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ORIGINAL ARTICLE

Profile of the use of sedoanalgesia in children under mechanical ventilation in an intensive care unit

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Deep Sedation, Analgesia, Substance Withdrawal Syndrome, Pediatric Intensive Care Units.

Abstract

Objective: To describe the use of analgesics and sedatives in children undergoing mechanical ventilation in a Pediatric Intensive Care Unit, identifying the drugs used, doses and duration, and to check for the occurrence of Withdrawal Syndrome. **Methods:** A cross-sectional, retrospective, descriptive and quantitative study was carried out. The participants were children admitted to a Pediatric Intensive Care Unit between July 2014 and June 2015, requiring analgesic and/or sedative therapy in continuous infusion and mechanical ventilation, who remained in the ward for more than 12 hours. **Results:** 41 individuals were enrolled, corresponding to 63% of hospitalized patients. The medications used for continuous sedoanalgesia were Midazolam, Ketamine and Fentanyl; they were used in low infusion doses for a mean time of 11.5 ± 11.4 days. Withdrawal Syndrome occurred in 39% of the patients, who used them for a mean period of 19.31 (± 11.57) days. There was a relationship between prolonged sedoanalgesia and the development of the syndrome ($p < 0.001$), since 70% of those who received continuous sedoanalgesia for a period of more than 7 days developed withdrawal symptoms. **Conclusions:** The use of analgesics and sedatives was a very frequent practice and, due to the prolonged use of the drugs, there was an important occurrence of Withdrawal Syndrome.

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INTRODUCTION

In the Pediatric Intensive Care Unit (PICU), the child is constantly exposed to intense physical and psychological stress. This adverse scenario, associated with the need for invasive ventilatory support, often requires the administration of sedatives and analgesics.

There is a preference for the use of continuous infusion analgesics in intensive care units[1,2]. In addition to treating anxiety, agitation and pain, the combination of analgesics and sedatives, due to their hypnotic effects, respiratory depressants and cough reflex, enables a better adaptation to Mechanical Ventilation (MV)[3].

However, excessive and incorrect use of sedoanalgesia may have negative repercussions, leading to an increase in the need for ventilatory support, length of stay and increased risk of infection. This is because the body begins to develop mechanisms that lead to physical dependence, determining a need to receive the drug in increasing doses to maintain the clinical effect[4]. This is called tolerance, which is defined by the decrease in the drug effect at the dose used with time. Thus, sudden suspension or reduction of sedoanalgesia may induce withdrawal syndrome, characterized by the appearance of a combination of signs and/or symptoms that are variable in presentation and severity (tachycardia, sweating, agitation, tremors, fever, etc.)[2,3,5].

To implement the sedoanalgesia protocols, it is necessary to have knowledge on the use of analgesics and sedatives in children in the intensive care setting, in addition to the repercussions resulting from this practice, such as the occurrence of withdrawal syndrome, which we propose here. Knowledge about prescribing sedoanalgesia and its consequences makes it possible to implement standardized measures that minimize the negative effects arising from it.

The objective of this study was to describe the use of analgesics and sedatives in children undergoing mechanical ventilation in a PICU, in order to identify the drugs used and their doses and duration; and to evaluate the incidence of withdrawal syndrome to sedoanalgesic drugs in these individuals, so that this knowledge makes it possible to implement protocols for managing sedoanalgesia.

METHODS

This is a retrospective, descriptive, cross-sectional observational study with a quantitative approach and secondary analysis of the data in the PICU of the Teresina Emergency Hospital (HUT). All the children admitted to the PICU between July 2014 and June 2015, who needed analgesic and/or sedative therapy under continuous infusion and who used mechanical ventilation, remained in the ICU for a period of more than 12 hours. Those patients who did not meet any of these criteria or whose information could not be located through the medical records were taken off the study.

Data collection was performed from September to October 2016, during which time, 65 charts were analyzed referring to all patients admitted to the PICU during the study period. After identifying 41 individuals who were using sedoanalgesics and ventilatory support, we defined the profile of the sedatives and analgesics used. We developed a form which we used to collect the data, in which we listed data on the child (gender and age), the use of sedoanalgesic drugs, their respective doses, interruption (abrupt or gradual) and duration of the therapy, besides the clinical indication of mechanical ventilation according to the basic pathology (sepsis, pulmonary dysfunction, neurological disorder and cardiovascular dysfunction). We searched and found the withdrawal Syndrome cases in the medical records, based on characteristic signs and symptoms manifested during weaning of the drugs.

We input the data in a Microsoft Office Excel 2010® worksheet and then analyzed in the R software version 3.2.2 for Windows®. We used the Student t-Test to compare independent samples between two means when the data were normal and homogeneous; otherwise we used the Mann-Whitney test. We tested the association between categorical variables using the Fisher's exact test, since some cases presented values lower than 5. The data was considered significant when p values were below 0.05.

This study was approved by the Research Ethics Committee of the Faculdade Integral Diferencial (FACID) (CAAE: 59723616.3.0000.5211).

RESULTS

In the twelve months of the study, from July 2014 to June 2015, 65 children were admitted to the PICU. Of this total, 24 patients were excluded, 9 because they did not have the medical records, 13 because they did not use continuous sedoanalgesia and/or mechanical ventilation and 2 because they had stayed less than 12 hours in the intensive care unit. Thus, at the end of the data collection, 41 individuals were considered eligible. This shows that, of the children admitted to the PICU, 63% received continuous intravenous sedoanalgesia and were submitted to MV for a period of more than 12 hours.

The mean age of the individuals was 2.27 ± 3.16 years. There was a higher frequency of females, representing 23 patients (56%), while 18 (44%) were males. For the administration of sedatives and analgesics, we used Midazolam, Fentanyl and Ketamine for continuous intravenous sedoanalgesia. The most frequently used drug combination was Midazolam and Fentanyl (24/58.5%), followed by Midazolam and Ketamine (13/31.7%) and Midazolam alone (4/9.8%). The mean continuous infusion dose and the mean time of use are shown in Table 1.

Regarding the prevailing clinical condition in each individual, which led to the indication of MV, the main cause was pulmonary dysfunction (18/43.9%), followed by sepsis (9/22%), neurological disorder (8/19.5%) and cardiovascular

dysfunction (5/12.2%). There was a significant association between the choice of sedoanalgesics and the recommendation of ventilatory support ($p = 0.037$), as one can see in Table 2.

The withdrawal cases were identified through the medical record survey of the respective diagnosis in medical records, in view of the manifestation of characteristic signs and symptoms during the hospitalization. Therefore, a total of 16 patients presented signs and symptoms corresponding to the withdrawal syndrome, which corresponds to 39% of the individuals using sedoanalgesics.

The majority of children undergoing more therapeutic interventions requiring increasing doses of sedoanalgesia showed more frequent withdrawal symptoms. Most of those who had more discreet interventions or no dose modification did not show the same degree of withdrawal development for sedoanalgesics (Table 3).

In this study, we also show the significant relationship ($p < 0.001$) between the sedoanalgesia duration and the withdrawal syndrome (Table 4). The 16 patients who developed withdrawal used sedoanalgesia for a mean period of 19.31 (± 11.57) days, whereas patients who did not present any characteristic signs and/or symptoms remained in use of the therapy for 6.48 (± 8.09) days, which reveals a statistically significant difference between the mean values of therapy durations ($p < 0.001$). The mean duration of sedoanalgesia with Midazolam and Fentanyl was significantly higher ($p < 0.006$) in subjects who presented with withdrawal syndrome.

We also assessed the forms of sedoanalgesia interruption. The main mode of treatment interruption, except for cases of death and transfer during hospitalization, was the reduction in the continuous infusion dose concomitant with the association with an equivalent weaning drug (14/34,15%). Among the patients studied, 41.5% (n = 17) used weaning drugs and the main combination used was Lorazepam and Clonidine, with or without methadone (16/39%).

12.2% (n = 5) of the studied children had abrupt withdrawal of sedoanalgesia and none of them had withdrawal syndrome ($p < 0.001$). However, of these patients whose sedoanalgesia was abruptly withdrawn, 80% (n = 4) used it for less than 3 days.

The occurrence of withdrawal syndrome was significantly higher ($p < 0.001$) in patients who had progressive withdrawal of sedoanalgesia (use of equivalent weaning drugs associated with decreasing continuous infusion dose). However, 85% of the children whose interruption of sedoanalgesia was performed in this manner remained in use for more than 7 days.

DISCUSSION

From these data obtained in a PICU, in one year, we report that a great part (63%) of the children admitted to this unit received continuous intravenous sedoanalgesia and were submitted to MV for a period superior to 12 hours. Rodrigues Júnior and Amaral[6] reported that in an Adult Intensive Care Unit, 37.4% of the patients used sedatives, and MV support was the main indication for sedation. Thus, we note that sedoanalgesia in the intensive care setting is quite frequent, especially when it is related to ventilatory support, because it inhibits the neuroendocrine effects caused by stress and, consequently, reduce oxygen consumption, to facilitate synchronization with the MV device[3,7].

In the severe patient, the sedatives and analgesics are preferably administered as an uninterrupted infusion. Midazolam, Fentanyl and Ketamine were identified as the most used drugs in the PICU where the research was carried out. For Martinbiancho1 and Sfoggia et al.[2], these agents are part of the group of the main sedoanalgesics used in PICUs, which are the benzodiazepines (Midazolam and Diazepam), chloral hydrate, opioids (Morphine and Fentanyl), barbiturates (Thiopental) Ketamine. In the present study, all patients submitted to MV received sedative analgesic therapy, the sedative was Midazolam, associated or not with an analgesic drug. In addition, we noticed that the indication of the sedoanalgesics was related to the basic pathology of each individual. The Midazolam and Fentanyl combination was the one of choice for patients with pulmonary dysfunction or neurological disorder. The second combination, Midazolam and Ketamine, was used with significantly greater frequency ($p = 0.037$) in patients with sepsis or cardiovascular dysfunction.

Table 1. Mean continuous infusion dose and mean time of sedoanalgesia administration to children submitted to mechanical ventilation in a PICU.

Variables	Sedoanalgesic drugs	n	Mean	Standard deviation
Dose	Midazolam (mg/kg/h)	41	0.30	0.14
	Fentanyl (µg/kg/h)	24	3.08	1.47
	Ketamine (µg/kg/min)	13	7.38	2.76
Time (days)	Midazolam	4	3.00	1.83
	Midazolam and Ketamine	13	10.46	10.45
	Midazolam and Fentanyl	24	13.46	12.28
	Total	41	11.49	11.38

Source: ARAÚJO (2016)
n= Absolute frequency.

Table2. Correlation of sedoanalgesic drugs and mechanical ventilation indication in children in a PICU.

MV indication	Sedoanalgesic drugs								*p**
	Midazolam		Midazolam and Ketamine		Midazolam and Fentany		Total		
	n	%	n	%	n	%	n	%	
Sepsis	0	0.00	5	38.46	4	16.67	9	21.95	0.037
Pulmonary dysfunction	2	50.00	4	30.77	12	50.00	18	43.90	
Neurological disorder	2	50.00	0	0.00	6	25.00	8	19.51	
Cardiovascular dysfunction	0	0.00	4	30.77	1	4.17	5	12.20	
Other	0	0.00	0	0.00	1	4.17	1	2.44	
Total	4	9.76	13	31.71	24	58.54	41	100.00	

Source: ARAÚJO (2016)
n= absolute frequency; %= relative frequency; *= Fisher's exact chi-square test; p-value below 0.05 is considered significant.

Table 3. Withdrawal syndrome according to increases in sedoanalgesic doses in children submitted to mechanical ventilation in a PICU.

Signs of tolerance	Withdrawal syndrome				Total		*p**
	Yes		No				
	n	%	n	%	n	%	
Increases in continuous infusion dose	0	0,00	4	100,00	4	9,76	0.002
Use of intermittent injections	6	75,00	2	25,00	8	19,51	
Increase in the continuous infusion dose and use of intermittent injection	7	63,64	4	36,36	11	26,83	
Unmodified dose	3	16,67	15	83,33	18	43,90	
Total	16	39,02	25	60,98	41	100,00	

Source: ARAÚJO (2016)
n= absolute frequency; %= relative frequency; *= Fisher's exact chi-square test; p-value below 0.05 is considered significant.

Table 4. Withdrawal syndrome according to the sedoanalgesia duration in children submitted to mechanical ventilation in a PICU.

Sedoanalgesia duration	Withdrawal syndrome				Total		*p**
	Yes		No				
	n	%	n	%	n	%	
< 3 days	0	0.00	12	100.00	12	29.27	< 0.001
3 to 7 days	4	33.33	8	66.67	12	29.27	
> 7 days	12	70.59	5	29.41	17	41.46	
Total	16	39.02	25	60.98	41	100.00	

Source: ARAÚJO (2016)
n= absolute frequency; %= relative frequency; *= Fisher's exact chi-square test; p-value below 0.05 is considered significant.

According to Bartolomé, Cid and Freddi[3], Midazolam is the benzodiazepine of choice for continuous administration in severely-ill pediatric patients, being four times more potent than Diazepam, with rapid onset and plasma-brain equilibrium time between 0.9 and 5.6 minutes. Morphine and its derivatives are drugs that act on opioid receptors, causing analgesia and sedation, but without causing amnesia. Therefore, they are frequently associated with benzodiazepines, as seen in 58.5% of the patients studied, with the main form of sedoanalgesia being the combination of Midazolam and the opioid Fentanyl. It presents a rapid onset of action and a shorter duration when compared to morphine, with a half-life plasma-brain balance of 6.4 minutes. In the study by Rodrigues Júnior and Amaral[6], Fentanyl was the most administered analgesic agent, corresponding to 58% of the cases, a fact similar to that evidenced in this study. This preference for the use of an opioid drug as an analgesic agent in patients in MV is due to the fact that, when combined with a benzodiazepine, there is a synergistic effect that enables the reduction of both doses and, consequently, reducing the damages caused by excessive sedoanalgesia[3].

No patient with a neurological disorder used the Midazolam and Ketamine combination, since the latter drug is believed to increase cerebral oxygen uptake and cerebral blood flow, fearing increased intracranial pressure levels. Ketamine was preferably administered in patients who had sepsis or cardiovascular dysfunction, because although it has a negative

inotropic effect and vasodilatory properties, it maintains hemodynamic stability due to its systemic action secondary to the release of catecholamines, in addition, the Midazolam and Fentanyl combination increases the likelihood of hypotension, especially in hypovolemic patients, and should be avoided in this group of patients.

Based on the Playfor[8] and Lago et al.[9] reviews, the mean doses administered for each sedoanalgesic drug can be considered as low. Some authors also correlate the risk of abstinence with the doses of sedoanalgesic medications used. In their study, Bicudo et al.[10] demonstrated that the cumulative total dose, daily dose and infusion rate are significantly related to the withdrawal syndrome associated with Fentanyl and Midazolam infusion discontinuation in children.

The median time of use of the sedoanalgesic drugs (11.5 ± 11.4 days) can be considered long. Many studies have shown negative consequences of the liberal and prolonged use of sedative and analgesic agents, especially when in the form of continuous infusion[2,9,11]. In this study, there was an important occurrence of Withdrawal Syndrome among the children evaluated (39%), with a great variability of signs and symptoms. A similar finding was found in the Fonsmark, Rasmussen and Carl's[12] study, which defined a 35% incidence of Withdrawal Syndrome in children in a PICU after sedoanalgesia discontinuation. In their studies, Bicudo et al.[10], Fernández-Carrión et al.[11] and Sfoggia et al.[2]reported withdrawal syndrome incidences of 50%, 50% and 49%, respectively; being this situation related to prolonged use of sedation and analgesia and high cumulative doses, according to the same authors.

Interventions to increase the dose of sedoanalgesics - either through intermittent injections or an increase in the rate of continuous infusion - are essential because of the development of mechanisms that generate tolerance, when the effect of the drug decreases with time, and there is a need to increase the dose of the drug to obtain the same result[4]. This culminates in an increase in the total cumulative dose of sedoanalgesic drugs, a fact that is related to the onset of withdrawal syndrome, as Fonsmark, Rasmussen and Carl[12] and Wildt et al.[13] have reported, which showed a significant association between the sedatives dose accumulation of sedatives with the manifestation of signs and symptoms of withdrawal.

Prolonged use is also related to the Withdrawal Syndrome. At first, it was noticed that a large number of children used continuous sedoanalgesia for a period of more than 7 days (17/41.5%), and of these, 12 presented signs and symptoms characteristic of withdrawal to sedoanalgesics, which represents an incidence of 70.6% in this group. In addition, all individuals who remained in sedoanalgesia for less than 72 hours did not present the typical clinical signs of the syndrome. Thus, it is possible to state that there is an association between the occurrence of withdrawal syndrome and prolonged sedoanalgesic therapies, especially when it extends over a period of more than 7 days. Some studies show that an infusion duration of sedatives and analgesics over 7 days are related to an occurrence of signs and symptoms of withdrawal ranging from 50% to 100%[2,3,9,10].

Among the combinations of sedatives and analgesics, it has been shown that the association of Midazolam and Fentanyl, when used for longer average times of use, is significantly related to a more frequent development of signs and symptoms of withdrawal. We found a correlation between the prolonged use of the opioid drug and the development of Withdrawal Syndrome, and there was no such relation with the use of Ketamine. Several studies have suggested that the association of Fentanyl with sedoanalgesia schemes seems to prolong the duration of therapy and lead to an increase in the occurrence of signs and symptoms of withdrawal[12,14,15]. This can be explained by the properties and characteristics of the interaction of opioids with their receptors. These drugs have the ability to induce tolerance after a few days of use and to produce withdrawal with abrupt reduction or withdrawal after prolonged use and/or high cumulative doses. However, in the study carried out by Lago et al.[9], they found that prolonged use of Ketamine may also produce tolerance and withdrawal.

In view of the above, the risk for withdrawal syndrome after the interruption of analgesics and sedatives should be considered in the case of high doses or prolonged use periods of approximately seven days. These doses should be gradually reduced to avoid the onset of symptoms, as was done in most cases. This behavior is in accordance with the protocols and guidelines for weaning of sedoanalgesia, in which the daily gradual reduction of the level of sedation is established, without abruptly removing the sedoanalgesic ones, associated with the progressive substitution of the intravenous drugs by drugs of longer duration by via enteral.

Currently, the most commonly used drugs for sedoanalgesia weaning are enteral methadone and morphine in the opioid group, Lorazepam and chlordiazole in the benzodiazepine group and alpha-2-agonists, such as Clonidine and Dexmedetomidine[3], as well as per reported in the present study, in which Lorazepam, Methadone and Clonidine were administered in 41.5% of subjects. The replacement of intravenous Fentanyl by enteral methadone shortens the time of ventilatory weaning in severe adult patients, as demonstrated by Wanzuita[15].

It has been demonstrated in the literature that one of the factors related to withdrawal syndrome is the abrupt interruption of continuous infusion of sedoanalgesia[3]. The results obtained contradict this statement. In this study, we noticed that most of the patients who had abrupt drug interruption made use of sedoanalgesia for a few days and, consequently, did not present withdrawal. Those who had gradual reduction and use of drugs for weaning from sedoanalgesia developed the syndrome more frequently, but used the medications for a longer time. Although there was no standardization protocol for the management of weaning and use of sedoanalgesics implemented at this PICU at the time this study was carried out, we report that the interruption of sedoanalgesia prioritized the

time elapsed from its onset. It has been suggested that clinical withdrawal has a greater relation to the therapy duration than to the form of interruption, since, for its manifestation, it is fundamental to establish the physical tolerance, which is induced by the prolonged administration of the medications.

They concluded that the use of analgesic and sedative drugs was a frequent practice in the study population. The main drugs used were Midazolam, Fentanyl and Ketamine in continuous infusion, identified as the main drugs applied in the sedoanalgesia, according to the clinical status of each patient. The mean infusion doses were considered low and the time of prolonged use, a fact that was associated to an important occurrence of withdrawal Syndrome. These data regarding the use of sedoanalgesia may reflect the reality of other PICUs. For a more objective definition of this information, we suggest prospective studies through the daily analysis of sedoanalgesia, since the study may be compromised by the scarcity of medical records.

Once the profile of sedoanalgesia use in a PICU and the consequences inherent to such practice are established, such as the occurrence of withdrawal in these patients, it is then necessary to establish protocols that guide the use and discontinuation of sedatives and analgesics, in order to promote physical and psychological comfort to these children with the least possible chance of harm. Therefore, the use of sedoanalgesia should be carefully analyzed by the medical team and individualized according to the patient, in order to always use the lowest dose possible and minimize the risks of adverse effects.

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