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Sufentanil use in critically ill children: a single-center experience

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Background: Critically ill children often require pain management or sedation due to their underlying conditions or the need for intensive care. However, the available drug options and their clinical reliability are frequently limited for these patients. This study explored the utility of sufentanil as an analgosedative in critically ill pediatric patients, drawing on clinical experience.

Methods: This single-center retrospective observational cohort study included patients under 19 years of age admitted to the pediatric intensive care unit (PICU) in a tertiary care children's hospital between March 2021 and September 2022, in whom sufentanil was used as the first-choice continuous analgosedative drug.

Results: In total, 225 patients were included. The most common reason for PICU admission was postoperative care (34.7%), followed by respiratory failure (20.0%), and cardiac problems (17.3%). The initial median starting and maximum doses of sufentanil were 0.5 μg/kg/hr (interquartile range [IQR], 0.3–1.0). The median durations of sufentanil use, mechanical ventilation support, and PICU stay were 1 days (IQR, 4–12), 6 days (IQR, 1–17) and 9 days (IQR, 5–27), respectively. In 199 (88.4%) patients, an appropriate analgesia/sedation level was achieved with sufentanil alone. However, 26 patients required additional drugs such as midazolam and ketamine infusion after administering the maximum dose of sufentanil, indicating the necessity for supplementary agents. No significant adverse effects or withdrawal symptoms were associated with sufentanil use.

Conclusion: Sufentanil may be a promising option for analgesia/sedation in critically ill pediatric patients, as it demonstrated no significant side effects or withdrawal symptoms. However, larger-scale randomized controlled research is necessary to generalize these results.

Keywords: Critically ill; Pediatrics; Sedation; Sufentanil

INTRODUCTION

Critically ill patients frequently require highly complex medico-surgical procedures, painful interventions, testing, and invasive monitoring, which can be extremely stressful and provoke agitation and anxiety for both the patient and the care team [1-4]. To alleviate this stress and promote early recovery, proper pain control and sedation management are essential.

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However, this can be particularly challenging in critically ill children due to factors such as varying ages, developmental stages, clinical statuses, and their unique pharmacokinetics and pharmacodynamics [2,5,6]. Furthermore, limited analgosedative options are available for these patients [5-7].

Sufentanil, a synthetic analog of fentanyl, is a potent analgesic that acts as a highly selective μ-opioid receptor agonist [8-10]. Since its initial development and introduction into clinical practice, sufentanil has primarily been used for anesthesia induction in high-risk surgical procedures. Consequently, most of the existing research on sufentanil has focused on its perioperative applications [11-19]. There remains a dearth of knowledge regarding its efficacy and safety as an analgosedative in critically ill pediatric patients, with few published reports detailing its use in pediatric intensive care units (PICUs) [5].

However, considering the pharmacologic properties of sufentanil published to date and several reports of its use in critically ill adults and neonates, sufentanil seems to hold promise as a potential analgosedative option for critically ill pediatric patients [20-23]. In this study, therefore, we aimed to evaluate the clinical utility of sufentanil as an analgosedative in critically ill pediatric patients, drawing from our own experiences with this drug at our institution's PICU.

METHODS

This study received approval from the Institutional Review Board of Asan Medical Center (No. 2020-0878). Due to the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its subsequent amendments. Additionally, this study adheres to the Strengthening the Reporting of Observational (STROBE) guidelines for reporting observational studies.

Study Design and Subjects

This was a single-center, retrospective observational cohort study. We screened all critically ill pediatric patients who were consecutively admitted to a 25-bed multidisciplinary PICU at a tertiary care academic referral hospital between March 2021 and September 2022 for enrollment. Our inclusion criteria were patients under 19 years of age who received sufentanil as the first-choice continuous analgosedative drug.

Data Collection

In this study, we conducted a retrospective review of electronic medical records for all included patients, gathering data on various baseline demographics such as underlying disorders, reasons for PICU admission, mechanical ventilator (MV) support usage, and the need for continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO). Additionally, we collected information on the duration of MV support and PICU stay, pain and sedation assessment scores, and all relevant aspects of sufentanil use, including the initial starting dose, maximum dosage for optimal pain control and sedation, duration of use, any withdrawal symptoms, adverse effects, and the requirements for additional analgosedative drugs.

Pain and sedation assessments were performed using various tools according to the patients' ages, such as the Neonatal Pain, Agitation and Sedation Scale (N-PASS); Face, Legs, Activity, Cry, Consolability (FLACC) scale; numeric rating scale (NRS); State Behavioral Assessment Scale (SBS), COMFORT Scale; and Richmond Agitation Sedation Scale (RASS) [24]. We established daily targeted goals for pain control and sedation levels. Based on the assessment scores, drug doses were adjusted. To evaluate withdrawal symptoms, we used the Withdrawal Assessment Tool-1 [25].

Statistical Analysis

Data were analyzed using IBM SPSS ver. 21.0 (IBM Corp.). Continuous variables are reported as medians with interquartile ranges. Categorical variables are expressed as numbers and proportions.

RESULTS

Baseline Characteristics of the Study Population

A total of 225 patients were included in the study, with 142 (55.7%) being boys. The median age and body weight of the patients were 1.9 years (0.6–6.8 years) and 10.9 kg (6.0–20.3 kg), respectively. Cardiac disorders were the most frequently encountered underlying conditions, affecting 70 patients (31.1%). The most common reason for PICU admission was postoperative care, accounting for 78 cases (34.7%). MV support was required for 196 patients (87.1%), while 26 patients (11.6%) needed CRRT. ECMO was applied to 15 patients (6.7%) during the study period (Table 1).

Sufentanil Use

Sufentanil was initiated without a loading dose, and the median initial starting dose was 0.5 μg/kg/hr (0.3–1 μg/kg/hr). The maximum dose required for optimal pain control and sedation level

Table 1. Baseline characteristics of the study population

Variable	Value (n=225)
Male	142 (55.7)
Age (yr)	1.9 (0.6–6.8)
Weight (kg)	10.9 (6.0–20.3)
Duration of PICU stay (day)	6 (1.0–17.0)
Duration of hospital stay (day)	5 (9.0–27.0)
Underlying disease	
Cardiac	70 (31.1)
Gastrointestinal/hepatic	55 (24.4)
Respiratory	41 (18.2)
Hematologic-oncologic	35 (15.6)
Neurologic	12 (5.3)
Genetic/endocrinologic	7 (3.1)
Nephrologic	5 (2.2)
Others	3 (1.3)
Causes of PICU admission	
Postoperative care	78 (34.7)
Respiratory failure	45 (20.0)
Cardiac problems	39 (17.3)
Hematologic-oncologic problems	17 (7.6)
Neurologic problems	16 (7.1)
Gastrointestinal/hepatic problems	14 (6.2)
Shock	11 (4.9)
Acute kidney injury	3 (1.3)
Others	2 (0.9)
Number of patients with MV	196 (87.1)
Duration of MV (day)	6 (1–17)
Number of patients with CRRT	26 (11.6)
Number of patients with ECMO	15 (6.7)
Duration of PICU stay (day)	9 (5–27)
Use of sufentanil	
Initial starting dose (μg/kg/hr)	0.5 (0.3–1)
Maximum dose (μg/kg/hr)	0.5 (0.3–1)
Duration of use (day)	1 (4–12)

Values are presented as number (%) or median (interquartile range).
PICU, pediatric intensive care unit; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

was also 0.5 μg/kg/hr (0.3–1 μg/kg/hr). The optimal dose for targeted pain control and sedation level after initiation was achieved within 4 hours. The median duration of sufentanil use was 4 days (1–12 days). When tapering, a total period of more than 1 week was needed to decrease the dose by 0.1 μg/kg/hr per day. If continuous usage was less than 1 week, tapering was performed at a faster rate according to the patient's condition and targeted pain control and sedation level.

In our study, vecuronium was started simultaneously with sufentanil in 38 patients requiring a secure neuromuscular blocking agent (NMB) effect. These patients underwent operations or procedures that required secure immobilization, such as tracheal anastomosis, esophageal reconstruction and anastomosis, facial flap operation, central-type ECMO catheter placement, or high risk of operation site bleeding. Patients with severe acute respiratory distress syndrome, severe bronchopulmonary dysplasia, and severe pulmonary hypertension crises also required additional NMB due to deteriorating clinical conditions.

Additionally, 23 patients required midazolam as a supplementary agent even after the maximum dosage of sufentanil was administered. In five patients, ketamine was also required as an adjunct to sufentanil, and two patients required both midazolam and ketamine. Notably, no significant adverse effects related to the use of sufentanil were observed during the study period, including respiratory depression or hemodynamic instability. Furthermore, we did not observe any significant withdrawal symptoms.

DISCUSSION

The results of the present study showed that sufentanil was safe and effective as an analgosedative drug in critically ill pediatric patients with substantial variation in their age, size and clinical conditions. In our study, we did not conduct a direct comparison between the effects of sufentanil and other analgesic sedatives, such as fentanyl. However, our findings can be partially supported and corroborated by previous reports on the physiochemical and pharmacological properties of sufentanil [8,10,21,22,26,27].

Previous research on pediatric patients has shown that sufentanil has a lower volume of distribution compared to fentanyl, necessitating less medication to achieve the desired drug concentration. The higher lipid solubility of sufentanil relative to fentanyl results in a shorter distribution time, faster onset, more rapid peak effect, and briefer distribution and elimination half-lives [26]. As a result, sufentanil is a more potent analgesic than fentanyl.

It was previously believed that a longer infusion duration led to a longer recovery time due to saturation and increased drug concentration in the peripheral compartment. The context-sensitive half-time refers to the time it takes for the drug concentration in the blood to decrease by 50% after stopping the infusion over varying time intervals [28]. Sufentanil exhibits a consistent, low context-sensitive half-time regardless of infusion duration, and its effect-site concentration decrement time is also consistently low. As a result, sufentanil is an ideal medication for prolonged use, as it allows for rapid elimination without the risk of cumulative effects. In our study, the median duration of sufentanil use

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was 4 days (1–12 days). However, no significant adverse effects were observed during the study period. Regarding withdrawal, when sedatives are used for more than 5 days, withdrawal symptoms may occur, which can be alleviated by carefully weaning and tapering medication use [25,29]. Nevertheless, our results demonstrated no significant withdrawal symptoms during the tapering process, and there was no need to increase medication use, as a smooth and successful taper was achieved throughout.

Sufentanil offers several advantages for use in critically ill patients. It is metabolized via hepatic cytochrome P450 CYP3A4 through oxidative N-dealkylation into inactive metabolites, with only a small portion (2%) excreted unchanged via the kidneys (2%) [30]. It does not produce active or toxic metabolites, nor is it eliminated through renal clearance. Consequently, accumulation does not occur in cases of renal insufficiency, which is frequently observed in critically ill pediatric patients [31,32]. This characteristic makes sufentanil a safe option for pain management in critically ill patients, even in instances of renal failure. In our study, 26 patients required CRRT due to acute kidney injury, yet no sufentanil-related adverse effects were observed compared to other patients.

Sufentanil is well-known for maintaining hemodynamic stability during infusion, more so than other opioids. Respiratory depression has also been rarely reported. Consistent with this, no adverse effects were observed in patients with hemodynamically unstable shock or those not receiving mechanical ventilation support. This, in contrast to most other sedative drugs, could be an incredibly significant advantage, as sufentanil has demonstrated the ability to be safely administered to critically ill children with multiple organ failure without causing hemodynamic instability or respiratory depression.

In our study, 88.4% of patients did not require additional analgesia/sedative medication, a result that can be attributed to the wide range of available doses and rapid onset of action associated with sufentanil use. This enabled easy and efficient adjustments of medication as needed, tailored to each patient's specific target goals. This flexibility in medication management proved to be an invaluable asset in the successful treatment of critically ill children, setting sufentanil apart as an exceptional analgesia/sedative option.

However, there are several limitations to this study. First, this was a single-center, retrospective observational cohort study with a relatively small sample size and a highly heterogeneous patient group. As a result, the findings may not be generalizable without further validation in a larger, prospective randomized case-control study. It is important to note that a significant number of patients in our study were administered NMB agents concurrently due to their clinical characteristics. This suggests a potential confounding factor in our results, and further investigation is needed to fully understand the implications of these findings. Therefore, caution should be exercised when drawing definitive conclusions about the efficacy of sufentanil administration in critically ill children.

In this study, the diversity in age, disease, and clinical condition profiles of the patients made it challenging to consistently measure pain and sedation using numerical methods. Instead, individually tailored approaches were employed using various tools, which may have introduced some differences in medication control. Our study did not utilize a protocol-based, nurse-driven approach for managing analgosedative medications. Rather, it primarily relied on the physician's discretion to set daily targeted goals and control analgesic/sedation, which could introduce bias.

Despite its limitations, this study is of considerable significance, as it represents one of the few systematic accounts of clinical experience using sufentanil for pain management and sedation in critically ill pediatric patients. Furthermore, there is a need for additional large-scale randomized controlled trials to compare the safety and efficacy of sufentanil with other analgosedative agents in this vulnerable patient population.

In conclusion, our study offers significant insights into the clinical application of sufentanil for pain management in critically ill pediatric patients. We propose that sufentanil can be utilized as a safe and effective analgosedative in critically ill pediatric patients across various age groups and with a wide range of clinical conditions. The findings of this study may lay the groundwork for future research on pediatric pain management in the intensive care unit.

CONFLICT OF INTEREST

Won Kyoung Jhang is an Editor-in-Chief, and Seong Jong Park is an editorial board member of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: WKJ, SJP. Data curation: WKJ. Formal analysis: WKJ. Investigation: WKJ. Methodology: WKJ, SJP. Validation: SJP. Writing - original draft: WKJ. Writing - review & editing: WKJ, SJP.

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