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Original Article (Pages: 6971-6976)

The Rate of Self-Extubation in Pediatric Intensive Care Unit Following Administration of Fentanyl, Midazolam and Midazolam-Fentanyl Combination: A Comparative Study

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Abstract

Background

Self-extubation is a problem in pediatric intensive care unit (PICU) and can be harmful for children. Level of sedation is a determining factor for self-extubation. The aim of this study was to compare thr rate of self-extubation and duration of ventilation following different sedative modalities.

Materials and Methods

This prospective and randomized study was done in Mofid Children Hospital, Tehran, Iran from October 2015 to September 2016. One hundred and fifty seven children from 1 month to 15 years of age with normal consciousness level requiring mechanical ventilation were included. The rate of self-extubation, and duration of ventilation were compared among 3 groups; Midazolam group (n= 50) 0.1 mg/kg/hr, Fentanyl group (n= 50) 2 mcg/kg/hr., and Midazolam-Fentanyl group (n= 57); midazolam 0.05 mg/kg/hr and fentanyl 1 mcg/kg/hr. All administrations were IV. Optimal level of sedation was 2-3 using Ramsay score.

Results: One hundred and fifty seven children were studied. The mean age of patients was 4.5 ± 1.5 years with an excess of boys (57.9% vs. 42.1%). Rate of self-extubation was lower in Midazolam-Fentanyl group; the difference was significant among 3 groups ($p < 0.01$). There was a significant difference in duration of ventilation in Midazolam- Fentanyl group compared the other groups (Midazolam group and Fentanyl group) ($p < 0.001$).

Conclusion

This study showed that combination therapy with Fentanyl + Midazolam was associated with lower rate of self-extubation and shorter duration of ventilation. In addition, this combination therapy seems safe.

Key Words: Children, Fentanyl, Midazolam, Sedation, Self-extubation.

*Please cite this article as: Salarian S, Mirrahimi B, Bagheri B. Rate of Self-Extubation in Pediatric Intensive Care Unit Following Administration of Fentanyl, Midazolam and Midazolam-Fentanyl Combination: A Comparative Study. Int J Pediatr 2018; 6(1): 6971-76. DOI: **10.22038/ijp.2017.27190.2338**

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Received date: Aug.23, 2017; Accepted date: Nov. 22, 2017

1- INTRODUCTION

Sedation is of great importance in pediatric intensive care unit (PICU). Adequate sedation is necessary to reduce anxiety, prevent post-traumatic stress disorders, proper ventilation, enhance analgesia and facilitate different procedures (1). A good sedative drug should cause rapid return to alertness. Of note, excessive sedation is associated with pulmonary and cardiovascular depression, tolerance, and dependence to ventilator. On the other hand, insufficient sedation can cause self-extubation. Self-extubation refers to unplanned removal of the endotracheal tube. It can be potentially life-threatening event and is associated with hypoxia and ischemia (2, 3). Re-intubation is also a risk factor for ventilator associated pneumonia and infections in critically ill children (4).

Clonidine, dexmedetomidine, fentanyl, midazolam, and propofol are drugs that can be used for sedation in PICU. At present, there are multiple practices for achieving to a proper sedation in PICU. They are usually a combination of analgesic and hypnotic drugs (5). Drug combinations are usually associated with enhanced efficacy and lower rate of untoward effects. To date, there is not an optimal sedation combination in PICU (6).

Ramsay Sedation Scale (RSS), Sedation-agitation Scale (SAS), COMFORT scale, Observers Assessment of Alertness/Sedation Scale (OAASS), Bispectral index (BIS), and middle latency auditory-evoked potential (AEP), are used to assess the level sedation and prevent complications of excessive or insufficient sedation. In this study, we compared different drug regimens to understand which one is more acceptable for sedation in critically ill children. Our purpose was to undertake a comparison the rate of self-extubation and duration of ventilation following different sedative modalities in PICU.

2- MATERIALS AND METHODS

2-1. Study Design and population

This prospective, open label, randomized, comparative study was done in PICU of Mofid Children Hospital, Tehran, Iran. During one year (2016) all admitted children aged from 1 month to 15 years who required mechanical ventilation with any underlying cause and had normal consciousness level, were included in the investigation. Study patients received sedative and analgesic drugs prescribed by intensivists. Patients were randomly assigned to 3 groups: midazolam 0.1 mg/kg/hr (IV), fentanyl 2 mcg/kg/hr (IV), and midazolam 0.05 mg/kg/hr (IV) plus fentanyl 1 mcg/kg/hr (IV). In cases with inadequate level of sedation, thiopental 0.5-1 mg/kg (IV) was added. The rate of self-extubation, level of sedation, duration of ventilation, vital signs, and cumulative dose of midazolam and fentanyl were compared among 3 groups.

2-2. Measuring tools

Ramsay sedation scale (RSS) was used to measure the level of sedation (7). Optimal sedation level was considered 2-3 according to RSS. Level of sedation is measured by 6 scores. The score 1 is condition of anxiety and restlessness and score 6 is condition of no response to stimuli.

2.3. Ethical consideration

The project was approved by local Ethics Committee and written informed consent was obtained from parents of children.

2-4. Inclusion and exclusion criteria

All admitted children from 1 month to 15 years of age and required mechanical ventilation with any underlying cause and had normal consciousness level were included in the study. The exclusion criteria were difficult airway management including structural abnormalities of the airways (Cleft palate, Pierre Robin

syndrome), and systemic disorders that affect intubation like Mucopolysaccharidosis.

2-5. Data Analyses

The data are shown as mean ± standard deviation [SD]. Descriptive statistics were calculated on all variables. One- way ANOVA was used to study differences among groups. P <0.05 was considered to denote statistical significances. Analysis was carried out using SPSS software version 18.0, Chicago, USA.

3- RESULTS

A total of 157 patients were studied between October 2015 and September 2016. Fifty patients were in midazolam group, 50 patients were included in fentanyl group, and 57 patients were in midazolam plus fentanyl group. Demographic and clinical characteristics of study subjects are shown in **Table.1**. The mean age was 4.5 ± 1.5 years with an excess of boys (57.9% vs. 42.1%). There were no significant differences in clinical and demographic characteristics of patients in 3 groups (P>0.05).

3-1. Midazolam group

The maximum dose in the midazolam group was 10 mg/kg/hr regardless of patient's weight. Five patients achieved Ramsay score 2-3 with midazolam 0.15-0. 2 mg/kg/hr. Maximum dose of midazolam was used for 25 patients to keep Ramsay score between 2 and 3.

Due to insufficient sedation, remaining 20 patients were administered thiopental 0.5-1 mg/kg/hr as an intermittent medication to keep Ramsay score between 2 and 3. In this group, 13 cases of self-extubation were seen. Mean duration of ventilation was 7.8 days and rate of self-extubation was 3.3 per 100 ventilator days. Data for drug dose and duration of ventilation are presented in **Table.2.**

3-2. Fentanyl group

The maximum dose used in fentanyl group was 5mcg/kg/hr. Four patients had the Ramsay score 2 with fentanyl 1mcg/kg/hr. Twenty-one patients required the maximum dose to keep the Ramsay score between 2 and 3 and 25 patients did not achieve sufficient sedation with maximum dose and were given thiopental 0.5 to 1 mg/kg/hr. Mean duration of ventilation was 7.3 days. There were 11 cases of self-extubation in this group; 7 patients had one self-extubation on the second day and 4 patients had two self-extubation during the ventilator course. The rate of self-extubation was 3.0 per 100 ventilator days.

3-3. Midazolam plus fentanyl group

In this group, 41 patients achieved Ramsay score 3 with the aforementioned doses, 11 patients required larger fentanyl dose; 3mcg/kg/hr to keep the Ramsay score between 2 and 3 and 5 patients required larger midazolam dose; 7mg/kg/hr. Five cases of self-extubation were noted in this group. Mean duration of ventilation was 4.3 days. Rate of self-extubation was 2.8 per 100 ventilator days. Total rate of self-extubation was 3.0 per 100 ventilator days.

3-4. Rate of self-extubation

As shown in **Table.3**, the rate of self-extubation was higher in midazolam and fentanyl groups compared to midazolam plus fentanyl group. The difference achieved a significant level (p<0.01).

3-5. Safety

No case of acute respiratory distress, severe hypotension and severe bradycardia was seen in the period of study. No patient died and no patient was withdrawn due to severe adverse events.

Table-1: Baseline characteristics of study patients in 3 groups

Variables	Midazolam (n=50)	Fentanyl (n=50)	Midazolam-Fentanyl (n=57)
Age (years)	5.3 ± 1.5	4.2 ± 1.7	4.9 ± 1.3
Male (%)	63	46.6	65
SBP (mmHg)	111 ±7.7	114 ± 7.7	111± 8.1
DBP (mmHg)	62 ± 6.2	63 ± 6.9	61± 6.4
Respiratory rate (breaths/min)	29 ± 3.2	27 ± 4.2	29 ± 4.6
Heart rate (beats/min)	115 ± 1.3	112 ± 1.3	115 ± 1.9

Data are shown in mean ± SD or percent.

Table-2: The doses of sedative drugs and duration of ventilation in 3 groups

Group	Min dose	Max dose	Ventilation duration(day)
Midazolam	0.1 mg/kg	10 mg/kg	7.8 ± 1.5
Fentanyl	2 mcg/kg	5 mcg/kg	7.3 ± 1.7
Midazolam-Fentanyl	0.05 mg/kg+1 mcg/kg	7 mg/kg+3 mcg/kg	4.3 ± 1.1 *

Data are shown in number or mean ± SD; * P<0.001 vs. Midazolam group and Fentanyl group.

Table-3: The rate of self-extubation per 100 ventilators days in 3 groups

Group	Rate of self- extubations	**Per**cent
Midazolam	3.3	47.3%
Fentanyl	3	39.5%
Midazolam +Fentanyl	2.8*	13.2 %

Data are shown in number or percent; *P<0.01 vs. Midazolam group and Fentanyl group.

4- DISCUSSION

In this comparative study, we investigated effect of different sedative modalities on rate of self-extubtion and duration of ventilation in children undergoing mechanical ventilation. Our study showed that there is a significant difference in the rate of self-extubation in monotherapy with fentanyl and midazolam and combination therapy with midazolam plus fentanyl. In addition, a significant difference was noted in ventilation days and need for thiopental rescue therapy. The combination therapy with midaozlam and fentanyl lead to reduced amount of drugs. The reduction in fentanyl and midazolam requirement was associated with lower rate of self-extubation and shorter ventilation duration. Of note, the adverse effects of sedative drugs including respiratory depression, dependence, tolerance, delusions, post-traumatic stress disorder, and depression and withdrawal syndrome are largely associated with the duration of treatment (1, 8-10). The excessive use of anesthetic and sedatives can lead to neurologic deficits and learning difficulties. There are a growing number of evidence warnings about effects of anesthesia on the developing neurons especially in children and adolescents (10-13). The pediatrics seems to be more prone to these negative effects and finding a way to reduce the duration of exposure is helpful. The present study showed that using the combination of benzodiazepines and an opioid could reduce duration of

ventilation and it was associated with lower rate of self-extubation. The combination of a benzodiazepine and an opioid would lead to fewer withdrawal symptoms (14). Further studies are needed to clarify which one is more related to withdrawal symptoms; duration of sedation or number of drugs. The trend of self-extubation was lower in midazolam plus fentanyl group. It could be explained by risk factors of self -extubation in pediatric population. Risk factors associated with self-extubation are age (younger patients), inadequate tube fixation, agitation, copious secretions, performance of patient procedures, and nursing workload (4, 5).

The age of patient is an important risk factor for self- extubation; Da Silva et al. reported that patients under 2 years and especially patients under 1 year are at higher risk of self-extubation compared with older patients (15). A study by Sadowski et al. showed that patients under 5 years are more susceptible for unplanned self-extubation (16). Compared with these studies, we had smaller sample size and it could be contributing to our findings. Interestingly, Kanthimathinathan' study demonstrated that rate of self-extubation is higher in younger critically ill patients (17). The duration of intubation is also a risk factor for self-extubation (18). Various studies have used different cut-off point to measure optimal sedation (19-21).

Two studies by Lamas (20, 21) have provided evidence for Bispectral index (BIS) and middle latency auditory-evoked potential (AEP) to assess the level of sedation in children after cardiac surgery and also in critically ill children. However, current data are not conclusive in pediatrics and more studies should be conducted to determine optimal sedation protocol. In addition to intensive care, fentanyl and midazolam can be used in other procedures like labor and magnetic resonance urography (22-24).

There are several limitations to our study that should be acknowledged. More information is required to determine whether current protocols can robustly decrease the incidence of self-extubation. Our findings can be confirmed in larger studies with pooled analysis on underlying causes of intubation. Further studies may be necessary to show that sedation guided by Ramsay sedation scale is reliable in critically ill children.

5- CONCLUSION

We aimed to undertake a comparison on rate of self-extubation and duration of ventilation following different sedative modalities in PICU. Our study showed that administration of midazolam plus fentanyl is associated with lower rate of self-extubation. This combination therapy could decrease the duration of ventilation in PICU and seems safe.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

The study was done by a grant from the vice chancellor of research of Shahid Beheshti University of Medical Sciences.

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