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Use of fentanyl and midazolam in mechanically ventilated children—Does the method of infusion matter?☆,☆☆,★

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ABSTRACT

Background and objective: Benzodiazepines and opioids are commonly used in pediatric intensive care unit. However, there is no previous study assessing the use of administering these drugs combined (single solution) or separately. We sought to evaluate the impact of these 2 different methods of providing sedation/analgesia in pediatric intensive care unit.
Methods: One hundred twelve patients mechanically ventilated for more than 48 hours were randomized to receive a protocolized sedation regime comprising midazolam and fentanyl either separately (group 1, 57 patients) or combined as a single solution (group 2, 55 patients). Primary end point variable was the cumulated dose of midazolam and fentanyl.
Results: The median cumulated doses of both fentanyl (0.19 vs 0.37 mg/kg, $P < .05$) and midazolam (28.8 vs 45.6 mg/kg, $P < .05$) required in group 2 were higher when compared with those of group 1. Moreover, group 2 patients had a significantly longer time of vasopressor drugs requirement and a higher number of patients developing tolerance.
Conclusion: Patients who received a single solution of midazolam and fentanyl had a higher cumulated dose of compared with those patients who did not. The potential risk for long-term neurologic effects on developing brains associated with this finding should be considered.

1. Introduction

Analgesic and sedative infusions are frequently used in pediatric intensive care units (PICUs) to provide continuous comfort to critically ill patients. The UK Paediatric Intensive Care Society's consensus have recommended the combination of midazolam and fentanyl in continuous infusion as the first choice for sedation/analgesia in PICU patients [1]. Despite this guideline, a recent survey about analgesia/sedation practices in PICUs has demonstrated wide variability in clinical practices [2]. Thus, the use of several drug classes, multiple agents, and large variations in doses, frequency, and routes of administration, and off-label use of analgesic drugs or untested drug combinations occur routinely often driven by individual preferences or local culture [2].

Despite the difficulties in establishing best practices, the administration of fentanyl-midazolam combination in a single solution has been used in different settings such as PICU [3], general anesthesia [4], intensive care unit (ICU) [5], and palliative care [6]. The reasons for this practice in the PICU setting may include difficulty of vein puncture, requirement of fluid restriction, prevention of catheter breaks and infection risk, limitation in material and human resources in low- and middle-incoming settings, and the theoretical "practicality" in the

Abbreviations: CA-BSI, catheter-associated bloodstream infection; CI, confidence interval; COMFORT b, COMFORT behavior scale; FLACC, Face, Legs, Activity, Cry, Consolability scale; IQR, interquartile ranges; IWS, iatrogenic withdrawal syndrome; MV, mechanical ventilation; PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality score; PELOD, Pediatric Logistic Organ Dysfunction score; SOS, Sophia Observation withdrawal Symptoms scale; SOS-D, SOS version adapted for delirium; VAP, ventilator-associated pneumonia.

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preparation of the solution. Midazolam and fentanyl mixed in polypropylene syringes have been shown to be physically and chemically compatible for up to 4 days after preparation [6]. Nevertheless, although it lacks clinical studies assessing the use of these 2 agents as a single solution in the PICU, the identification of this clinical practice in the literature is confusing due to the use of different terms ("co-sedation," "midazolam-fentanyl combination," "midazolam and fentanyl," "and "midazolam-fentanyl mixture").

Although there has been a long-standing use of these agents in PICUs in the "real world," to support such a practice, there is no prospective clinical trial randomizing patients according to these 2 common methods of delivering fentanyl and midazolam and addressing the differences and outcomes of these methods. At the same time, there is a growing body of evidence showing deleterious long-term neurologic effects of benzodiazepines and opioids on developing brains [7].

Although explanatory trial is the best design to evaluate the efficacy of an intervention in a well-defined and controlled setting, a pragmatic trial is designed to test interventions in the full spectrum of everyday clinical settings in order to maximize applicability and generalizability. The research question under investigation is whether an intervention actually works in real life; the intervention is evaluated against other ones (established or not) of the same or different class, in routine practice settings [8].

We hypothesized that the use of a combined solution would imply in a higher cumulative amount of benzodiazepine/opioid and, consequently, would lead to worse outcomes when compared with patients receiving these same drugs separately. Hence, the primary objective of this study was to compare the differences of cumulated doses of midazolam and fentanyl when administered as a separated solution or single (combined) solution.

2. Methods

2.1. Study design

This pragmatic randomized clinical trial was performed in an 8-bed PICU of a tertiary hospital from January 2012 through December 2014. Although our PICU has a sedation algorithm guided by scores in which the administration of sedatives and analgesics are individually titrated to effect, the method to deliver concurrent sedation using fentanyl and midazolam is not strictly defined. The institutional review board approved the study and written informed consent was obtained from parents or the patients' legal guardian(s) for all eligible patients (Brazilian Clinical Trials Registry—RBR-3j6rdg).

2.2. Inclusion and exclusion criteria

All consecutive patients aged between 1 month and 16 years requiring mechanical ventilation (MV), with an expected duration of at least 48 hours and in need of sedative/analgesic drugs infusion, were eligible for enrollment. Patients were not included if they presented with severe neurologic injury or central nervous system impairment that could affect the assessment of the sedation level. Also, patients were excluded if they received any neuromuscular blocking agent or another sedative/analgesic drug (eg, ketamine, dexmedetomedine, clonidine, thiopental, thionembutal, and chloral hydrate) during the study period. Daily interruption of sedation is not a standard of care in our PICU.

2.3. Randomization and masking

After enrollment, patients were randomly assigned to 1 of 2 strategies, using blocks of 4, in a 1:1 ratio for each group and the infusion(s) started. Treatment allocation of the consecutive patients was concealed by random selection of opaque sealed envelopes from an opaque box. Every envelope contained an identification displaying group 1 (drugs administered separately, not in the same solution) and group 2 (drugs combined in the same solution) that the investigators had manually assigned to each treatment group before initiating the study. Because of practical reasons, none of the participants or personnel providing care were masked to the group assignment (Fig. 1).

2.4. Intervention

All mechanically ventilated patients received sedation and analgesia as recommended by the United Kingdom Paediatric Intensive Care Society Sedation, Analgesia and Neuromuscular Blockade Working Group [1]. Postoperative pain management initially included the use of analgesics (nonsteroidal anti-inflammatory drugs or acetaminophen) for background pain on a planned intermittent basis. Preemptive nonpharmacologic interventions (eg, consolation, posture change, heat or cold pack, or diaper change) and/or additional analgesia were provided for breakthrough pain. Systemic analgesia with opioid was further administered if score assessment still suggested pain after 2 consecutive hours. Nonopioid analgesics were routinely given to decrease the amount of opioids administered [1].

The study drugs (midazolam and fentanyl) were started immediately after the onset of MV. Sedation and analgesia levels were assessed by nurses every 4 hours by using the COMFORT behavior scale (COMFORT b; range, 6-30) [9] and the Face, Legs, Activity, Cry, Consolability scale (FLACC; range, 0-10) [10] respectively. Group 1 patients had the infusion of the 2 drugs performed through 2 distinct intravenous lines, each one containing each drug individually diluted. In each line, an infusion rate of 1 mL/h corresponded to 0.2 mg kg^{-1} h^{-1} and 2 μg kg^{-1} h^{-1} of midazolam and fentanyl, respectively. For group 2 patients, a single syringe containing the midazolam-fentanyl solution was prepared in such a way that an infusion rate of 1 mL/h matched to 0.2 mg kg^{-1} h^{-1} of midazolam and 2 μg kg^{-1} h^{-1} of fentanyl. The initial infusion rate was 0.5 mL/h for both groups. Subsequently, in order to achieve and maintain a COMFORT b score between 11 and 22 [9] and a FLACC score lower than 4 [10], the solutions were adjusted in increments or decrements of 0.5 mL/h. A COMFORT b score lower than 11 implied oversedation, whereas a score higher than 22 defined undersedation [9].

If COMFORT b score was higher than 22 during 2 consecutive hours or in cases of urgent need to avoid accidental extubation or central venous line dislocation, boluses equivalent to the hourly drug infusion amounts of midazolam or fentanyl were given alternately. Likewise, patients received supplementary doses of fentanyl when FLACC score was higher than 4. Intravenous bolus doses of sedative/analgesic could also be given prior to an anticipated noxious stimulation such as chest physiotherapy, suctioning, or procedures, to reduce patient-ventilator dyssynchrony and for those patients who required intrahospital transport to the radiology department.

When the sedation score pointed to an increase in medication, in group 1, the attending physician increased the infusion rate of benzodiazepine or opioid, alternately, in increments of 0.5 mL/h ((midazolam: 0.1 mg kg^{-1} h^{-1}; fentanyl: 1 μg kg^{-1} h^{-1}). Similarly, patients in group 2 had their infusion rate increased in increments of 0.5 mL/h (midazolam: 0.1 mg kg^{-1} h^{-1}; fentanyl: 1 μg kg^{-1} h^{-1}). If analgesia and sedation were insufficient despite the maximum allowed midazolam (0.6 mg kg^{-1} h^{-1}) and fentanyl (10 μg kg^{-1} h^{-1}) dosage [1], the child was excluded from the study and treated with other sedative/analgesic drug (chloral hydrate or ketamine). On the other hand, when the COMFORT b score was lower than 11, infusion rates were reduced in decrements of 0.5 mL/h. For patients in group 1, we first reduced the opioid infusion and, after 15 minutes, if the COMFORT b score still remained lower than 11, we decreased midazolam's infusion rate. Patients were kept within the desired sedation level (COMFORT b scores ≥11 and ≤22) while on weaning from MV. When the clinical condition had improved enough in order to judge the patient ready for extubation, we discontinued the drugs infusion.