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Incidence of iatrogenic withdrawal syndrome and associated factors in surgical pediatric intensive care

Short title: Withdrawal syndrome and associated factors in surgical PICU

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ABSTRACT

Background: Iatrogenic withdrawal syndrome (IWS) is a complication of prolonged sedation/analgesia in pediatric intensive care unit (PICU) patients. The epidemiology of IWS is poorly understood, as validated diagnostic tools are rarely used. The main objective of our study was to use the WAT-1 score to assess the incidence of IWS in our unit. The secondary objectives were to evaluate the consequences of IWS, associated factors, and management modalities.

Material and methods: From July 2018 to January 2019, 48 children receiving endotracheal ventilation and sedation/analgesia by continuous infusion (>48 h) of benzodiazepines and/or opioids were included. As soon as sedation/analgesia was decreased and until 72 h after its complete discontinuation, the WAT-1 score was determined every 12 h. Substitution therapy was used for 98% of patients upon opioid and/or benzodiazepine withdrawal. IWS was defined as a WAT-1 score ≥ 3 . Factors associated with IWS were assessed by univariate analysis.

Results: IWS occurred in 25 (52%) patients. IWS was associated with a higher number of ventilator-associated pneumonia episodes (17 [68%] vs. one [4%]) and a longer PICU stay (13 [7; 25] vs. 9.0 [5.0; 10.5]) ($p < 0.001$). Overall, 11 patients developed IWS after less than 5 days of sedation/analgesia. Severe head injury was associated with IWS ($p = 0.03$). Neither sedation discontinuation nor IWS prevention was standardized.

Conclusion: The high incidence and adverse consequences of IWS require improved prevention. Risk groups should be defined and a standardized withdrawal protocol established. The occurrence of IWS should be monitored routinely using a validated score.

Keywords: substance withdrawal syndrome; hypnotics and sedatives; surgical intensive care; pediatrics; mechanical ventilation; ventilator-associated pneumonia.

1. INTRODUCTION

Children admitted to pediatric intensive care unit (PICU) require analgesia and sedation due to the pain, discomfort, stress, and anxiety induced by their condition and the invasive treatments it requires. In the absence of effective analgesia and sedation in the PICU, patients may experience long-term posttraumatic disorders (1). A combination of benzodiazepines (BZD) and opioids is generally used but may lead to side effects including iatrogenic withdrawal syndrome (IWS) (2,3). IWS, first described in newborns (4,5), is a set of somatic and behavioral manifestations in patients weaned too quickly off medications to which they have developed tolerance and dependency (6). The Withdrawal Assessment Tool (WAT-1) was specifically developed to assess pediatric IWS (7). The score ranges from 0 to 12, and values of 3 or more indicate IWS.

The primary objective of this study was to determine the incidence of IWS in a surgical PICU using the WAT-1. The secondary objectives were to determine the timing of IWS, identify risk factors, and assess the preventive and therapeutic measures used in our PICU.

2. MATERIAL AND METHODS

2.1 Ethical aspects

Ethical approval (APHP.5 Research Ethics Committee. IRB registration: #350481) and parental informed consent were obtained according to the current French law.

2.2 Design and patients

We conducted a prospective single-center observational study in the surgical PICU of the Necker-Enfants Malades University Hospital, between July 1, 2018 and January 31, 2019. We

included consecutive patients aged more than 28 days and less than 18 years who received endotracheal ventilation and required a continuous infusion of BZD and/or opioids for more than 48 h.

We did not include patients whose sedation/analgesia was started in another department, patients transferred out of our unit while still under sedation/analgesia, patients without WAT-1 score data, or patients not covered by the French statutory health insurance system. Patients aged ≤ 28 days were not included due to their physiological peculiarities and to the specificities of neonatal care.

2.3 Data collection

The primary endpoint was the incidence of IWS defined as a WAT-1 score ≥ 3 . We also studied the incidence of IWS in two subgroups consisting of patients given sedation/analgesia for more than 5 days and of patients with severe head injuries, respectively.

Sedation/analgesia was prescribed daily to a COMFORT-B score target (8) according to usual practice in our PICU (deep sedation if COMFORT-B score < 11 , comfortable sedation between 11 and 17, borderline sedation between 17 and 22, and weak sedation if > 22).

The WAT-1 score (7) is composed of 11 items chosen from among the 19 items of the Opioid and Benzodiazepine Withdrawal Score. The items include the symptoms most frequently found during withdrawal syndrome (motor disorders, behavioral disorders, dysautonomia, and gastrointestinal symptoms). The score is determined based on the symptoms of diarrhea, vomiting, and/or temperature $> 37.8^{\circ}\text{C}$ recorded during the last 12 h; pre-stimulus observation (State Behavioral Scale [SBS] ≥ 1 or awake and distressed, sweating, repeated yawning or sneezing); observation during verbal or motor stimulation (startle to touch, muscle tone, tremor, uncoordinated or repetitive movements); and post-stimulus observation (time to return to calm [SBS < 0]). Physicians or nurses monitored the sedation scales and physicians adapted

the drugs. A third drug was possibly added according to the physician's judgment based on the WAT-1 score.

For our study, the WAT-1 score was determined at least once every 12 h until 72 h after discontinuation of the continuous BZD and/or opioid infusion or until patient discharge from the PICU, whichever occurred first. Values of 3 or more have been determined to indicate IWS (7).

For each patient, we recorded all WAT-1 scores and the highest WAT-1 score. We also collected the following data: age; body weight; sex; medical history; number of previous surgeries and general anesthesia; reason for admission; reason for and duration of endotracheal intubation; history of the current surgery; Pediatric Logistic Organ Dysfunction 2 (PELOD 2) score (9); nature and cumulative dosage of sedatives and analgesics (reported in sufentanil equivalent and midazolam equivalent), with the maximum hourly dosage and total duration; nature and duration of adjuvant sedatives/analgesics; procedures for weaning from sedation/analgesia; complications; and length of PICU stay.

2.4 Statistical analysis

We used R[®] and NCSS 10 Statistical Software[®] (2015, Kaysville, UT, USA) for the statistical analyses. Normality of quantitative variables was assessed using the Shapiro–Wilk test; variables are reported as mean±SD if normally distributed and as median [interquartile range] otherwise. Categorical variables are reported as number (%).

Factors associated with IWS were assessed by univariate analysis. Comparisons of continuous variables were made with Student's *t* test if normally distributed and the Mann–Whitney test otherwise. Categorical variables were compared using the chi-square test or Fisher's exact test if the sample size was less than 5. All tests were two-sided and values of $p < 0.05$ were considered significant.

3. RESULTS

3.1 Patients

During the 7-month study period, of the 639 children admitted to our surgical PICU, 396 (62%) required endotracheal ventilation, including 93 (14.5%) for longer than 48 h. Of these, 27 (29.0%) did not meet our inclusion criteria and 18 met the exclusion criteria, thus leaving 48 patients for the study (**Figure 1**).

Table 1 reports the main patient features. Most patients had morbidities before PICU admission and 21 (44%) had prior surgery, including more than twice for 16 patients. Surgery was the main reason for PICU admission (27/48, 56%) and was usually scheduled (19/27, 70%). Of the 16 (33%) patients with severe head injuries, 11 required intubation for coma (Glasgow Coma Scale score ≤ 8), three for seizures, and two for both. Emergency surgery was required before PICU admission for seven of the 16 patients due to brain lesions or intracranial hypertension. Of the patients with head injuries, five also had chest injuries and one had severe hemorrhagic shock.

3.2 Sedation/analgesia

All patients received opioids for analgesia and 46 (96%) received BZD. **Table 2** reports the main drugs used. Median duration of the continuous infusion was 5 days (3–7) for opioids and 5 days (4–7) for BZD.

Initial thiopental sedation was given to nine (19%) patients, for a median duration of 4 days (3–4); of these patients, seven subsequently received a continuous BZD infusion. Most patients also received other drugs for sedation/analgesia, as detailed in **Table 2**. Only four (8%) patients received only sufentanil and midazolam.

3.3 Monitoring and sedation/analgesia discontinuation

The COMFORT B scale was used to adapt sedation levels. Continuous opioid infusion was stopped without gradual dosage tapering in 52% of patients; in the remaining 48%, median tapering time was 1.0 days (1.0–2.5) with a range of 1–20 days. Continuous BZD infusion was stopped gradually in 56% of patients, with a median tapering time of 1.0 day (1.0–4.5). Substitution therapy was used for 98% of patients upon opioid and/or BZD withdrawal. Patient-controlled morphine analgesia was used to replace sufentanil for 85% of patients. Other drugs used were chlorpromazine (35%), alpha-2-agonists (dexmedetomidine or clonidine, 25%), hydroxyzine (17%), ketamine (8%), and dipotassium clorazepate (6%).

3.4 Factors associated with the occurrence of IWS

We collected 729 WAT-1 scores, with a median score of 9.0 (7.0–12.3) per child. Overall 25 (52%) children experienced IWS (WAT-1 score \geq 3). The median WAT-1 score was 5 (4–6), and the highest score of 8 was found in three cases. Among the children sedated for more than 5 days, 68% experienced IWS. One or more WAT-1 scores were missing for 23% of the patients.

In patients with IWS, median time to the highest WAT-1 score was 2.0 days (1.0–3.3) after BZD withdrawal and 2 days (1–3) after opioid withdrawal. Median duration of IWS was 24 h (12–60).

IWS was associated with significant increases in the occurrence of ventilator-associated pneumonia ($p < 0.001$), duration of mechanical ventilation ($p < 0.001$), and PICU length of stay ($p < 0.001$) (**Table 3**).

Patients with IWS received higher cumulative and maximum opioid dosages ($p < 0.001$ for both) and had a longer opioid treatment duration ($p = 0.003$) compared to other patients. They

also had higher cumulative BZD dosages ($p<0.001$) and longer BZD treatment duration ($p=0.003$). However, of the 25 patients with IWS, 11 received sedation/analgesia for less than 5 days. Severe head injury was significantly associated with IWS ($p=0.03$). Among factors related to management, IWS was significantly more common when the opioid dosage was decreased gradually ($p=0.042$) and when substitution was with chlorpromazine ($p=0.017$) or clonidine ($p=0.001$) (**Table 4**).

For opioids, we found a mean dose of $9.66 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ (sufentanil-equivalent) in the group with IWS versus a mean dose of $6.12 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ (sufentanil-equivalent) in the group without IWS ($p=0.005$). For benzodiazepines, we found a mean dose of $6.12 \text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ (midazolam-equivalent) in the group with IWS versus a mean dose of $3.19 \text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ (midazolam-equivalent) in the group without IWS ($p=0.01$) (**Table 4**).

Age, severity, number of previous surgeries/general anesthesia, and use of combined sedation/analgesia medications were not associated with IWS.

3.5 Management of IWS

The treatment of IWS was not standardized. Of the 25 patients with IWS, six (24%) required the reintroduction of a continuous opioid and/or BZD infusion, eight (32%) received neuroleptics, two (8%) had their pre-existing neuroleptic treatment intensified, eight (32%) received alpha-2-agonists, one had an increase in the pre-existing alpha-2-agonist treatment, five (20%) received dipotassium clorazepate, and three (12%) received hydroxyzine. Finally, in one case, patient-controlled analgesia with morphine was introduced.

3.6 Characteristics of patients with severe head injuries

IWS occurred in 12 (75%) of the 16 patients with severe head injury (**Table 5**). The median continuous opioid infusion duration was 4.5 days (3.0–6.3), with a median cumulative dosage

of 35.9 $\mu\text{g.kg}^{-1}$ (19.8–61.2) sufentanil equivalent. The median continuous BZD infusion duration was 4.5 days (4.0–5.0), with a median cumulative dose of 20.8 mg.kg^{-1} (10.1–31.0) midazolam equivalent. Of the 16 patients with severe head injury, seven (44%) had their midazolam infusion preceded by a thiopental infusion for a median duration of 4.0 days (3.0–4.0). Infusion durations for opioids and BZD were shorter for patients with severe head injuries than in the overall population but without statistical significance ($p=0.33$ and $p=0.11$, respectively). The median cumulative doses of opioids and/or BZD were within the lowest quartile of the range in the group of 25 patients with IWS. Chlorpromazine was used as an alternative for withdrawal in 44% of patients with severe head injuries compared to 35% of the overall population ($p=0.77$). None of the patients with severe head injuries received dexmedetomidine.

We found a median of 8 days (5.5–12.5] of endotracheal ventilation in the group with head trauma versus 6 days (4–10) in the group without head trauma ($p=0.45$). The rate of ventilator-associated pneumonia (VAP) was 57.6 per 1,000 ventilator days in the group with head trauma versus 34.7 per 1,000 ventilator days in the group without head trauma ($p=0.21$).

4. DISCUSSION

Our study showed a high frequency of IWS among patients admitted to the PICU, notably those with severe head injuries, as diagnosed using the WAT-1 score. Using larger amounts of sedatives and analgesics by continuous infusion was associated with a higher risk of IWS. Nevertheless, IWS warrants a gradual decrease in opioid dose and the use of chlorpromazine or clonidine upon discontinuation. Nearly half of the patients experienced IWS despite receiving sedation/analgesia for only 3–5 days.

IWS manifests as physical and behavioral symptoms that vary according to the underlying health condition and type of sedatives and analgesics used (10, 11). As opioids and

benzodiazepines are generally given in combination, the contribution of each class to IWS remains unclear (12). IWS may be associated with increased morbidity and longer hospital stays (13). In fact, in our study IWS was associated with significant increases in ventilator-associated pneumonia episodes, but head trauma patients are ventilated and sedated longer than postoperative patients and they have more VAP, longer sedation, longer duration of endotracheal ventilation, and longer PICU length of stay. They therefore have stronger withdrawal syndrome and, as a result, sedation is gradually reduced and clonidine is prescribed more often. However, these associations do not demonstrate causality and should be interpreted carefully.

The lack of specificity of the behavioral symptoms of IWS raises diagnostic challenges in the PICU (14). In addition, definitions of IWS vary, hindering the performance of valid studies. A 2015 systematic literature review found that only 50% of studies published between 1980 and 2014 used a validated diagnostic tool (15), and among them half used the Finnegan score, which has been validated only with neonates (4). This uncertainty around the definition of IWS had hampered studies carried out to identify risk factors and preventive strategies(14–16). The use of validated scores to identify IWS is therefore crucial (17). Most studies published in the literature have included patients who received sedation at least for 5 days (7, 10, 15, 18, 19). This cutoff of 5 days has been chosen in the 2016 European clinical guidelines: “Recommendation: The potential risk of opioid and/or benzodiazepine iatrogenic withdrawal syndrome should be considered after 5 days of continuous administration of these drugs” (14). Nevertheless, the results of the study by da Silva (20), showing the occurrence of withdrawal syndrome for sedation durations of less than 5 days, convinced us to include children receiving sedation/analgesia for a period of at least 48 h.

The WAT-1 was developed in 2008 as a simple and reproducible tool that can be used easily at the bedside (7) and was subsequently validated (21). The Sophia Observation Withdrawal

Symptoms Scale (SOS) is also available and has shown good diagnostic performance with 83% sensitivity, 93% specificity, and 98% negative predictive value (22). However, we chose the WAT-1 because it has been more extensively validated (18). In Addition, the WAT-1 has been used for years in our PICU, where the nurses are accustomed to and very satisfied with this score.

In univariate analysis, the potential risk factors for IWS such as higher treatment dosages and durations are consistent with previous data (23). Age was not associated with IWS, but we did not include neonates. the number of previous surgeries was also not associated with IWS. By contrast, severe head injury was significantly associated with IWS, with an incidence of 75% in this subgroup, although the exposure to sedatives/analgesics was within the lowest quartile of the range in the overall group with IWS. Thiopental was given to nearly half of the patients with severe head injuries, and IWS has been reported after barbiturate therapy (6), suggesting a possible source of bias. To our knowledge, this is the first study showing that head injury may be associated with an increased risk of IWS in PICU patients. However, an analysis of prospective data showed that pre-existing cognitive dysfunction was associated with IWS in children given sedation/analgesia for more than 5 days (23).

Monitoring the level of sedation/analgesia using a validated tool is crucial to minimize the use of drugs (16). Using COMFORT B, as done with our patients, has been reported to significantly reduce the duration of endotracheal ventilation, PICU length of stay, and the frequency of IWS (8). A 2017 review showed that using multiple sedatives was an independent risk factor for withdrawal syndrome (23).

A 2017 literature review focused on opioids and benzodiazepine withdrawal modalities in the PICU (24). Studies have suggested tapering schedules adapted to each individual patient according to the risk of IWS (25).

Alpha-2-agonists, particularly dexmedetomidine, are increasingly used for sedation in PICUs (26). In a survey conducted by the American Academy of Pediatrics, dexmedetomidine was used as the first-line sedative agent in 59.9% of cases and as a co-sedative in 82.3% of cases (27). Evidence of the potential usefulness of dexmedetomidine in preventing IWS is emerging (28). However, the use of dexmedetomidine for longer than 24 h may also be followed by IWS (29).

Our finding that the use of clonidine or chlorpromazine upon continuous sedative/analgesic infusion discontinuation was associated with IWS is consistent with an earlier report (18), but it seems difficult to confirm this because these drugs were introduced to prevent IWS. The efficacy of these two drugs for preventing IWS has not been demonstrated in adequately powered randomized controlled trials. Methadone was not used for continuous infusion withdrawal in our PICU, despite having been found effective in preventing IWS in PICU patients (19) and being recommended in 2008 guidelines (16) in a dosage equivalent to the opioid dosage previously given by continuous infusion.

Our work has several limitations. The single-center design, with a limited number of patients and staff members, precluded a valid multivariate analysis. However, few studies on IWS are available, and most of them had fewer than 50 patients. The percentage of included patients is low in comparison to all admitted patients during the study time frame. Sedation/analgesia for more than 48 h was an inclusion criterion, and since our PICU is a surgical one, most patients often have shorter lengths of stay. Secondly, we did not consider the potential role of non-pharmacological factors in the occurrence of IWS. Moreover, we did not look at organizational factors such as collaboration between healthcare providers or staff workload. However, we noted the absence of a standardized protocol for sedation/analgesia withdrawal in our PICU. While current recommendations do not provide specific details on how best to discontinue sedation in PICUs to prevent the occurrence of IWS (16), the use of standardized

protocols has been found to be beneficial (30). Finally, the WAT-1 score was not designed for children with neurological impairments. However, we used this score although a substantial proportion of our patients had severe head injuries. Fifth, the sample size is too small to determine the correlation between IWS and the type of surgery. Moreover, it would be difficult to determine whether the symptoms described by the WAT-1 score are related to IWS or to the head injury. Finally, the timing of the initiation of WAT-1 monitoring and the exact duration of the decrease in sedation/analgesia were difficult to determine due to the variability in management strategies related to the absence of a standardized protocol.

5. CONCLUSION

A high incidence of IWS, as diagnosed using the WAT-1 score, was observed among patients admitted to our surgical PICU. Studies are needed to develop a standardized protocol for preventing IWS after sedation/analgesia withdrawal, using routine WAT-1 monitoring to assess effects. The early identification of patients at high risk for IWS would allow adjustments to be made in the management strategy, such as the earlier initiation of alternative drugs.

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7. TABLES

Table 1: Main patient characteristics

	N=48
Age, years, median (IQR)	2.0 (0.6–6.2)
Male sex, <i>n</i> (%); sex ratio	30 (63%); 1.67
Medical history, <i>n</i> (%)	
Unremarkable	17 (35%)
Multiple malformation syndrome	9 (19%)
Prematurity	7 (15%)
Encephalopathy	2 (4%)
Other	13 (27%)
Number of previous surgeries, <i>n</i> (%)	
0	27 (56%)
1	2 (4%)
2	3 (6%)
≥ 3	16 (33%)
PELOD 2 score, median (IQR)	4 (3–5)
Initial health condition, <i>n</i> (%)	
Surgery	27 (56%)
▪ Planned	19 (70%)
▪ Emergent	8 (30%)
▪ ENT surgery	11 (41%)
▪ Neurosurgery	6 (22%)
Trauma	16 (33%)
▪ Head injury	16 (33%)
○ Coma	13
○ Seizures	5
○ Hematomas	11
○ Contusions	12
○ Intracranial hypertension	8
○ Osmotherapy	7
○ Emergency surgery	7
▪ Chest injury	5 (10%)
Respiratory distress	3 (6%)
Medical neurological condition	2 (4%)
▪ Seizures	2 (4%)
▪ Coma	0
Heart condition	0

IQR: interquartile range; PELOD: Pediatric Logistic Organ Dysfunction, ENT: ear–nose–throat.

Table 2: Characteristics of sedation/analgesia

	<i>N</i> (%)	Length, days, median (IQR)
Opioids	48 (100%)	5.0 (3.0–7.0)
▪ Sufentanil	46 (96%)	
▪ Morphine	4 (8%)	
Benzodiazepines	46 (96%)	5.0 (4.0–7.0)
▪ Midazolam	44 (92%)	
▪ Clonazepam	2 (4%)	
Other drugs		
▪ Ketamine	32 (67%)	5.0 (3.0–7.0)
▪ Thiopental	9 (19%)	4.0 (3.0–4.0)
▪ Chlorpromazine	8 (17%)	4.0 (3.5–7. 2)
▪ Dexmedetomidine	7 (15%)	5.0 (3.5–11.0)
▪ Clonidine	1 (2%)	3.0 (3.0–3.0)
▪ Regional analgesia	3 (6%)	5.0 (4.5–5.0)
Combinations		
▪ SUF/MDZ	4 (8%)	
▪ SUF/MDZ/KET	16 (33%)	
▪ SUF/MDZ/DEX	2 (4%)	
▪ SUF/MDZ/KET/CHLOR	4 (8%)	

IQR: interquartile range; SUF: sufentanil; MDZ: midazolam; KET: ketamine; DEX: dexmedetomidine, CHLOR: chlorpromazine.

Table 3: Consequences of idiopathic withdrawal syndrome (defined as a WAT-1 score ≥ 3)

	WAT-1 ≥ 3 (<i>N</i> =25)	WAT-1 <3 (<i>N</i> =23)	<i>p</i>
Unplanned tracheal extubation	3 (12%)	1 (4%)	0.60
Ventilator-associated pneumonia	17 (68%)	1 (4%)	<0.001
Time on endotracheal ventilation, days	9 (6–13)	5 (4–7)	<0.001
Length of PICU stay, days	13 (7–25)	9.0 (5.0–10.5)	<0.001
Length of hospital stay, days	24 (17–33)	18.0 (11.0–26.50)	0.114

The data are median (interquartile range) or number (percentage).

WAT-1: Withdrawal Assessment Tool score; PICU: pediatric intensive care unit.

Table 4: Potential risk factors for iatrogenic withdrawal syndrome by univariate analysis.

	WAT-1 \geq3 (N=25)	WAT-1 <3 (N=23)	<i>p</i>
Age, years	2.0 (1.0–6.0)	1.8 (0.3–7.0)	0.462
▪ \leq2 years	12 (48%)	12 (52%)	1
Males	15 (60%)	15 (65%)	0.057
Medical history			
▪ Prematurity	3 (12%)	4 (17%)	0.696
▪ Encephalopathy	1 (4%)	1 (4%)	1
Number of previous surgeries	0.0 (0.0–4.0)	0.0 (0.0–2.0)	0.466
PELOD 2 score	4.0 (3.0–7.0)	4.0 (3.0–5.0)	0.363
Head injury	12 (48%)	4 (17%)	0.03
Opioids			
▪ Total dose, $\mu\text{g}\cdot\text{kg}^{-1}$ sufentanil-equivalent	42.3 (34.3–128.5)	17.3 (13.2–35.9)	< 0.001
▪ Highest dose, $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$	0.58 (0.50–0.77)	0.43 (0.35–0.50)	< 0.001
▪ Total length of treatment, days	6.0 (4.0–10.0)	4.0 (3.0–5.5)	0.003
▪ Length of treatment <72 h	1 (4%)	3 (13%)	0.338
▪ Length of treatment 3–5 days	10 (40%)	14 (61%)	0.248
▪ Length of treatment >5 days	14 (56%)	6 (26%)	0.07
Benzodiazepines			
▪ Total dose, $\text{mg}\cdot\text{kg}^{-1}$ midazolam-equivalent	33.20 (20.75–63.20)	14.00 (5.59–20.35)	< 0.001
▪ Highest dose, $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$	0.42 (0.30–0.56)	0.29 (0.20–0.42)	0.053
▪ Total length of treatment, days	6 (5; 9)	4 (3–5.5)	0.003
▪ Length of treatment <72 h	1 (4%)	2 (9%)	1
▪ Length of treatment 3–5 days	10 (40%)	15 (65%)	0.138
▪ Length of treatment >5 days	12 (48%)	6 (26%)	0.069
Other drugs			
▪ Thiopental	7 (28%)	2 (7%)	0.140
▪ Ketamine	19 (76%)	13 (57%)	0.261
▪ Chlorpromazine	4 (16%)	4 (17%)	1
▪ Dexmedetomidine	4 (16%)	4 (17%)	1

Modalities of continuous sedation**withdrawal**

▪ Tapering, opioids	16 (64%)	7 (30%)	0.042
▪ Tapering, benzodiazepines	17 (68%)	10 (43%)	0.156
▪ Substitution therapy with morphine	23 (92%)	18 (78%)	0.178
PCA			
▪ Substitution therapy with chlorpromazine	13 (52%)	4 (17%)	0.017
▪ Substitution therapy with clonidine	7 (28%)	0	0.009
▪ Substitution therapy with dexmedetomidine	4 (16%)	2 (9%)	0.668
▪ Substitution therapy with hydroxyzine	4 (16%)	4 (17%)	1
▪ Substitution therapy with clorazepate dipotassium	3 (12%)	0	0.235

The data are median (interquartile range) or number (percentage).

WAT-1: Withdrawal Assessment Tool score; PELOD: Pediatric Logistic Organ Dysfunction;

PCA: patient-controlled analgesia.

Table 5: Characteristics of patients with severe head injury (N=16)

Total dose of opioids, $\mu\text{g}\cdot\text{kg}^{-1}$ sufentanil-equivalent	35.9 (19.8–61.2)
Total length of opioids, days	4.5 (3.0–6.3)
Total dose of benzodiazepines, $\text{mg}\cdot\text{kg}^{-1}$ midazolam-equivalent	20.8 (10.1–31.0)
Total length of benzodiazepines, days	4.5 (4.0–5.0)
Other drugs	
▪ Thiopental	9 (56%)
▪ Ketamine	9 (56%)
▪ Chlorpromazine	3 (19%)
▪ Dexmedetomidine	0
Modalities of continuous sedation withdrawal	
▪ Tapering, opioids	6 (38%)
▪ Tapering, benzodiazepines	9 (56%)
▪ Substitution therapy with morphine PCA	15 (94%)
▪ Substitution therapy with chlorpromazine	7 (44%)
▪ Substitution therapy with clonidine	3 (19%)
▪ Substitution therapy with dexmedetomidine	0
Ventilator-associated pneumonia	57.6 per 1,000 ventilator days
Length of mechanical ventilation, days	8.0 (5.8–12.3)
Length of PICU stay, days	11.5 (9.0–20.3)

The data are median (interquartile) or number (percentage).

VAP: ventilator-associated pneumonia; PCA: patient-controlled analgesia.

Figure

Figure 1: Study flowchart

Figure 1: Flow chart

