Protocolized Sedative Weaning vs Usual Care in Pediatric Critically Ill Patients: A Pilot Randomized Controlled Trial

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ABSTRACT

Aims: The prolonged use of benzodiazepines and opioids can lead to an increase in the incidence of withdrawal syndrome. One of the known risk factors is the lack of a sedative-weaning protocol. This study established a sedative-weaning protocol and compared this protocol with the usual care of weaning in high-risk critically ill children.

Materials and methods: This was an open-label, randomized controlled trial in a tertiary-care hospital. We recruited children aged 1 month to 18 years who had received intravenous sedative or analgesic drugs for at least 5 days. The exclusion criteria were patients who had already experienced the withdrawal syndrome. We established a weaning protocol. Eligible patients were randomly divided into the protocolized (intervention) and usual care (control) groups. The primary objective was to determine the prevalence of the withdrawal syndrome compared between two groups.

Results: Thirty eligible patients were enrolled (19 in the intervention and 11 in the control group). Baseline characteristics were not significantly different between both the groups. The prevalence of the withdrawal syndrome was 84% and 81% of patients in the intervention and control group, respectively. The duration of the initial weaning phase was shorter in the intervention group than in the control group (p value = 0.026). The cumulative dose of morphine solution for rescue therapy in the intervention group was statistically lower than that in the control group (p value = 0.016).

Conclusion: The implementation of the sedative-weaning protocol led to a significant reduction in the percentage of withdrawal days and length of intensive care unit stay without any adverse drug reactions. External validation would be needed to validate this protocol.

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Keywords: Benzodiazepine, Critically ill children, ICU sedation, Opioid, Weaning, Withdrawal syndrome.

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INTRODUCTION

Sedative and analgesic medications, particularly benzodiazepines and opioids, are widely used in pediatric intensive care units (PICU) to facilitate care and provide physical comfort for critically ill children. These agents reduce anxiety, provide pain relief, enhance ventilator synchrony, and increase procedural success rate with less patient discomfort. However, prolonged use of these medications may lead to iatrogenic withdrawal syndrome (IWS) during weaning, especially within 24–72 hours after weaning.1–4 Generally, the incidence rate of IWS among patients admitted to PICU is 34–57%.1,5,6 The incidence rate can reach 80–100% if sedation is extended for greater than 5 days with continuous infusions.2,6 These patients not only suffer from withdrawal symptoms, such as insomnia, abnormal movements, tachycardia, sweating, vomiting, and diarrhea,5 but also from unnecessary investigations that consume time, money, and resources. Furthermore, the IWS can lead to prolonged mechanical ventilation and lengthening of PICU stay.7

Risk factors for IWS include younger age, prolonged exposure, high cumulative doses of sedative medications, type of sedative agents, and the route of administration.8 One of the important risk factors is the lack of a sedative-weaning protocol.9 Presently, there is no worldwide, standardized sedative-weaning protocol. Sedation is usually weaned depending on physician practice. The objectives of this study were to establish a sedative-weaning protocol and to compare the withdrawal symptom rates between our sedative-weaning protocol and the usual care weaning in the at-risk critically ill children.

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MATERIALS AND METHODS

Patients

This study was an open-label, randomized controlled trial comparing the sedation-weaning protocol (intervention group) with the usual care (control group). Eligible participants included...
all ventilated patients aged 1 month to 18 years who had received opioid or benzodiazepine continuous infusions for at least 5 days. Children who had already experienced IWS, allergy to methadone, received potential risk of serious drug interaction with methadone, end-stage disease, and refusal of informed consent were excluded. The study was performed between March 2017 and February 2018 in a PICU in a tertiary-care academic center in Thailand. Before initiation, this trial was registered online at the US National institutes of Health (ClinicalTrials.gov) # NCT03018977. This study was approved by the Institutional Review Board in accordance with the Declaration of Helsinki. All participants provided informed written consent.

Established Sedation-weaning Protocol
The PICU physicians and clinical pharmacist established the sedation-weaning protocol based on previous studies.2,6 Fentanyl infusion was converted to oral methadone based on patients' weight and preconversion dose per day. Midazolam infusion was converted to oral lorazepam (Flowchart 1). The conversion ratio of fentanyl to oral methadone was 1:6.5. The conversion ratio of midazolam to intravenous lorazepam was 1:0.5 and intravenous lorazepam to oral lorazepam was 1:2. Therefore, the conversion ratio of intravenous midazolam to oral lorazepam was 1:1. However, for safety reasons, we decided to use the ratio of 1:0.1. The overlapping period from initiation of oral sedative agents to discontinuation of opioid/benzodiazepine infusion was 12 hours. Patients were classified into two groups as high-risk and low-risk groups after lorazepam and methadone doses were achieved for 24 hours without withdrawal symptoms (see in the definitions part). In the high-risk group, either methadone or lorazepam dose was reduced by 10% of the pretaper dose every day, while in the low-risk group these medications were reduced by 20% of pretaper dose everyday. If patients received more than one medication, each medication was reduced every other day. The bedside nurses used the Withdrawal Assessment Tool-Version1 (WAT-1) for assessing the withdrawal syndrome. The WAT-1 scale ranges from 0 to 12, with higher scores indicating more withdrawal symptoms. A WAT-1 score >3 was indicative of the withdrawal syndrome.10 When the

Flowchart 1: Protocol for intervention group: Initial phase. *Reduced doses 50% in patients who had renal or hepatic impairment

Next day,
Total daily dose of oral methadone = previous daily dose of oral methadone + (oral MSS x 0.2)
= Methadone .......... mg/ day po divided q 6 h (max 10 mg/ dose)
In case of lorazepam alone:
Total daily dose of oral lorazepam = previous daily dose of oral lorazepam + (IV midazolam x 0.2)
= Lorazepam .......... mg/day po divided q 12 h (max 2 mg/dose)
WAT-1 score > 3, morphine solution syrup and midazolam were used as rescue medications for withdrawal syndrome. If this occurred, the dose of the respective medications would increase back to the previous level, and weaning would be held for 24 hours. The sedation-weaning protocol had two phases, an initial phase and a tapering phase as shown in Flowcharts 1 and 2.

**Methods**

All sedated patients were assessed for the level of sedation using the state behavioral scale (SBS). The target of SBS was 0 to (−2) in the ventilated patient who relies on the severity of disease, and the target of SBS was 0 to (−1) during the mechanical ventilator weaning. Demographic data were recorded, including age, sex, comorbid disease, all sedative and rescue medications, withdrawal symptoms, and any adverse events during the study. When patients were considered clinically ready to be weaned off sedative medications, they were randomly assigned into two groups by stratified block of four using a computer-generated assignment. A stratified randomization was performed for patients with high or low risk of withdrawal syndrome. The control group was managed by four pediatric intensivists, while the intervention group was managed using the sedation-weaning protocol and was controlled by pediatric residents or pediatric critical care fellows. When sedated patients were ready for weaning, the fentanyl and midazolam infusions were weaned to 1–2 μg/kg/hour and 0.1–0.2 mg/kg/hour as per physician discretion, respectively (see Flowchart 1). The parenteral sedative medications were calculated to total daily dose and switched to enteral medication based on the conversion ratio as described earlier. The WAT-1 score was recorded by bedside nurses every 4 hours with continuous monitoring until all sedative medications were stopped for 72 hours. When the WAT-1 was score > 3, all physicians were notified to rule out other causes of high scores. If the IWS was confirmed, the rescue agent was given and the recording was done every hour. We used the Consolidated Standards of Reporting Trials (CONSORT 2010) guideline in the reporting of the methods, results, and discussion of this study.

**Definitions**

Patients who had a high risk of withdrawal syndrome were defined as those who had at least one of the following findings: (1) total cumulative dose of fentanyl greater than 0.5 mg/kg; (2) cumulative equivalent dose of midazolam greater than 40 mg/kg; and (3) the duration of intravenous continuous opioid/sedative infusion was over 10 days.

The withdrawal syndrome was defined as a WAT-1 score > 3. The percentage of withdrawal days was defined as the numbers of days that patients developed withdrawal symptoms divided by total weaning days. Total weaning days was defined as the duration from the time that patient switches from intravenous opioid/sedative to enteral medication until the successful discontinuance of all sedative medications.

The initial phase was defined as the period of transition from continuous intravenous infusion of fentanyl 1–2 μg/kg/hour and

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**Flowchart 2: Protocol for intervention group: Tapering phase.** *Reduced doses 50% in patients who had renal or hepatic impairment*
midazolam 0.1–0.2 mg/kg/hour converted to steady doses of enteral medication (Flowchart 1).

The tapering phase was defined as the period from steady doses of enteral medications until the cessation of all sedative medications (Flowchart 2).

Outcome Measurement

The primary outcome was the prevalence of withdrawal syndrome. The secondary outcomes were length of hospitalization, duration of sedative weaning time, duration of mechanical ventilation, duration of using noninvasive positive pressure ventilation, and sedation-related adverse events.

Statistical Analysis

The sample size was calculated by two independent proportion formula with a power of 80% and a two-tailed $\alpha$ risk of 0.05. We calculated the sample size estimation based on the incidence of IWS among patients after exposure to sedative agents in previous studies. This study aimed to decrease the withdrawal syndrome from 80% to 40%. The sample size was 23 patients in each group.

Statistical analysis was performed using the SPSS (version 20.0; IBM, Armonk, NY). Demographic data were descriptively analyzed for statistically significant differences between the intervention group and the control group. Outcome measures were reported using median (interquartile range, IQR). The unpaired Student’s $t$ test and Mann–Whitney $U$ test were used for continuous variables with and without normal distribution, respectively. Chi-square and Fisher exact test were used for categorical variables. The per-protocol analysis was used. A $p$ value of <0.05 was considered statistically significant, and mean difference or risk ratio with 95% confidence interval (CI) was reported.

RESULTS

From March 2017 to February 2018, a total of 489 patients were admitted to the PICU and were assessed for eligibility. Eighty-four patients were eligible. Of these, 46 patients were excluded: 36 due to potent drug interaction with methadone (for QTc prolongation) and 10 refused informed consent. Thirty-eight patients were randomized, 21 into the protocol group and 17 into the usual care group. During the weaning process, 8 patients were excluded. Five patients were suspected of developing allergy to enteral sedative drugs. Two patients were not allowed to take oral medications due to worsening gastrointestinal problems, and one patient was suspected of delirium. As a result, 30 patients remained in the study protocol, which were 19 patients in the protocol group and 11 patients in the usual care group (Flowchart 3).

The median age was 1.65 years, with 17 (57%) males enrolled. All patients received mechanical ventilation with the median duration time of 10 days before sedative weaning. The prevalence of IWS was 83%. The baseline characteristics were not significantly different between the two groups, except PRISM III (Table 1). The sedative medications included fentanyl, midazolam, dexmedetomidine, and chloral hydrate. These medications prior to the study were not different in the protocol and the usual care groups in terms of dose and duration. There were 11 and 6 patients with a high risk of withdrawal syndrome in the protocol group and usual care group, respectively. Nineteen (63%) patients developed withdrawal symptoms within 24 hours after starting weaning sedative medications. In addition, there were four patients (two patients in the protocol group) who developed the withdrawal syndrome after all weaning medications were stopped.

The prevalence of the IWS was not different between the groups (84% and 81% in the protocol and the usual care group, respectively). The prevalence of IWS and clinical outcomes are shown in Table 2. The protocol group had a significantly lower percentage of withdrawal days than the usual care group (mean difference [95%CI]: 17.85 [4.43–31.27], $p$ value = 0.011). Length of ICU stay was significantly longer in the usual care group than in the protocol group (mean difference [95%CI]: 13.64 [0.58–26.7], $p$ value = 0.041). The dosages of the weaning sedative agents (methadone and lorazepam) were not significantly different between the groups in terms of average doses, cumulative doses, and duration (Table 2). Morphine solution for rescue therapy was significantly lower in the protocol group than in the usual care group (Fig. 1). The cumulative dose of morphine solution for rescue therapy in the protocol group was statistically lower than in the usual care group (mean difference [95%CI]: 2.5 [0.38–5.42], $p$ value = 0.016). The complications during weaning were not different between the groups. There was one patient in the usual care group who had oversedation (drowsiness and miosis) likely caused by methadone.

DISCUSSION

Mechanically ventilated children require sedative and/or analgesic medications to facilitate intensive care. The prevalence rate of IWS is high, particularly in those patients receiving sedative medications for longer than 5 days. A previous study showed the incidence of IWS was greater than 80% despite the use of a weaning protocol strategy, and the incidence of IWS approached 100% in patients who received sedative medication for longer than 9 days. In our study, the median duration of fentanyl and midazolam was 9 and 8 days, respectively. The prevalence of IWS in our study was 83%. Previous studies have shown the onset of withdrawal occurs from 11 hours to 2 months after cessation of medications. Our study showed that among patients who had withdrawal symptoms ($n = 25$), 19 patients (63%) developed the withdrawal symptoms within 24 hours after cessation of medications. The symptoms of opioid and benzo diazepine withdrawal are largely overlapping and include diarrhea, vomiting, sweating, or fever. However, gastrointestinal symptoms have been more commonly described for opioid withdrawal, while hallucination is more frequently observed in benzodiazepine withdrawal. The symptoms in this study could not definitively be distinguished by which medications caused them.

Methadone, lorazepam, clonidine, or dexmedetomidine are commonly used as an adjunctive therapy for opioid or benzodiazepine withdrawal. Our study used methadone and lorazepam as primary medications for weaning therapy. Several prior studies demonstrated various opioid weaning strategies by using methadone to prevent opioid withdrawal. In some studies, the sedative agents were weaned more than 25 to 50% within 24 hours. The incidence of IWS was nearly 100% in high-risk patients. We assumed that the weaning rate might not be appropriate. The 10 to 20% tapering rate per day has been suggested to be more promising. However, neither optimal dose of transition nor conversion strategies have been established to significantly prevent the IWS. Most studies showed that 40 to 80% of patients develop IWS. Several previous studies reviewed the conversion of intravenous fentanyl to oral methadone. The proposed conversion ratio varied from 1:1 to 1:16.7. A prior retrospective study had the intravenous fentanyl to oral methadone
Flowchart 3: Consolidated standards of reporting trials (CONSORT) diagram for the study. NPO, nothing per oral

Table 1: Baseline characteristics of children in the protocol group and those in the usual care group

|                                | Protocol group (n = 19) | Usual care group (n = 11) | p     |
|--------------------------------|-------------------------|---------------------------|-------|
| Age (year)                     | 1.57 (0.81–4.91)        | 1.73 (0.53–5.44)          | 0.966 |
| Male, n (%)                    | 12 (63.2)               | 5 (45.5)                  | 0.346 |
| Body weight (kg)               | 10 (7–14)               | 8.3 (5.7–15.6)            | 0.651 |
| Comorbidities, n (%)           |                         |                           | 0.590 |
| None                           | 4 (21.1)                | 2 (18.2)                  |       |
| Cardiology                     | 4 (21.1)                | 1 (9.1)                   |       |
| Oncology                       | 3 (15.8)                | 1 (9.1)                   |       |
| Pulmonology                    | 2 (10.5)                | 2 (18.2)                  |       |
| Others                         | 6 (31.7)                | 5 (45.5)                  |       |
| Reasons for PICU admission, n (%) |                      |                           | 0.424 |
| Postoperative                  | 6 (31.6)                | 1 (18.2)                  |       |
| Emergency condition            | 13 (68.4)               | 9 (81.8)                  |       |
| PRISM III                      | 4 (0–7)                 | 7 (3–11)                  | 0.038 |
| MV days prior to weaning       | 10 (8–16.5)             | 13 (7.5–32.75)            | 0.324 |
| ICU days prior to weaning      | 10 (8–17)               | 11 (8–16)                 | 0.619 |
| High risk of IWS, n (%)        | 11 (57.9)               | 6 (54.5)                  | 0.858 |
| Cumulative doses prior enrolment |                       |                           |       |
| Fentanyl (μg/kg)               | 521.9 (267.1–715.3)     | 470.0 (223.6–748.0)       | 0.880 |
| Midazolam (mg/kg)              | 17.0 (11.1–53.3)        | 29.1 (13.3–41.5)          | 0.726 |
| Dexmedetomidine (μg/kg)        | 48.7 (30.6–103.2)       | 129.8 (18.2–216.8)        | 0.328 |

Values are median (IQR); PRISM III, The Pediatric Risk of Mortality III; MV, mechanical ventilation; ICU, intensive care unit; IWS, iatrogenic withdrawal syndrome
conversion ratio of approximately 1:2.5. The conclusion showed this conversion ratio was associated with less withdrawal and reduced the need for rescue opioids. However, the median WAT-1 score at 48 hours, 72 hours, and 96 hours was greater than 3 (defined as withdrawal syndrome). In addition, the initial doses of fentanyl prior to conversion to methadone was high (4 μg/kg/hour). In our study, we used the conversion ratio of intravenous fentanyl to oral methadone was 1:6.5 with the dose of intravenous fentanyl at initiation of enterol methadone was 1–2 μg/kg/hours for safety concern.

In our study, we hypothesized that the patients in the protocol group would have a reduced rate of IWS compared to the usual care group because a sedative-weaning protocol has been demonstrated as a protective factor to prevent the IWS. However, the occurrence of IWS was not decreased with the sedative-weaning protocol. We postulate three potential reasons.

First, the majority of the patients in this study represented a very high-risk group because of the prolonged duration of exposure and high cumulative dose. Twenty-two (73%) patients received more than one sedative/opioid medications prior to weaning. Prolonged exposure to fentanyl, high cumulative dose during sedation period, and fentanyl itself are key factors contributing to the IWS. Most studies agree that the exposure to opioid of greater than 5 days is a potential risk factor to develop the IWS. Our study showed the median duration of sedation was 10 days (range 8–16) and the prevalence of IWS was 83%, which was similar to prior study. Katz et al. reported that the incidence of IWS was 100% if the exposure to fentanyl by continuous infusion was more than 9 days.

Second, the overlapping period between the initiation of oral sedations and the discontinuation of infusion are also elemental factors. Several studies have shown the prevalence of IWS ranged from 10 to 43% when the overlapping period of fentanyl infusion was 2 to 3 days. This study showed the overlapping period of fentanyl infusion was 12 hours which was a shorter period of discontinuation after methadone initiation. This might be the cause of the IWS in our patients. Therefore, a longer overlapping period might be helpful.

Last, the protocol group was weaned by 10 to 20% of previous daily dose, and only one medication per day was weaned, while the usual care group was weaned 25 to 30% of previous daily dose and one or more medications were weaned per day. Once a protocol was in place, the usual care group might also be practiced similar to protocolized weaning. Therefore, it would reduce the possibility of demonstrating any differences among the outcomes of the two groups. However, the protocol group had a lower dose of morphine solution for rescue than the usual care group (0.08 mg/kg/day and 0.37 mg/kg/day, respectively, p value = 0.005). The protocol group also had a lower total dose of morphine solution than the usual care group (0.69 mg/kg/day vs. 0.44 mg/kg/day, p = 0.006).

Table 2: Prevalence of iatrogenic withdrawal syndrome and morbidities in the two groups

|                        | Protocol group | Usual care group | p    |
|------------------------|---------------|-----------------|------|
| Occurrence of IWS, n (%) | 16 (84)       | 9 (81)          | 0.865|
| %Withdrawal days**     | 15 (9–29)     | 38 (17–54)      | 0.029*|
| Total weaning period (days) | 12 (9–20)     | 11 (8–22)       | 1    |
| Duration of initial phase | 1 (1–3)       | 3 (2–4)         | 0.026*|
| Duration of tapering phase | 10 (8–16)     | 8 (6–16)        | 0.605|
| Methadone              |               |                 |      |
| Average dose (mg/kg/day) | 0.69 (0.45–0.85) | 0.44 (0.27–1.36) | 0.666|
| Cumulative dose (mg/kg) | 6.44 (4.10–10.43) | 4.23 (1.44–20.48) | 0.565|
| Duration (days)        | 10 (9–18)     | 10 (6–19)       | 0.940|
| Lorazepam              |               |                 |      |
| Average dose (mg/kg/day) | 0.17 (0.13–0.23) | 0.22 (0.17–0.35) | 0.222|
| Cumulative dose (mg/kg) | 1.56 (1.08–3.55) | 2.30 (1.73–3.82) | 0.264|
| Duration (days)        | 9 (7–17)      | 10 (8–18)       | 0.707|
| ICU stay (days)        | 15 (13–34)    | 29 (18–43)      | 0.031*|
| Mechanical ventilation (days) | 12 (9–16)    | 13.5 (11.5–34.5) | 0.237|
| Adverse drug reactions, n (%) | 0 (0)        | 1 (9.1)         | 0.181|

Values are median (IQR), IWS, iatrogenic withdrawal syndrome; ICU, intensive care unit

*p < 0.05

**%withdrawal day = [withdrawal symptoms(days)/total weaning (days)] × 100%
care group (0.16 mg/kg/day and 1.47 mg/kg/day, respectively, p value = 0.002). Also, the percentage of withdrawal days was significantly less in the protocol group when compared to the usual care group, although IWS incidence was similar. This probably points toward the benefits of protocolized weaning. In addition, this study showed the protocol group had lower the length of ICU stay than the usual group which it might reduce the cost of ICU stay. Therefore, we assumed that a risk-stratified weaning protocol and a 10 to 20% daily taper is more appropriate.

The strength of this study is the establishment of a weaning protocol that improved the outcomes in the protocol group in high-risk critically ill children. In addition, this sedative-weaning protocol may be applied in other hospitals that do not have pediatric intensivist or clinical pharmacist. Our institute continues to use this sedative-weaning protocol in our PICU and will distribute to other hospitals for validation.

This study has some limitations. First, as this study was a pilot RCT, it was limited to a single center with a relatively small population. Based on the calculated sample size, the recruited patients in this study could not be reached because of the limitation of duration. This lack of sample size may decrease the power of the pilot RCT. It is important to interpret the findings of this pilot study with caution. Therefore, the extended duration of the study with the multicenter collaboration is needed to validate the weaning protocol. Second, this study was unblinded. All physicians known the WAT-1 scores from the bedside nurses. It might be biased. We minimized this potential bias using these solutions. Bedside nurses used the WAT-1 strictly as the guidance of this assessment tool. The staffs manipulated the weaning process by their own preference in the usual care group, while the residents and fellows strictly followed the sedative-weaning protocol in the protocol group. Third, the process of weaning in the usual care group might be influenced by bias from the weaning protocol (similar to the Hawthorne effect). However, we reduced this bias by assigning the residents and fellows to strictly follow the weaning protocol, while the attending staff personally weaned the sedative drugs in the usual care group. The results showed that the daily dose of weaning between the two groups was different.

**Conclusion**

We successfully implemented the sedative-weaning protocol for critically ill children in the PICU of a university hospital. The protocol led to a significant reduction in the percentage of withdrawal days, rescue medications, and length of ICU stay without any adverse drug reactions. External validation would be needed to validate this protocol.

**References**

1. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. Crit Care Med 1994;22(5):763–767. DOI: 10.1097/00003246-199405000-00009.
2. Franck LS, Naughton I, Winter I. Opioid and benzodiazepine withdrawal symptoms in paediatric intensive care patients. Int J Crit Care Nurs 2004;20(6):344–351. DOI: 10.1016/j.ijccn.2004.07.008.
3. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation. Crit Care Med 2008;36(8):2427–2432. DOI: 10.1097/CCM.0b013e318181600d.
4. Best KM, Boullata JI, Curley MA. Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: a systematic review and conceptual model. Pediatr Crit Care Med 2015;16(2):175–183. DOI: 10.1097/PCC.0000000000000306.
5. Fonsmark L, Rasmussen YH, Carl P. Occurrence of withdrawal in critically ill sedated children. Crit Care Med 1999;27(1):196–199. DOI: 10.1097/00003246-199901000-00052.
6. Fernández-Carrión F, Gaboli M, González-Celador R, Gómez de quero-Masia F, Fernández-De migue l S, Murga-Herrera V, et al. Withdrawal syndrome in the pediatric intensive care unit. incidence and risk factors. Med Intensiva 2013;37(2):67–74. DOI: 10.1016/j.medi.2012.02.010.
7. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Crit Care Med 2000;28(6):1212–1213. DOI: 10.1097/00003246-200006000-00079.
8. Best KM, Asaro LA, Franck LS, Wypij D, Curley MA. Randomized evaluation of sedation titration for respiratory failure baseline study 1. patterns of sedation weaning in critically ill children recovering from acute respiratory failure. Pediatr Crit Care Med 2016;17(1):19–29. DOI: 10.1097/PCC.0000000000000572.
9. Best KM, Wypij D, Asaro LA, Curley MA. Randomized evaluation of sedation titration for respiratory failure study I. patient, process, and system predictors of iatrogenic withdrawal syndrome in critically ill children. Crit Care Med 2017;45(1):e7–e15. DOI: 10.1097/CMM.0000000000001953.
10. Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MA. The 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(6):573–580. DOI: 10.1097/PCC.0b013e3181818328.
11. Curley MA, Harris SK, Fraser KA, Johnson RA, Arnold JH. State behavioral scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatr Crit Care Med 2006;7(2):107–114. DOI: 10.1097/01.PCC.0000200955.40962.38.
12. Altman DG, Schulz TF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134(8):663–694. DOI: 10.7326/0003-4819-134-8-200104170-00012.
13. Oschman A, McCabe T, Kuhn RJ. Dexametomidine for opioid and benzodiazepine withdrawal in pediatric patients. Am J Health Syst Pharm 2011;68(13):1233–1238. DOI: 10.2146/ajhp100257.
14. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in children after long-term administration of sedatives and/or analgesics: a literature review. “assessment remains troublesome”. Intensive Care Med 2007;33(8):1396–1406. DOI: 10.1007/s00134-007-0696-x.
15. Robertson RC, Darsey F, Fortenberry JD, Pettignano R, Harty G. Evaluation of an opiate-weaning protocol using methadone in pediatric intensive care unit patients. Pediatr Crit Care Med 2000;1(2):119–123. DOI: 10.1097/00130478-200010000-00005.
16. Meyer MM, Berens RJ. Efficacy of an enteral 10-day methadone wean to prevent opioid withdrawal in fentanyl-tolerant pediatric intensive care unit patients. Pediatr Crit Care Med 2001;2(4):329–333. DOI: 10.1097/00130478-200110000-00009.
17. Siddappa R, Fletcher JE, Heard AM, Kimela D, Cinimo M, Heard CM. Methadone dosage for prevention of opioid withdrawal in children. Paediatr Anaesth 2003;13(9):805–810. DOI: 10.1046/j.1460-9595.2003.01153.x.
18. Berens RJ, Meyer MT, Mikhailov TA, Colpaert KD, Czarnecki ML, Ghanyem NS, et al. A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients. Anesth Analg 2006;102(4):119–123. DOI: 10.1213/00003246-200606000-00001.
19. Jeffries SA, Mcglinn R, Pittfield AF, Carr RR. Use of methadone for prevention of opioid withdrawal in critically ill children. Can J Hosp Pharm 2012;65(1):12–18. DOI: 10.4212/cjhp.v65i1.1098.
20. Giby K, Vaillancourt R, Varughese N, Vadeboncoeur C, Pouliot A. Use of methadone for opioid weaning in children: prescribing practices and trends. Can J Hosp Pharm 2014;67(2):149–156. DOI: 10.4212/cjhp.v67i2.1342.
21. 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(3):228–239. DOI: 10.1111/pa.13056.

22. Honey BL, Benefield RJ, Miller JL, Johnson PN. Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. Ann Pharmacother 2009;43(9):1506–1511. DOI: 10.1345/aph.1M161.

23. Srinivasan V, Pung D, O’Neill SP. Conversion from prolonged intravenous fentanyl infusion to enteral methadone in critically ill children. World J Clin Pediatr 2017;6(2):110–117. DOI: 10.5409/wjcp.v6.i2.110.

24. Carnevale FA, Ducharme C. Adverse reactions to the withdrawal of opioids and benzodiazepines in paediatric intensive care. Inten Crit Care Nurs 1997;13(4):181–188. DOI: 10.1016/s0964-3397(97)80012-2.

25. Bowens CD, Thompson JA, Thompson MT, Breitzka RL, Thompson DG, Sheeran PW. A trial of methadone tapering schedules in pediatric intensive care unit patients exposed to prolonged sedative infusions. Pediatr Crit Care Med 2011;12(5):504–511. DOI: 10.1097/PCC.0b013e3181fe38f5.