVICU**	4	8.7	8.7	67.4
	PICU***	4	8.7	8.7	76.1
	Cardiology	2	4.3	4.3	80.4
	Neumology	2	4.3	4.3	84.8
	Neurology	2	4.3	4.3	89.1
	Intermediate Care	2	4.3	4.3	93.5
	Hematology	1	2.2	2.2	95.7
	Neurosurgery	1	2.2	2.2	97.8
	Oncology	1	2.2	2.2	100.0
	Total	46	100.0	100.0	

*Neonatal intensive care unit.
**Cardiovascular intensive care unit.
***Pediatric intensive care unit.

Most cases of IWS were related to opioids (89.1% of 46 cases), of which 26 patients received fentanyl (63.4% of 41 patients) and 9 patients received buprenorphine (22% of 41 patients) (Table 9), with a maximum fentanyl dose of 6.8 mcg/kg/h in one patient, while most reached 3 mcg/kg/h (9 patients, 34.6% of 26 patients) (Table 10), receiving it for up to 91 days for fentanyl (Table 11) with a cumulative dose of 4.87 mg/kg corresponding to that patient. Most patients (14 of 26) had a cumulative dose ≥0.5 mg/kg (Table 12), considered a risk factor for IWS.

Table 9: Use of opioids

Opioids		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Sufentanil	3	6.5	7.3	7.3
	Morphine	3	6.5	7.3	14.6
	Buprenorphine	9	19.6	22.0	36.6
	Fentanyl	26	56.5	63.4	100.0
	Total	41	89.1	100.0	
Lost	No opioids	5	10.9		
Total	46	100.0			

Table 10: Maximum dose of fentanyl mcg/kg/h

Fentanyl mcg/kg/h		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	6.8	1	2.2	3.8	3.8
	5.0	1	2.2	3.8	7.7
	4.1	1	2.2	3.8	11.5
	4.0	5	10.9	19.2	30.8
	3.5	1	2.2	3.8	34.6
	3.0	9	19.6	34.6	69.2
	2.0	7	15.2	26.9	96.2
	1.7	1	2.2	3.8	100.0
	Total	26	56.5	100.0	
Lost	No fentanyl	20	43.5		
Total	46	100.0			

Table 11: Total days of fentanyl administration

Total, days		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	3	2	4.3	7.7	7.7
	5	3	6.5	11.5	19.2
	8	2	4.3	7.7	26.9
	10	2	4.3	7.7	34.6
	11	3	6.5	11.5	46.2
	12	2	4.3	7.7	53.8
	13	1	2.2	3.8	57.7
	14	1	2.2	3.8	61.5
	15	1	2.2	3.8	65.4
	16	3	6.5	11.5	76.9
	17	1	2.2	3.8	80.8
	21	1	2.2	3.8	84.6
	35	1	2.2	3.8	88.5
	37	1	2.2	3.8	92.3
	45	1	2.2	3.8	96.2
	91	1	2.2	3.8	100.0
	Total	26	56.5	100.0	
Lost	No fentanyl	20	43.5		
Total	46	100.0			

Table 12: Cumulative dose of fentanyl mg/kg

Total, days		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	0.20	4	8.7	15.4	15.4
	0.30	4	8.7	15.4	30.8
	0.35	2	4.3	7.7	38.5
	0.40	2	4.3	7.7	46.2
	0.50	2	4.3	7.7	53.8
	0.59	1	2.2	3.8	57.7
	0.60	3	6.5	11.5	69.2
	0.70	2	4.3	7.7	76.9
	0.80	1	2.2	3.8	80.8
	0.86	1	2.2	3.8	84.6
	0.90	1	2.2	3.8	88.5
	1.70	1	2.2	3.8	92.3
	2.40	1	2.2	3.8	96.2
	4.87	1	2.2	3.8	100.0
	Total	26	56.5	100.0	
Lost	No fentanyl	20	43.5	3.8	100.0
Total	46	100.0	56.5	100.0	

Of the 46 patients, 20 received benzodiazepines (43.5% of the total 46 cases), most with midazolam (16 patients, 80% of 20) and the rest with clonazepam (Table 13), with a maximum dose of 960 mcg/kg/h in one case and a cumulative dose of 824 mg/kg. Half of the cases (8 of 16) had a risk factor since they received doses higher than 300 mcg/kg/h (Table 14). The days of reported maximum dose were 106 in one patient (Table 15). Similarly to fentanyl, the cumulative dose of midazolam considered a risk factor, which most patients received, was ≥43 mg/kg, corresponding to 10 of 16 patients (Table 16).

Table 13: Use of benzodiazepines

Benzodiazepines		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Clonazepam	4	8.7	20.0	20.0
	Midazolam	16	34.8	80.0	100.0
	Total	20	43.5	100.0	
Lost	No benzodiazepines	26	56.5		
Total	46	100.0			

Table 14: Maximum dose of midazolam mcg/kg/h

Midazolam mcg/kg/h		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	100	2	4.3	12.5	12.5
	190	1	2.2	6.3	18.8
	200	4	8.7	25.0	43.8
	235	1	2.2	6.3	50.0
	300	1	2.2	6.3	56.3
	400	2	4.3	12.5	68.8
	526	1	2.2	6.3	75.0
	600	1	2.2	6.3	81.3
	625	1	2.2	6.3	87.5
	650	1	2.2	6.3	93.8
	960	1	2.2	6.3	100.0
	Total	16	34.8	100.0	
Lost	No midazolam	30	65.2		
Total	46	100.0			

Table 15: Total days of midazolam administration

Total days		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	2	1	2.2	6.3	6.3
	5	2	4.3	12.5	18.8
	6	1	2.2	6.3	25.0
	10	2	4.3	12.5	37.5
	11	2	4.3	12.5	50.0
	15	1	2.2	6.3	56.3
	16	1	2.2	6.3	62.5
	19	1	2.2	6.3	68.8
	27	1	2.2	6.3	75.0
	28	2	4.3	12.5	87.5
	99	1	2.2	6.3	93.8
	106	1	2.2	6.3	100.0
	Total	16	34.8	100.0	
Lost	No midazolam	30	65.2		
Total	46	100.0			

Table 16: Accumulated dose of midazolam mg/kg

Midazolam mg/kg		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	8.0	1	2.2	6.3	6.3
	14.0	2	4.3	12.5	18.8
	16.8	2	4.3	12.5	31.3
	25.0	1	2.2	6.3	37.5

Valid	43.0	1	2.2	6.3	43.8
	48.0	1	2.2	6.3	50.0
	54.0	1	2.2	6.3	56.3
	60.0	1	2.2	6.3	62.5
	93.0	1	2.2	6.3	68.8
	95.0	1	2.2	6.3	75.0
	105.0	1	2.2	6.3	81.3
	108.0	1	2.2	6.3	87.5
	182.0	1	2.2	6.3	93.8
	824.0	1	2.2	6.3	100.0
	Total	16	34.8	100.0	
Lost	No midazolam	30	65.2		
Total	46	100.0			

IWS occurred with the withdrawal or reduction in most cases, mainly in relation to fentanyl (25 of 46 cases, 54.3%), followed by midazolam and buprenorphine (7 cases each, 15.2%) (Table 17).

Table 17: IWS due to tapering or discontinuation of the drug

Drug		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Fentanyl	19	41.3	41.3	41.3
	Midazolam	7	15.2	15.2	56.5
	Buprenorphine	7	15.2	15.2	71.7
	Dexmedetomidine	3	6.5	6.5	78.3
	Fentanyl and midazolam	3	6.5	6.5	84.8
	Fentanyl and dexmedetomidine	3	6.5	6.5	91.3
	Morphine	2	4.3	4.3	95.7
	Buprenorphine and midazolam	1	2.2	2.2	97.8
	Sufentanil	1	2.2	2.2	100.0
	Total	46	100.0	100.0	

Discussion

Our results showed that the clinical manifestations of IWS are variable and will depend on the assessment scale used in the pediatric patient, preferably WAT-1 for suspected opioid IWS and SOS for benzodiazepines. We found that the most frequent clinical manifestation is irritability/agitation.

Most of the services requesting support for IWS did not perform rating scale scores, which are important for an appropriate early and differential diagnosis since it is a diagnosis of exclusion and, as such, a sequence of evaluation measures must be carried out to rule out other entities.

Our findings suggest that the drug most frequently associated with IWS is fentanyl, which is consistent with the literature review given the characteristics of this drug. We also observed that although the infusion doses in our patients were mostly 3 mcg/kg/h, the duration of administration must be considered since the cumulative dose turned out to be risky in most of these patients, with recorded values of ≥0.5 mg/kg as described in the literature. The same applies to midazolam, where we observed a maximum dose of 960 mcg/kg/h, and even though this administration is not prolonged, it is itself a risk for IWS. Similarly to fentanyl, the days of drug administration must be considered, as it was observed that the majority of cases had a cumulative dose ≥43 mg/kg, considered in the literature as a risk factor.

As has been reported in various studies, both in IWS, the drug most associated with the clinical presentation of this condition is fentanyl, in the context of hospital use for sedoanalgesia, followed in our study by midazolam and buprenorphine.

We did not find previous studies that covered the pediatric population like ours, since most focus on neonatal withdrawal syndrome. Therefore, even though there is no clear precedent, it is evident that IWS develops more easily in younger patients and that other patient characteristics, as well as the proper administration and gradual withdrawal of opioids and benzodiazepines, should be considered.

One of the main limitations of our study is the sample size in relation to the study period limit, given that we focused

specifically on fentanyl and midazolam, even though during the process we encountered IWS secondary to other drugs such as buprenorphine, morphine, sufentanil, and dexmedetomidine.

For this reason, we suggest that future studies expand the sample size, the study period, and take into account other drugs related to iIWS.

Conclusions

Our study provides evidence regarding the clinical characteristics of pediatric patients with iatrogenic withdrawal syndrome, where we found that irritability is the most frequent clinical manifestation according to both the WAT-1 and SOS scales, followed by sweating and abnormal movements for WAT-1, and tachycardia, sweating, and tremors for SOS.

The demographic profile of our study population leaned toward the male sex, with a wide range of weights due to the variety of age ranges, and it was shown that the younger patients were the ones who most frequently presented the syndrome. The pediatric pain management team identified patients with IWS using assessment scales validated in the pediatric population. The WAT-1 scale was applied, obtaining positive scores of 3, 4, 6 with a maximum of 8 points, and SOS scores of 4, 5, 6 with a maximum of 7 points.

Half of the services that consult pediatric pain management for IWS do not properly assess clinical manifestations using WAT-1 and/or SOS scales.

The opioid most associated with IWS was fentanyl, with a maximum dose of 6.8 mcg/kg/h, although most received a dose of 3 mcg/kg/h, with a maximum duration of 91 days and cumulative doses of 4.87 mg/kg. Most patients had a cumulative dose ≥0.5 mg/kg, considered a risk factor for IWS. Regarding midazolam, the maximum dose was 960 mcg/kg/h; half of the population that received midazolam had doses >300 mcg/kg/h, with a maximum administration time of 106 days, and in most patients, the cumulative dose was ≥43 mg/kg, considered a risk factor for IWS.

These findings could be the starting point for addressing IWS across the entire pediatric population and providing new data for future research.

Refrences

1. Klein K, Pereira JS, Curtinaz KALJ, Jantsch LB, Souza NS, et al. Strategies for the management and prevention of withdrawal syndrome in critically ill pediatric patients: a systematic review. Rev Bras Ter Intensiva. 2022. 34: 507-518.
2. Sneyers B, Duceppe MA, Frenette AJ, Burry LD, Rico P, et al. Strategies for the prevention and treatment of iatrogenic opioid and benzodiazepine withdrawal in neonates, children, and critically ill adults: a systematic review of clinical studies. Drugs. 2020. 80: 1211-1233.
3. Ávila-Alzate JA, Gómez-Salgado J, Romero-Martín M, Martínez-Isasi S, Navarro-Abal Y, et al. Assessment and treatment of the withdrawal syndrome in paediatric intensive care units: Systematic review. Medicine (Baltimore). 2020. 99.
4. Sanavia E, Mencía S, Lafever SN, Solana MJ, Garcia M, et al. Protocol for rotation of sedative and analgesic drugs in critically ill children with prolonged sedation: evaluation of its implementation and effectiveness in reducing withdrawal syndrome. Pediatr Crit Care Med. 2019. 20: 1111-11117.
5. MacDonald I, Alvarado S, Marston MT, Gomez Tovar L, Chanez V, et al. A systematic review of clinical practice guidelines and recommendations for the management of pain, sedation, delirium, and iatrogenic withdrawal syndrome in pediatric intensive care. Front Pediatr. 2023. 11:1264717
6. Umer A, Lilly C, Curry H, Kumar A, Maxwell S, et al. Variations and similarities in the care and management of neonatal withdrawal syndrome in tertiary care hospitals in West Virginia. J Perinatol. 2022 42: 397-398.
7. Motta E, Luglio M, Delgado AF, Carvalho WB. Importance of the use of protocols for the management of analgesia and sedation in pediatric intensive care unit. Rev Assoc Med Bras (1992). 2016. 62: 602-609.
8. Mondardini MC, Sperotto F, Daverio M, Amigoni A. Analgesia and sedation in critically ill pediatric patients: an update from the recent guidelines and point of view. Eur J Pediatr. 2023. 182: 2013-2026.
9. Kelley-Quon LI, Zamora AK, Ourshalimian S, Kim E, Leventhal AM, et al. Abstinencia iatrogénica de opioides en lactantes hospitalizados. J Perinatol. 2022. 42: 399-400.
10. Ista E, Tibboel D, van Dijk M. Opioid and benzodiazepine withdrawal syndrome: can we predict and prevent it? Pediatr Crit Care Med. 2015.16: 195-196.
11. Best KM, Wypij D, Asaro LA, Curley MA. Random evaluation of sedation titration for researchers in the respiratory failure study. Predictors of the patient, process, and system of iatrogenic withdrawal syndrome in children with severe illnesses. Crit Care Med. 2017. 45.
12. da Silva PS, Reis ME, Fonseca TS, Fonseca MC. Opioid and benzodiazepine withdrawal syndrome in pediatric ICU patients: Which risk factors are important? J Addict Med. 2016. 10: 110-116.
13. Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MA. Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. Pediatr Crit Care Med. 2008. 9: 573-580.
14. Sperotto F, Ramelet AS, Daverio M, Mondardini MC, von Borell F, et al. CONSORTIUM of Analgosedation on behalf of the Pharmacology Section and the Nursing Sciences Section of the European Society of Pediatric and Neonatal Intensive Care. Assessment and management of iatrogenic withdrawal syndrome and delirium in pediatric intensive care units across Europe: an ESPNIC survey. Pharmacotherapy. 2023. 43: 804-815.
15. Ista E, van Dijk M. Knowing Risk Factors for Iatrogenic Withdrawal Syndrome in Children May Still Leave Us Empty-Handed. Crit Care Med. 2017. 45: 141-142.
16. Bicudo JN, de Souza N, Mângia CM, de Carvalho WB. Síndrome de abstinência associada à interrupção da infusão de fentanil e midazolam em pediatria. Rev Assoc Med Bras (1992). 1999. 45: 15-18.
17. Paglioli-Neto E, Pilger V, Tondo L, Zanotto M, Giongo M. Lactente em abstinência de cocaína, relato de caso. Sci Med (Porto Alegre). 2022. 32: 42602.

18. Wachman EM, Schiff DM, Silverstein M. Neonatal Abstinence Syndrome: Advances in Diagnosis and Treatment. JAMA. 2018. 319: 1362-1374.
19. Hintze TD, Miller JL, Neely SB, Lim SY, Gupta N, et al. Characterization of early versus late opioid iatrogenic withdrawal syndrome in critically ill children transitioning from fentanyl infusions to methadone. J Opioid Manag. 2023. 19: 43-56.
20. Geslain G, Ponsin P, Lãzãrescu AM, Tridon C, Robin N, et al. Incidence of iatrogenic withdrawal syndrome and associated factors in surgical pediatric intensive care. Arch Pediatr. 2023. 30: 14-19.
21. McAlister S, Connor JA, Engstrand S, McLellan MC. Validation of the withdrawal assessment tool-1 (WAT-1) in pediatric cardiovascular patients on an inpatient unit. J Spec Pediatr Nurs. 2023. 28.
22. Mangat AK, Schmölzer GM, Kraft WK. Pharmacological and non-pharmacological treatments for the Neonatal Abstinence Syndrome (NAS). Semin Fetal Neonatal Med. 2019. 24: 133-141.
23. Fernández Carrión F, Pérez A. Withdrawal syndrome in the PICU. Protoc Diagn Ter Pediatr. 2020. 3: 3-15.
24. Kocherlakota P. Neonatal abstinence syndrome. Pediatrics. 2014. 134: 547-561.
25. Dervan LA, Yaghmai B, Watson RS, Wolf FM. The use of methadone to facilitate opioid weaning in pediatric critical care patients: a systematic review of the literature and meta-analysis. Paediatr Anaesth. 2017. 27: 228-239.