

SEDATION AND ANALGESIA IN THE MECHANICALLY VENTILATED PEDIATRIC PATIENT

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Abstract

Aim. The aim of this study was to evaluate the sedation and analgesia regimens in PICU patients undergoing mechanical ventilation in our clinic. *Material and methods.* A four years observational study (January 2010 – December 2013) was conducted in the First PICU of Emergency Hospital for Children "Louis Turcanu" Timisoara and included 108 children, aged 0-18 years, who required mechanical ventilation for more than 24 hours. Sedation was achieved using benzodiazepines (Midazolam), opioids (Fentanyl or Morphine) and Propofol, as continuous infusion sedation or as intermittent bolus sedation. The levels of sedation and analgesia were based on Ramsay Sedation Scale. Sedation was considered appropriate at a Ramsay Scale of 2-4. *Results.* We used a number of 4 protocols for sedation during mechanical ventilation: one protocol used intermittent bolus medication (Midazolam) and 3 protocols used one drug or combinations of at least 2 drugs in continuous infusion. Midazolam bolus protocol was used only in a limited number of newborns (3.7%), in a dose of 0.1 mg/kg/dose. The mean number of boluses administered in 24 hours was 6.12±1.04. Ramsay Scale had a mean of 4.14±0.24. Midazolam in continuous infusion protocol was used in 38.88% of patients. The mean infusion dose of Midazolam was 0.31±0.08 mg/kg/h. Ramsay Scale had a mean of 3.43±0.35. Midazolam and Morphine in continuous infusion protocol was used in 2.77% of patients. The mean dose for Midazolam was 0.27±0.035 mg/kg/h and for Morphine 0.027±0.003 mg/kg/h. Ramsay scale had a mean of 2.21±0.57. Midazolam and Fentanyl in continuous infusion protocol was used in 54.62% of patients. The mean dose of Midazolam was 0.24±0.04 mg/kg/h and 2.9±0.6 mg/kg/h for Fentanyl. Ramsay Scale had a mean of 2.52±0.15. *Conclusions.* We consider that the combination of Midazolam and Fentanyl in continuous infusion is the best option for children, and adequate analgesia and sedation are achieved in a relatively short period of time. The association of Morphine with Midazolam in continuously infused was abandoned due to observed adverse effects.

Key words: sedation, analgesia, mechanical ventilation, child

Introduction

Appropriate sedation and analgesia are important parts of critical ill patient care and was described as inducing a state of comfort, without inducing coma (1). Sedatives and analgesics reduce anxiety, pain and agitation; facilitate mechanical ventilation and invasive procedures used commonly in PICU. Sedatives administered to critically ill children should be titrated according to the desired effect, since both under- and over-sedation can have negative effects.

Sedation in mechanically ventilated patients is necessary because they are unaware about the gravity of the situation (2) and because of the lack of control and inability to communicate (3). Also ventilated patients require analgesia because this category of patients is the most vulnerable to pain, which is caused by various invasive procedures; the presence of the endotracheal tube; immobilization for long periods; maneuvers such as suction of secretions from the airways. Among these, most patients indicated the presence of endotracheal tube as a major cause of pain and distress (4).

A superficial sedation during mechanical ventilation may cause undesired incidents such as accidental extubation, pull on the catheters, tubes and other devices, desynchronization with the ventilator and secondary hypoxia. On the other hand, excessive sedation was associated with a longer duration of ventilation and hospitalization, delayed patient recovery and may predispose to the occurrence of withdrawal phenomena (5).

An important aspect of sedation and analgesia in mechanically ventilated patients is the occurrence of withdrawal phenomena after discontinuation of medication. The drug dependence is encountered at any age and is most commonly manifested by insomnia, nightmares, agitation and anxiety. Factors associated with this syndrome are dependent on high doses and prolonged administration of opiates and/or benzodiazepines (6).

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A wide variety of pharmacological agents are now available for sedation and analgesia. An ideal sedative agent would have rapid onset of action, provide adequate sedation, allow rapid recovery after discontinuation, be easy to administer, lack drug accumulation, have few adverse effects, and interact minimally with other drugs. Unfortunately, sedatives have adverse effects, the potential to prolong mechanical ventilation, and may increase ICU (intensive care unit) stay and health care costs (7).

Aim

The aim of this study was to evaluate the sedation and analgesia regiments in PICU (pediatric intense care unit) patients undergoing mechanical ventilation in our clinic.

Material and Methods

A four years observational study (January 2010 – December 2013) was conducted in the Pediatric Clinic I of Emergency Hospital for Children "Louis Turcanu" Timisoara, University of Medicine and Pharmacy "Victor Babes" Timisoara and included 108 children who required endotracheal intubation and mechanical ventilation.

All patients mechanically ventilated for more than 24 hours, aged 0-18 years were eligible for inclusion.

Exclusion criteria was represented by: mechanical ventilation < 24 hours; patients in cerebral death, with Glasgow coma score < 6; noninvasive ventilation; and preterm babies, patients with congenital immunodeficiency

disorders, malignant or surgical diseases were excluded from the study.

Criteria for intubation were: apnea, impaired alveolar ventilation (PaCO₂ > 55 mmHg), inadequate oxygenation despite FiO₂ > 60% (PaO₂ < 60 mmHg) and for airway protection.

Demographic data (gender, age, weight), reason for mechanical ventilation (MV), number of days on ventilator, hospital length of stay, outcome (discharge, transfer, death), and pediatric risk of mortality score (PRISM) III (8) were collected in all patients.

All patients were mechanically ventilated using pressure limit: SIMV (synchronized intermittent mandatory ventilation) or A/C (assist control). Vital parameters including respiratory rate, heart rate, and non-invasive blood pressure (NIBP) were documented. The oxygen saturation of each child was monitored continuously by pulse oximetry.

Sedation was achieved using benzodiazepines (Midazolam), opioids (Fentanyl or Morphine) and Propofol, as continuous infusion sedation or as intermittent bolus sedation.

The protocols for the infusion of sedatives (mode of administration, dosage) are shown in Table 1.

The levels of sedation and analgesia were based on Ramsay Sedation Scale (9). The scale determines the state of consciousness in 6 levels: level 1, where the patient is anxious or restless to level 6, in which the patient is completely unresponsive to stimuli (Table 2).

Table 1. Protocols for sedation and analgesia in the study patients.

<i>Sedative and analgesic drug</i>	<i>Protocol</i>
<i>Midazolam</i>	Intravenous bolus of 0.1-0.2 mg/kg every 15 min as needed Continuous infusion at 0.1-0.2 mg/kg/h; dosage to be increased at 0.3 mg/kg/h until adequate sedation is achieved
<i>Fentanyl</i>	Intravenous bolus of 1-2 mcg/kg every 15 min as needed Continuous infusion at 1-2 mcg/kg/h; dosage to be increased at 4 mg/kg/h
<i>Morphine</i>	Continuous infusion at 0.01 mg/kg/h; dosage to be increased at 0.03 mg/kg/h
<i>Propofol</i>	Intravenous bolus of 1-2 mg/kg every 1 hour as needed Continuous infusion at 1-2 mg/kg/h; dosage to be increased at 4-5 mg/kg/h

Table 2. Ramsay Sedation Scale.

<i>Awake levels</i>	1	Patient anxious, agitated or both
	2	Patient cooperative, orientated and tranquil
	3	Patient responds to commands only
<i>Asleep levels</i>	4	A brisk response to a light glabellar tap
	5	A sluggish response to a light glabellar tap
	6	No response

In our study, sedation was considered appropriate at a Ramsay Scale of 2-4. Sedation assessment was performed by intensive care nurses at hourly intervals. The presence of a score of 1 required supplementation of sedative medication to avoid the patient's fight with the ventilator. A value of 5 or 6 at three successive determinations led to reduction of medication to avoid over sedation.

We used a number of 4 protocols for sedation during mechanical ventilation:

- one protocol used intermittent bolus medication (Midazolam) in 4 patients (3.7%) and
- 3 protocols used drugs in continuous infusion:
 - Midazolam continuous infusion in 42 patients (38.88%)
 - Midazolam and Morphine in 3 patients (2.77%)
 - Midazolam and Fentanyl in 59 patients (54.62%);
 and of these patients:
 - In 3 patients we associated continuous infusion with Propofol
 - In 4 patients we associated continuous infusion of neuromuscular blocking agents

This study was approved by the Hospital institutional review board and parents informed consent in writing was taken.

Statistical analysis was performed using Microsoft Excel 2007 software. Results are expressed as percent (%) and mean±standard deviation (M±SD).

Results

A total of 108 PICU patients receiving mechanical ventilation for a minimum of 24 hours met the inclusion criteria and were included in the study.

Study population characteristics are shown in Table 3. More than 50% of the patients were males. The mean age of the study group was 2.3 years; more than 50% were infants aged less than a year. The mean duration of mechanical ventilation was 9 days and the mean hospital length of stay was 25 days. The median value of PRISM III score on admission was 17, corresponding to a predicted death rate of 22%. Mortality rate for intubated patients was 31.48%.

Table 3. Study population characteristics.

	N=108
Age (M±SD) month (0-216)	27.65±51.00
Age, N (%):	
0-1 month	11 (10.18)
1 month-1 year	61 (56.48)
1-3 years	17 (15.74)
3-6 years	5 (4.62)
> 6 years	14 (12.96)
Sex, N (%)	
Male	74 (68.51)
Female	34 (31.48)
Ventilator days (M±SD)	9.36±8.52
Hospital length of stay (M±SD)	24.7±18.66
Outcome, N (%)	
Discharged	68 (62.96)
Death	34 (31.48)
Transferred to another hospital	6 (5.55)
PRISM III score (M±SD)	17±6.83

1. Midazolam bolus protocol

This protocol was used only in 4 newborns (3.7%).

The pathology of newborns who have received this type of intermittent sedation was: neonatal respiratory distress syndrome in 2 (1.85%) patients and the other two (1.85%) patients were with congenital cardiac malformations. We reported in this group 2 (1.85%) deaths.

The mean duration of mechanical ventilation was 11.25±7.36 days and the mean duration of hospitalization was 20.25±7.5 days.

Consciousness of these patients has been altered without the need to establish a protocol for continuous

sedation. Midazolam was administered as intermittent sedation in dose of 0.1 mg/kg/dose, the mean number of boluses administered in 24 hours was 6.12±1.04.

Ramsay Scale had a mean of 4.14±0.24.

2. Midazolam in continuous infusion protocol

This protocol was used in 41 (38.88%) patients.

Analysis by age group reveals the use of this protocol mainly in the age group 1 month-1 year (45%) (Figure 1).

The main reasons for intubation and mechanical ventilation for this group were extremely various, but mostly being represented by acute respiratory failure (Figure 2).

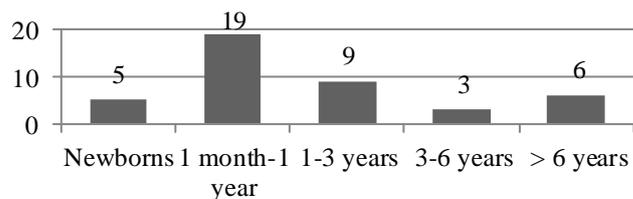


Figure 1. Age group distribution for Midazolam in continuous infusion protocol.

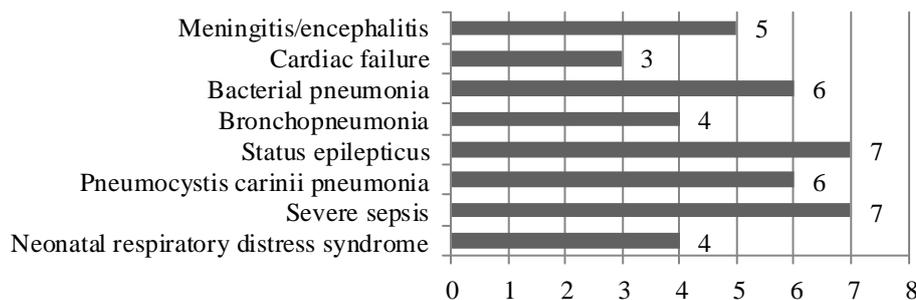


Figure 2. The main diagnosis on admission in PICU for Midazolam in continuous infusion protocol.

Survival in this group was 63.41%.

The mean duration of MV was 7.35 ± 6.31 days and the mean duration of hospitalization was 22.4 ± 22.37 days.

The starting dose of Midazolam infusion was 0.1 mg/kg/h, the dose being adjusted according to the Ramsay Scale. Increasing the dose of midazolam to prevent agitation was required in all cases after about 24 hours. The mean infusion dose of Midazolam was 0.31 ± 0.08 mg/kg/hr.

Ramsay Scale had a mean of 3.43 ± 0.35 . Maintaining an adequate level of sedation was achieved by administration of additional boluses of Propofol (1 mg/kg) and Fentanyl (1 mcg/kg).

3. Midazolam and Morphine in continuous infusion protocol

This protocol was used in 3 (2.77%) patients. All patients had acute respiratory failure. One patient died.

The mean duration of MV was 5 ± 4.35 days and the mean duration of hospitalization was 24.33 ± 15.04 days.

The starting dose of infusion was 0.1 mg/kg/h for Midazolam and 0.01 mg/kg/h for Morphine. Dose escalation was necessary in all cases, the mean dose for Midazolam being 0.27 ± 0.035 mg/kg/h and for Morphine 0.027 ± 0.003 mg/kg/h.

Ramsay scale had a mean of 2.21 ± 0.57 . For episodes of agitation we administered boluses of Midazolam (0.1 mg/kg) or Propofol (1 mg/kg).

Regarding side effects, all patients had gastric stasis and bilious vomiting, necessitating discontinuation of enteral feeding and transition to total parenteral nutrition. These digestive disorders were the main reason that we stopped using Morphine to sedate mechanically ventilated patients.

4. Midazolam and Fentanyl in continuous infusion protocol

It was used in 59 (54.62%) patients, representing the most common protocol to facilitate mechanical ventilation in our study.

Distribution by age group reveals the use of this protocol mainly in the age group 1 month - 1 year (68%) (Figure 3).

The main pathology for the establishment of MV in this group was extremely variable, represented mainly by respiratory disorders in 67% of cases (Figure 4). Survival in this group had the highest rate (72.88%).

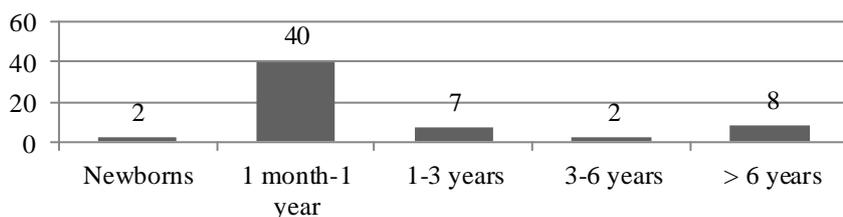


Figure 3. Age group distribution for Midazolam and Fentanyl in continuous infusion protocol.

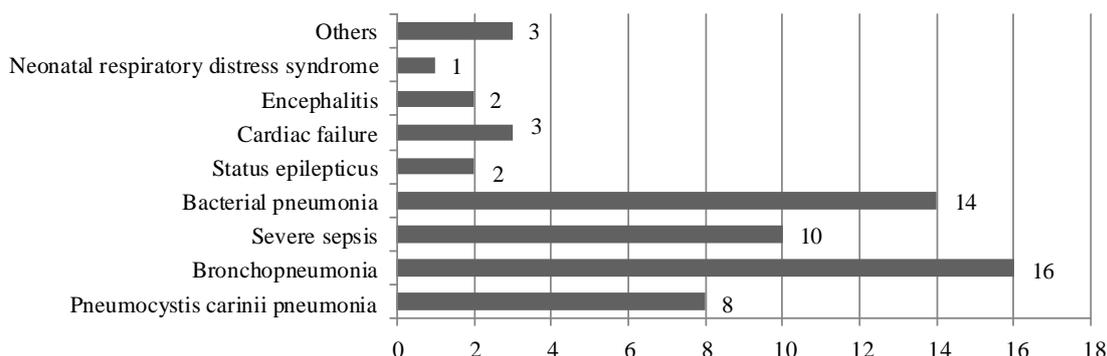


Figure 4. The main diagnosis on admission in PICU for Midazolam and Fentanyl in continuous infusion protocol.

The mean duration of MV was 11.03 ± 9.7 days and the mean duration of hospitalization was 26.86 ± 16.39 days. It can be noted that patients in this group required the greatest number of days of ventilation and hospitalization in the entire study group.

The starting dose of infusion was 0.1 mg/kg/h for Midazolam and 1 mg/kg/h for Fentanyl. Tolerance of medication was installed relatively quickly, in about 24 hours; so it was necessary to increase the rate of infusion. The mean dose of Midazolam was 0.24 ± 0.04 mg/kg/h and the mean dose of Fentanyl was 2.9 ± 0.6 mg/kg/h.

Ramsay Scale had a mean of 2.52 ± 0.15 . Supplemental boluses from this combination of Midazolam and Fentanyl equivalent with the dose per hour or Propofol (1 mg/kg) were needed.

Because the installation of tolerance to this protocol, with the need for high doses of opiates (which led to the installation of the chest wall stiffness), in 3 patients (2.77%) Propofol was associated in continuous infusion at a rate of 2 mg/kg/h. In 4 patients (3.7%) continuous infusion of neuromuscular blocking agents (Rocuronium) was associated at a dose of 0.3 mg/kg/h, thereby allowing to decrease the dose of opioid.

Discussions

Monitoring the level of sedation and analgesia in mechanically ventilated patients is essential, allowing an optimum patient comfort and good synchronization with the ventilator when given minimal doses of sedatives and analgesics.

Currently there are many sedation assessment scale, most commonly used in pediatric sedation are Ramsay Scale (9), COMFORT Scale (10), Richmond agitation and sedation Scale (RASS) (11) and Bispectral Index Score (BIS) (12) - score goal resulted from mathematical analysis of electroencephalogram.

In our study, the effectiveness of sedation and analgesia was based on the Ramsay scale, which was considered appropriate at a value of 2-4.

There are currently many drugs used for facilitation of mechanical ventilation, but without a uniform conduct of

their choice. Despite their widespread use, analgo-sedative drugs still lack data supporting appropriate dosing, safety, and efficacy of combined therapies, and optimal drug regimens for sedation during mechanical ventilation (13). In many intensive care units, sedatives are infused continuously (14). As compared with intermittent bolus infusion, this approach provides a more constant level of sedation and may increase patient's comfort.

We analyzed a total of four protocols for sedation/analgesia, one using only bolus medication. The most common sedation protocol used was the combination of Midazolam and Fentanyl in continuous infusion.

The choice of agent and the way in which they are used varies widely between and within ICUs. Propofol is the preferred iv infusion sedation agent in most U.S. ICUs and is gaining in popularity compared with other sedatives (15). In the United Kingdom, the most common sedative agents used in PICUs continue to be Midazolam and Morphine (16). A prospective multicenter patient-based study in France shown that Midazolam is the agent most commonly drug used for sedation, and for analgesia Sufentanil and Fentanyl are the most frequently used opioids (17). Recent Italian guidelines for sedation shown that benzodiazepines are the most commonly used drugs to sedate mechanically ventilated patients (18).

A review published last year by Vet et al (19) highlights several specific aspects about the use of sedatives in mechanically ventilated pediatric patients. After exclusion criteria, the authors analyzed 25 studies, in total 1,163 mechanically ventilated children aged 0-18 years. The most common drugs used were benzodiazepines (Midazolam in 22 studies) and opioids (Morphine in 14 studies). Other drugs used were: fentanyl, ketamine, clonidine, propofol, barbiturates, and dexmedetomidine hydrochloride in various combinations. In all these studies a number of 12 different scales of sedation have been used, the most common being the COMFORT scale, followed by Ramsay scale. Regarding the degree of sedation in these patients, optimal sedation was achieved in 57.6% of patients, under-sedation in 10.6% and over-sedation in 31.8%. The authors concluded that over-sedation in mechanically ventilated children is more

common than under-sedation and highlight the importance of finding an optimal and unitary strategy for sedation in PICU.

Conclusions

In our study, we had better results using a continuous infusion sedation protocol. Our experience in the management of mechanically ventilated patients showed that the combination of Midazolam and Fentanyl in

continuous infusion is the best option for children, and adequate analgesia and sedation are achieved in a relatively short period of time. This combination provides a lower Ramsay score, at lower doses of Midazolam.

The association of Morphine in continuously infused Midazolam was abandoned due to observed adverse effects. All patients had gastric stasis, bilious vomiting and ultimately paralytic ileus, requiring discontinuation of enteral feeding and transition to total parenteral nutrition.

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