ANALGESIA AND SEDATION DURING MECHANICAL VENTILATION IN CHILDREN

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Abstract

Introduction: Sedation and analgesia are important parts of patient management in the intensive care unit. It is necessary to minimize the perception and response to anxiety and pain. Children who are not adequately sedated or are experiencing pain may become tachycardic and hypertensive, and are at risk of losing their airway and central lines.

Material and method: This study was a retrospective review of pediatric patients undergoing endotracheal intubation and mechanical ventilation in PICU (Pediatric Intensive Care Unit) of Emergency Hospital for Children "Louis Turcanu" Timisoara between January 2005 and December 2009. The aim of this study was to evaluate the sedation and/or analgesia regiments in PICU patients undergoing endotracheal intubation in our clinic.

Results: A total of 134 PICU patients receiving mechanical ventilation were included in the study. 88 (65.67%) patients were male. We use for sedation during mechanical ventilation continuous infusion of midazolam and fentanyl in 54 (40.30%) patients, continuous midazolam infusion in 38 (28.36%) patients, and bolus intermittent sedation with midazolam in 20 (14.93%) patients. All newborns (n=45) received continuous infusion only with midazolam. The median duration of mechanical ventilation was 7.7 days, range 48 hours to 83 days. The medium length of stay in hospital was 14.22 days, range 48 hours to 97 days. There were 63 (47.01%) deaths in the PICU, consisting of 60 who died without weaning from mechanical ventilation. Highest mortality rate can be observed in newborns and highest survival rate in infants.

Conclusions: 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 achieve relatively in a short period of time. In ventilated newborns, continuous midazolam infusion is enough for obtaining a proper sedation.

Key words: PICU, mechanical ventilation, analgesia, sedation, midazolam, fentanyl

Introduction

In the emergency room and critical care environment, management of the airway to ensure optimal ventilation and oxygenation is of prime importance. Although initial efforts should be directed toward improving oxygenation and ventilation without intubating the patient (1), these interventions may fail and the placement of an endotracheal tube may be required.

Sedation and analgesia are important parts of patient management in the intensive care unit (ICU). It is necessary to minimize the perception and response to anxiety and pain. Children who are not adequately sedated or are experiencing pain may become tachycardic and hypertensive, and are at risk of losing their airway and central lines. Conversely, oversedation can cause cardiovascular and respiratory depression and may interfere with a comprehensive neurologic examination. In patients who undergo prolonged sedation, tolerance and tachyphylaxis develop, and these lead to increasing sedative requirements (2).

A wide variety of pharmacological agents are now available for sedation and analgesia, and while recommendations have been made regarding "the best" sedative and analgesic regimes for ICU patients (3) practice varies widely between and within ICUs. An ideal sedative agent would have rapid onset of action, be effective at providing adequate sedation, allow rapid recovery after discontinuation, be easy to administer, lack drug accumulation, have few adverse effects, interact minimally with other drugs, and be inexpensive (4). Unfortunately, sedatives have adverse effects, have the potential to prolong mechanical ventilation, and may increase health care costs.

However, despite their widespread use, analgo-sedative drugs still lack data supporting appropriate dosing, safety, and efficacy of combination therapies, and optimal drug regimens for sedation during mechanical ventilation (5). Many clinical tools available for assessing and monitoring sedation have limited utility in children (3,4).

In many intensive care units, sedatives are infused continuously (6,7). As compared with intermittent bolus infusion, this approach provides a more constant level of sedation and may increase patients' comfort (8,9). However, administration of sedatives by continuous infusion has been identified as an independent predictor of a longer duration of mechanical ventilation as well as a longer stay in the intensive care unit and in the hospital (10).

Material and method

This study was a retrospective review of pediatric patients undergoing endotracheal intubation and mechanical ventilation in PICU (Pediatric Intensive Care Unit) of Emergency Hospital for Children "Louis Turcanu" Timisoara between January 2005 and December 2009.

All patients mechanically ventilated over 24 hours were eligible for inclusion. Data elements included the following: demographic variables (age, weight, sex), underlying diseases, intubation indication, medications used, and administration of an additional sedative.

Criteria for intubation were: apnea, impaired alveolar ventilation ($PaCO_2$>55 mmHg), inadequate oxygenation despite FiO_2>60% (PaO_2<55 mmHg) and the inability of patients to maintain their airways open.

All patients were mechanically ventilated A/C (assist control) or SIMV (Synchronized Intermittent Mandatory Ventilation). 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 on central line.

Sedation on our intubated patients was achieved with benzodiazepine (midazolam) ± fentanyl as a continuous sedation or as intermittent bolus sedation. We excluded paralyzed patients who are a separate group and should not be included in the continuous sedation group, because those patients particularly need continuous sedation while being paralyzed.

The protocols for the infusion of sedatives are shown in Table 1. Nurses adjusted the dosage and rate of infusion according to standard procedures at our institution (to achieve a score of 3 or 4 on the Ramsay sedation scale, which measures sedation on a scale of 1 [agitated or restless] to 6 [asleep and unresponsive to stimuli][15]).

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

Sedative and analgesic drug	**Protocol**
Midazolam	Intravenous bolus of 0.1–0.2 mg/kg every 15 min as needed
	Continuous infusion at 0.1–0.2 mg/kg/hr; dosage to be increased at 0.3 mg/kg/hr until adequate sedation is achieved
Fentanyl	Intravenous bolus of 1–2 mcg/kg every 15 min as needed
	Continuous infusion at 2–4 mcg/kg/hr; dosage to be increased at 5–10 mg/kg/hr
Propofol	Intravenous bolus of 2–4 mg/kg every 1 hour as needed

The aim of this study was to evaluate the sedation and/or analgesia regiments in PICU patients undergoing endotracheal intubation in our clinic. Additional sedation and analgesia were achieved in order to maintain endotracheal tube placement, to facilitate continued oxygenation and ventilation in an intubated patient.

Results

A total of 134 PICU patients receiving mechanical ventilation were included in the study. Distribution of cases by the year of admission (Figure 1) was as follows: 28 children (20.89%) in 2005; 27 (20.14%) in 2006; 30 (22.38%) in 2007; 28 (20.98%) in 2008 and 21 (15.67%) in 2009.

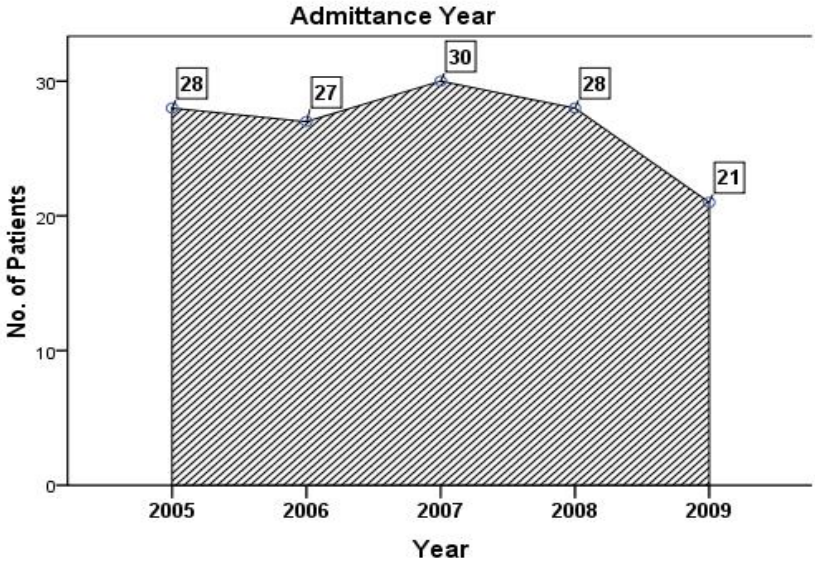

Figure 1: Admittance year repartition.

Of the 134 mechanically ventilated children, 88 (65.67%) patients were male (Figure 2). Forty-five (33.58%) patients were newborn, 40 (29.85%) infants, 23 (17.16%) patients aged 1 to 3 years, 10 (7.46%) patients aged 3 to 6 years, and 16 (11.90%) patients over the age of six years (Figure 3). Of them, age distribution on year of admission was: in 2005 – 10 newborn, 8 infants, 5 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; in 2006 - 10 newborn, 7 infants, 5 patients aged 1 to 3 years, 1 patient aged 3 to 6 year, 4 patients over the age of six years; in 2007 - 10 newborn, 8 infants, 7 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; in 2008 - 11 newborn, 8 infants, 4 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; and in 2009 - 4 newborn, 9 infants, 2 patients aged 1 to 3 years, 3 patients aged 3 to 6 years, 3 patients over the age of six years (Figure 4).

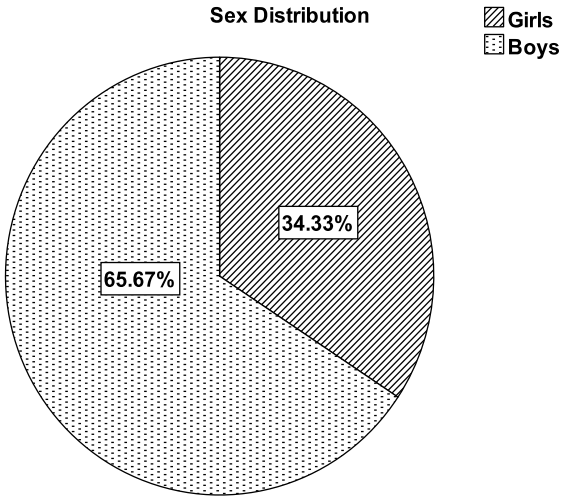

Figure 2: Sex distribution.

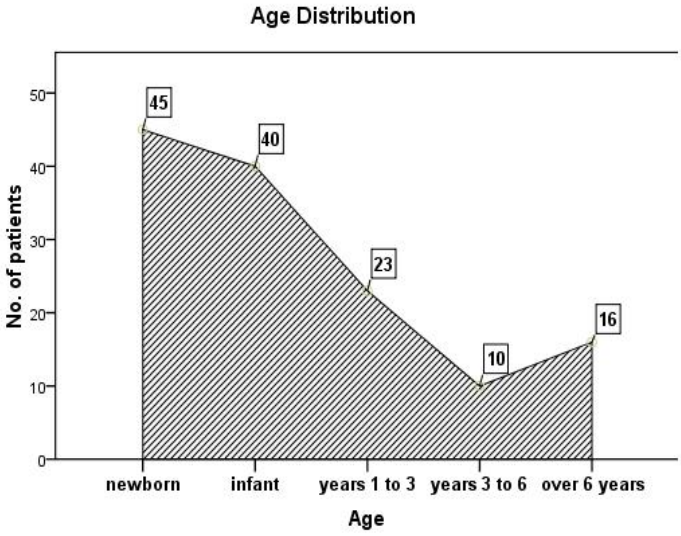

Figure 3: Age distribution.

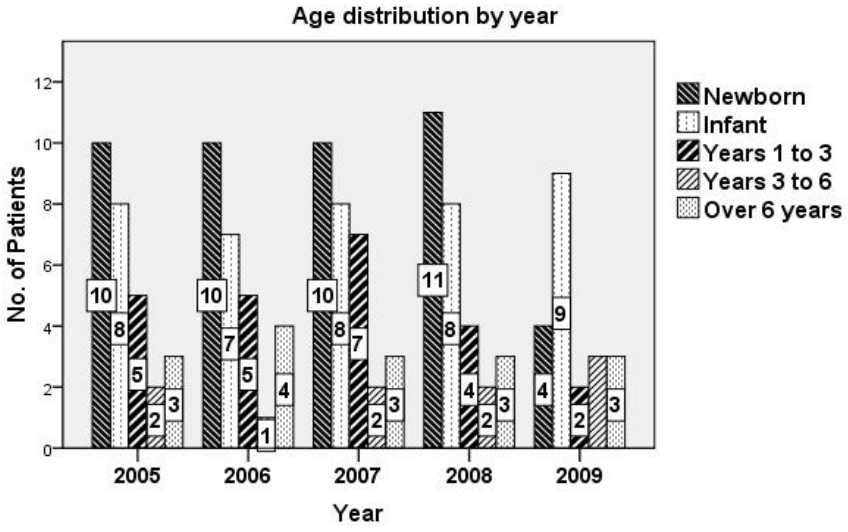

Figure 4: Age distribution by year.

Main diagnosis in patients that required mechanical ventilation was: bronchopneumonia (n=36), neonatal respiratory distress syndrome (n=16), pneumocystis carinii pneumonia (n=12), bacterial pneumonia (n=11), meningoencephalitis (n=10), status epilepticus (n=10), neonatal sepsis (n=9), pleuropneumonia (n=8), severe sepsis (n=6), meningitis (n=5), severe heart malformations (n=4), brain hemorrhage (n=4), lung tumor (n=2), electrocution (n=1), and chilothorax (n=1) (Figure 5). The associate conditions in mechanically ventilated patients were: brain hemorrhage (n=16), cerebral palsy (n=11), acute renal failure (n=11), heart malformations (n=9), Duchene muscular dystrophy (n=6), hydrocephaly (n=5), chronic renal failure (n=3), nephritic syndrome (n=2), laryngomalacia (n=2), Down syndrome (n=1), systemic lupus erythematosus (n=1), epidermolysis bullosa (n=1), and hypertrophic cardiomyopathy (n=1) (Figure 6).

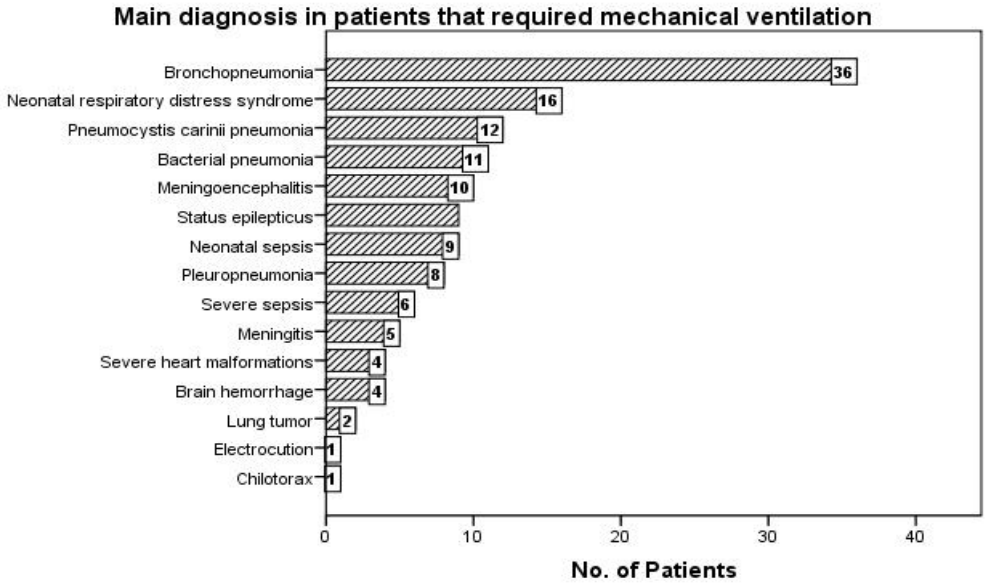

Figure 5: Main diagnosis in patients that required mechanical ventilation.

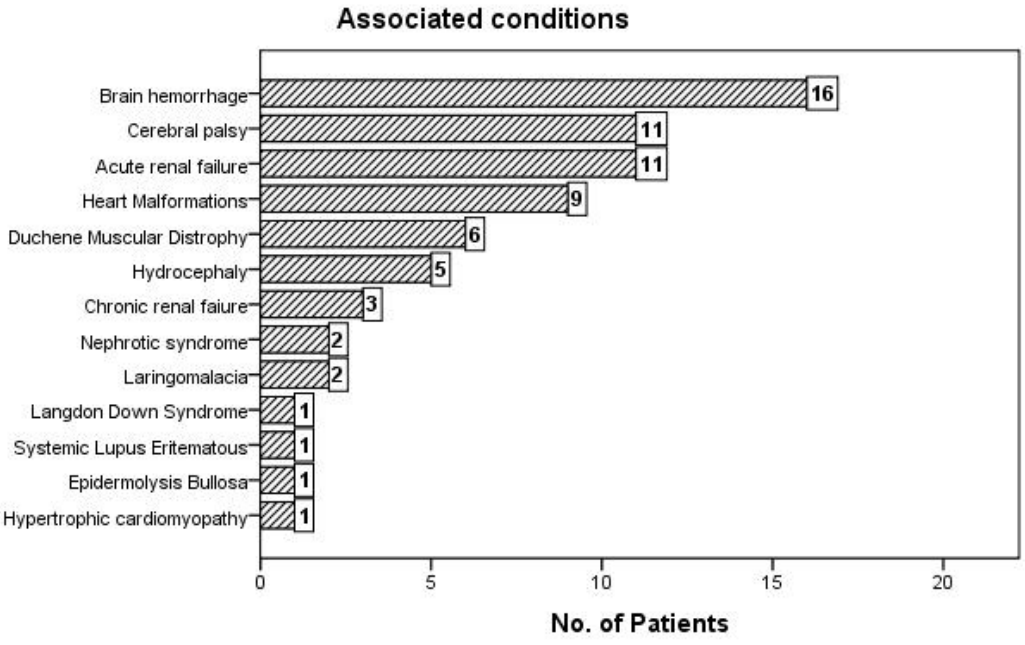

Figure 6: Associated conditions on intubated pacients.

We use for sedation during mechanical ventilation continuous infusion of midazolam and fentanyl in 54 (40.30%) patients, continuous midazolam infusion in 38 (28.36%) patients, and bolus intermittent sedation with midazolam in 20 (14.93%) patients. Twenty-two (16.42%) children did not require continuous or intermittent sedation (Figure 7) because they were with severe brain damage (hemorrhage or palsy). All newborns (n=45) received continuous infusion only with midazolam.

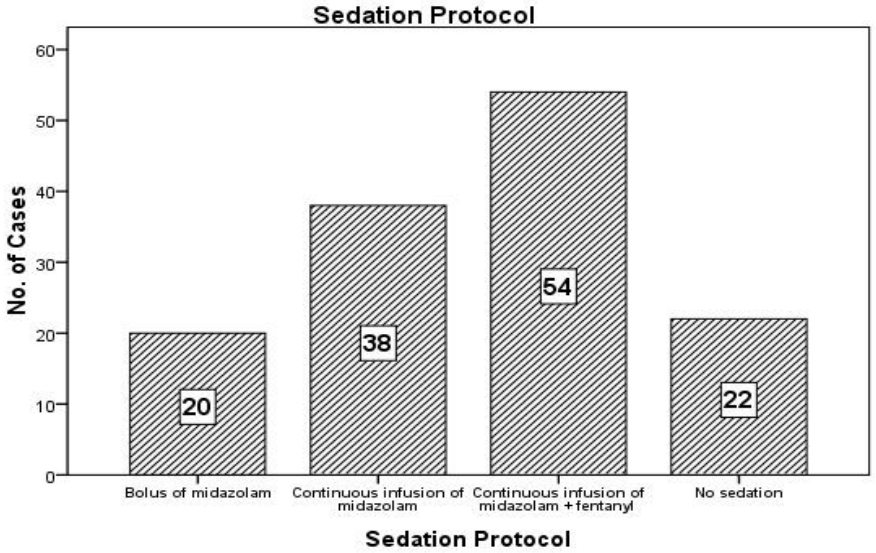

Figure 7: Sedation protocol.

We started continuous infusion with midazolam at 0.1 mg/kg/hr and with fentanyl at 2 mcg/kg/hr. After 24 hours, because of the patient agitation, we had to increase dosage at 0.2-0.3 mg/kg/hr for midazolam and 4-10 mcg/kg/hr for fentanyl. Patients with continuous infusion sedation protocol (n=92) required additional sedation boluses for patient-ventilator asynchrony episodes, which were made with midazolam (0.1–0.2 mg/kg/bolus); midazolam (0.1–0.2 mg/kg/bolus) and fentanyl (1–2 mcg/kg/bolus); or propofol (2–4 mg/kg/bolus) (Table 1). The withdrawal was made subtracting half the rate of infusion at 24 hours. As side effects for continuous infusion with midazolam ± fentanyl, 8 patients presented bradycardia without hemodynamic consequences.

The median duration of mechanical ventilation was 7.7 days, range 48 hours to 83 days (Figure 8). The medium length of stay in hospital was 14.22 days, range 48 hours to 97 days (Figure 9).

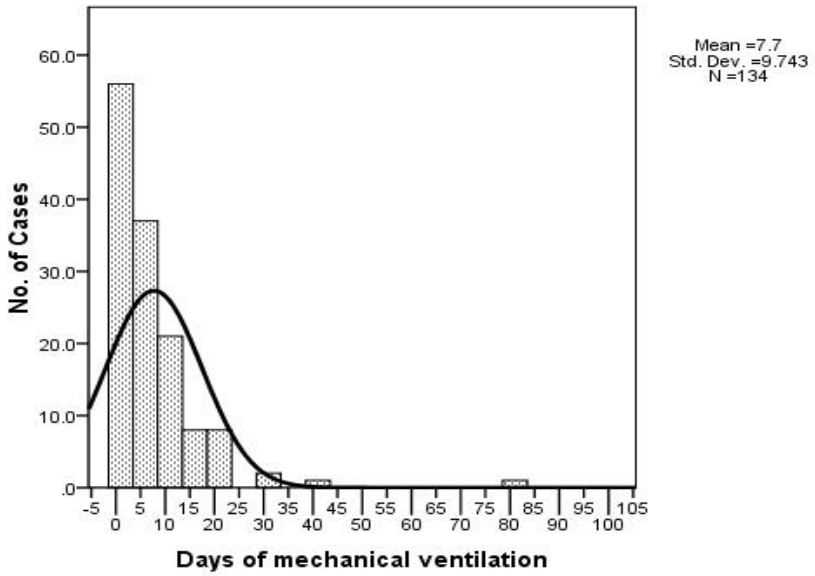

Figure 8: Days of mechanical ventilation.

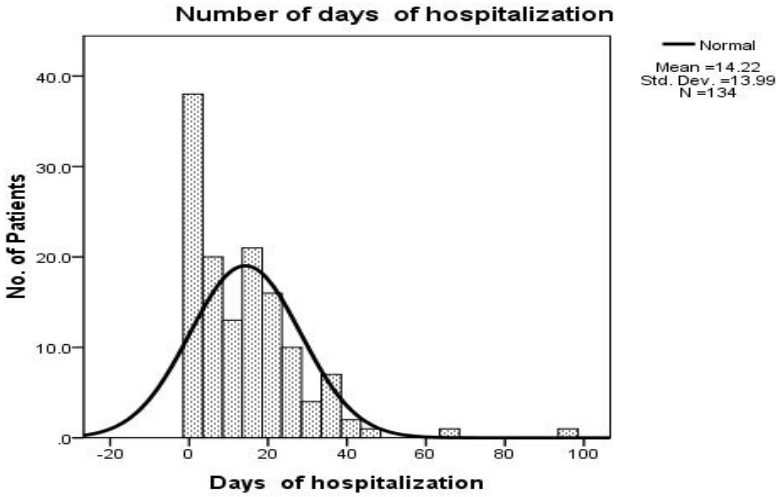

Figure 9: Days of hospitalization.

There were 63 (47.01%) deaths in the PICU (Figure 10), consisting of 60 who died without weaning from mechanical ventilation. Survival rate by age was as follow: newborn – 30 (22.38%) deceased and 15 (11.19%) discharged; infants - 10 (7.46%) deceased and 30 (22.38%) discharged; aged 1 to 3 years - 11 (8.20%) deceased and 12 (8.95%) discharged; aged 3 to 6 years - 6 (4.47%) deceased and 4 (2.98%) discharged; over the age of six years - 6 (4.47%) deceased and 10 (7.46%) discharged (Figure 11). Highest mortality rate can be observed in newborns and highest survival rate in infants.

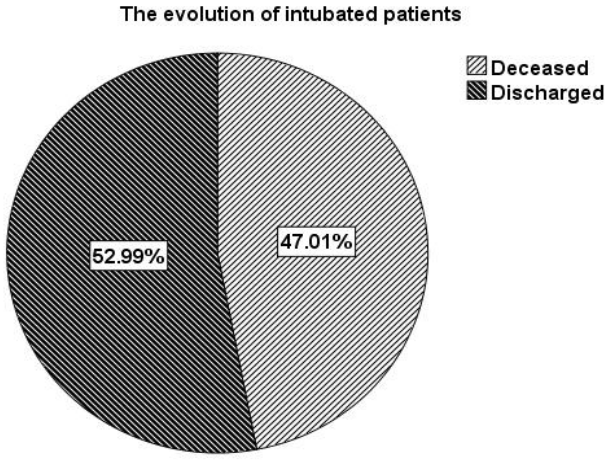

Figure 10: The evolution of intubated patients.

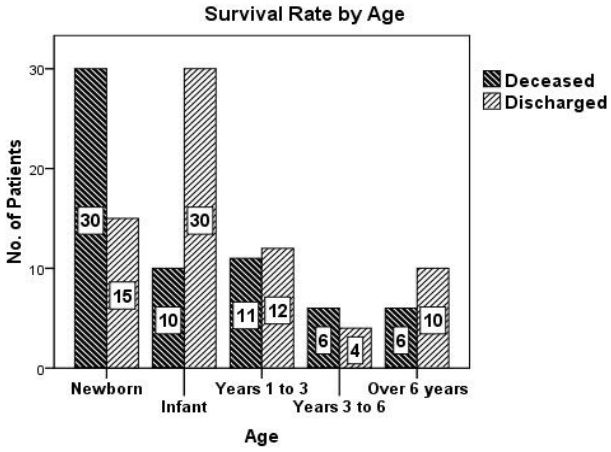

Figure 11: Survival rate by age.

All of the patients received low tidal volume ventilation, antibiotics, continuous correction of homeostasis, management of enteral feeding and pulmonary physiotherapy. After extubation we applied noninvasive respiratory therapy.

Discussions

We had an average of 26.8 mechanically ventilated patients per year (Figure 1). Of these, most (65.67%) were male (Figure 2).

In terms of allocation by age group may find that most patients (63.43%) were aged less than 1 year, while the age group 3-6 years had the lowest number of cases (7.46%) (Figure 3).

Analyzing annual distribution by age group may find a significant reduction in the number of newborn patients since 2008, explained by the establishment of a Neonatal Intensive Care Department in our Hospital (Figure 4).

Principal diagnosis which required mechanical ventilation was bronchopneumonia (28.86%), severe respiratory pathology being involved in 50% of cases

followed by neonatal pathology (24.62%) and CNS disorders (18.65%) (Figure 5). 51.49% of cases had an associated chronic pathology, the most common being brain hemorrhage in newborns and cerebral palsy in children (Figure 6).

The highest survival rate was in 1 month-1 year (75%) and over 6 years (62.5%) age groups and the highest death rate was in newborns (66.6%) (Figure 11).

The largest number of days of ventilation was met at the age group 1 month-1 year (mean = 10.15) and the lowest number of days of hospitalization in children aged between 3 and 6 years (mean = 3.20) (Figure 12).

Days of Ventilation

Age group	Mean	N	Std. Deviation
0-1 luna	5.76	45	12.410
1 luna - 1 an	10.15	40	8.634
1-3 ani	7.74	23	7.454
3-6 ani	3.20	10	1.874
> 6 ani	9.81	16	8.175
Total	7.70	134	9.743

Figure 12. Number of days of ventilation related do age group.

The most important goal during mechanical ventilation in the ICU is to achieve patient comfort and patient–ventilator synchrony. Once proper analgesia has been established, a sedative should be added. Currently, multiple agents are used, usually according to personal preference. Few agents have been evaluated rigorously by more than one or two randomized controlled trials. The Society of Critical Care Medicine and the American College of Critical Care Medicine formed a panel of experts to establish practice guidelines for intravenous analgesia and sedation of adult patients in ICUs. A national survey of the use of sedating agents (11) showed that most ICUs do not use protocols nor do they adhere to practice guidelines. A recent randomized trial in Australia provided no evidence of a substantial reduction in the duration of mechanical ventilation or length of stay, in either the intensive care unit or the hospital, with the use of protocol-directed sedation compared with usual local management (12).

The choice of agent and the way in which they are used varies widely between and within ICUs. Recent surveys of PICU practice in the United States and Great Britain (U.K.) indicate that there is wide variation in practice both within the U.S. and between countries (13,14,15). In the United States, 11 different sedatives are commonly used for the same or similar indications, and at least 20% of PICU's recently surveyed responded that they either "routinely" or "frequently" used eight different sedatives to reduce anxiety and facilitate mechanical ventilation (14,15). In the United Kingdom, the most common sedative agents in use in PICU's continue to be midazolam and morphine (16). A prospective multicenter patient-based study in France shown that midazolam is the agent most commonly used for sedation, and for analgesia sufentanil and fentanyl are the most frequently used opioids (17). Recent Italian guidelines for sedation cite that benzodiazepines are the most commonly used drugs to sedate mechanically ventilated patients (18). Propofol is the preferred IV infusion sedation agent in most U.S. ICU's and is gaining in popularity compared with other sedatives (19). Like others European country, we prefer a continuous combination infusion of midazolam and fentanyl for infants and children, and continuous midazolam infusion in newborn.

Recent interest has centered on dexmedetomidine, a selective alpha-2 agonist with sedative and anxiolytic properties, with comparison primarily to benzodiazepines on the assumption that benzodiazepines represent the standard of care for patients requiring mechanical ventilation for more than short periods of time (20,21).

Several recent papers have directly compared benzodiazepine use to propofol. The study by Carson et al (22) concluded that propofol resulted in fewer ventilator days when compared with intermittent lorazepam for patients ventilated > 48 hrs.

Richmann PS et al, in a recent study, observed that in mechanically ventilated patients, co-sedation with midazolam and fentanyl by constant infusion provides more reliable sedation and is easier to titrate than midazolam alone, without significant difference in the rate of adverse events (6).

Conclusions

In our study, we had better results using 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 achieve relatively in a short period of time. In ventilated newborns, continuous midazolam infusion is enough for obtaining a proper sedation.

Directing treatment to specific and individualized goals will assure that patient needs are met. All currently available sedatives for use in the ICU have limitations. Kress JP et al (23) reported no important differences in any important patient outcomes when comparing different

classes of drugs as long as a strategy directed at limiting complications of drug accumulation was adhered to. Rather than seeking an ideal drug, strategies of drug administration that focus attention on principles of sedative pharmacology in critical illness should be utilized.

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