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Impact of the implementation of a sedation and analgesia protocol in a pediatric intensive care unit

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ABSTRACT

Introduction. Adequate sedation and analgesia is essential in the management of patients requiring mechanical ventilation (MV). The implementation of protocols and their monitoring is recommended; mixed results on adherence and impact have been reported.

Objectives. To assess the impact of the implementation of a sedation and analgesia protocol on the use of benzodiazepines, opioids, and evolution in the pediatric intensive care unit (PICU) in patients requiring MV for more than 72 hours.

Methods. Before-and-after, uncontrolled study in the PICU of a children's hospital. The study was developed in 3 stages: pre-intervention for situational diagnosis (from April to September 2019), intervention, and post-intervention for implementation of a sedation and analgesia protocol, education on use, and monitoring of adherence and impact (from October 2019 to October 2021).

Results. A total of 99 and 92 patients were included in the study in the pre- and post-intervention stages, respectively. Patients had a more severe condition, were younger, and had a lower weight in the pre-intervention period. After adjusting for severity and age, the group comparison in the post-intervention stage showed a reduction in days of continuous infusion of opioids (6 ± 5.2 versus 7.6–5.8, $p = 0.018$) and days of continuous infusion of benzodiazepines (3.3 ± 3.5 versus 7.6 ± 6.8, $p = 0.001$). No significant differences were observed in days of MV and total days of benzodiazepine use.

Conclusion. The implementation of a sedation and analgesia protocol resulted in a reduction in the use of continuous infusion of drugs.

Key words: *clinical protocols; analgesia; mechanical ventilation; pediatric intensive care unit.*

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INTRODUCTION

Sedation and analgesia are crucial components in the care of critically ill patients, especially those requiring mechanical ventilation (MV). The purpose of sedation and analgesia is to mitigate patient pain, anxiety, and agitation; induce amnesia; and optimize comfort and adaptation to MV.[1] The guidelines developed by expert consensus recommend implementing protocols and monitoring them to optimize the control of sedation and analgesia.[2–6]

Adherence to a sedation and analgesia protocol would prevent variability in the administered treatment and thus optimize it, and avoid errors and adverse events. However, according to surveys, the percentage of adherence has been observed to be low: 18% in 45 PICUs at national level[7] and 51% in 161 PICUs in 18 countries.[8]

It would be reasonable to estimate that adherence to a sedation and analgesia protocol would result in better outcomes; however, the publications on this topic have reported conflicting results at the pediatric level.[9,10]

OBJECTIVES

Primary. To assess the impact on the length of days in the PICU in children who required MV after the implementation of a sedation and analgesia protocol, compared to a historical registry.

Secondary. To describe the impact on total days and days of continuous infusion of opioids and benzodiazepines, days of MV, and total length of stay in days, compared to the historical registry. Adherence was assessed to identify compliance with the sedation and analgesia protocol.

METHODS

Design

A quasi-experimental, uncontrolled, before-and-after study was carried out after implementation, with a comparison to a historical cohort. We selected this type of design because the protocol was implemented as a quality improvement intervention and a new standard of care in the PICU.

The study was conducted in 3 stages:

1. Pre-intervention (from April to September 2019), aimed at performing a situational diagnosis of the different indicators through the collection and retrospective analysis of medical records.
2. Intervention (October 2019), which consisted of the protocol optimization and active participation of the health care team, aimed at achieving systematization in the daily use of the sedation and analgesia protocol.
3. Post-intervention (from November 2019 to October 2021), during which the progression of protocol adherence was monitored through direct observation and/or analysis of clinical records by the investigators responsible for the study and its impact on outcomes.

Population

The study was carried out at the PICU of Hospital General de Niños Pedro de Elizalde (HGNPE). This is a polyvalent, primary care PICU with 11 beds for patients aged 1 month to 18 years with different conditions, except for cardiovascular postoperative care and post-transplant care.

All patients aged ≥ 1 month and under 18 years and requiring MV for more than 72 hours were consecutively included in the study over a 24-month period (November 1st, 2019 to November 30th, 2021). Deceased patients, those who required referral to another institution from the PICU (to prevent underreporting of length of stay in the PICU); those who underwent or had previously undergone a tracheostomy; and those whose neurological status precluded adequate monitoring of sedation and analgesia (neurological sequelae, severe hypotonia, dystonia, etc.) were excluded. Our population was compared to a historical cohort (April 1st, 2019 to September 30th, 2019), which met the same inclusion and exclusion criteria.

Intervention

The original version of the sedation and analgesia protocol was developed by investigators Pedro Taffarel and Facundo Jorro Barón, based on existing bibliography. The final version is the result of consensus among the different physicians working at the PICU, who participated in the review, improvement, and approval of the final protocol. Lastly, the protocol was submitted for validation by different health care providers in this field.

For a better organization and understanding, the protocol was divided into 3 sections:

1. Initial management of patients exposed to MV (*Supplementary material: Figure 1*).
2. Refractoriness to first-line sedation and analgesia (*Supplementary material: Figure 2*).
3. Weaning from sedation and analgesia, adapted from Amirnovin et al.[11] (*Supplementary material: Figure 3*).

Consensus was sought among key actors within the PICU, staff physicians, on-duty physicians, chief residents of pediatric intensive care, kinesiologists, and nurses.

Forty-five-minute training sessions were held to explain the importance and characteristics of the sedation and analgesia protocol; these were repeated on different days and at different times; which allowed to reach more than 80% of the PICU health care team. Evidence on the implementation and impact of sedation and analgesia protocols and monitoring tools was presented. Visible posters of the protocol, different sedation and analgesia scales, and opioid and benzodiazepine conversion tables[12,13] were posted in the PICU (*Supplementary material*). A section was added to computerized instructions to record rescue sedation and analgesia. A daily reminder included in the electronic health care checklist was used to reinforce the control of sedation and analgesia scores, defining daily objective ranges.[14]

Sample

The sample size was estimated based on the historical PICU registry, with a median length of stay of 10 days and a standard deviation of 2.4 days for patients requiring MV for more than 72 hours. A minimum precision of 1 day was sought, assuming an 80% statistical power and a 5% alpha error; the minimum sample required in each period was 92 patients.

Statistical analysis

Outcome indicators were analyzed on the basis of incidence at each stage. Categorical variables were expressed as absolute values or percentages, whereas continuous variables were described as measures of position and dispersion based on their parametric or non-parametric distribution.

For the bivariate analysis, the χ^2 test was used; while Student's t test or the Mann-Whitney U test were used for quantitative variables (depending on whether or not normality criteria were met). In addition, the analysis of variance was used to compare several means, and *p* values below 0.05 were considered significant. Values were adjusted for severity (PIM 3 score) and age with logistic regression. The STATA 13.0 software for Mac was used for data analysis.

Bioethical aspects

An informed consent waiver was requested for the study because the sedation and analgesia protocol was considered a new standard of care. In addition, recorded data of participating patients were anonymized, and study investigators committed not to link them in the future. This study was approved by the Ethics Committee and by the Research and Teaching Department of Hospital General de Niños Pedro de Elizalde, and registered in the Research Registry of the City of Buenos Aires under number 223.

RESULTS

During the study period, 574 patients were admitted; of them, 53.5% required MV and 33.3% required MV for more than 3 days. The inclusion of patients in the study by period was performed as shown in *Figure 1*.

In relation to the characteristics of the patients registered in each period, a greater severity (PIM 3 score), a younger age, and a lower weight were observed during the pre-intervention stage. In addition, the proportion of admissions due to respiratory failure was higher (*Table 1*).

The rate of adherence to the protocol included as part of the intervention was 90.2% in the post-intervention stage. At this stage, withdrawal syndrome (WS) was diagnosed in 12% of patients (N = 11); no data were available for comparison in the historical cohort. Only 2 patients required the implementation of the protocol for refractory patients.

The results obtained in the comparison of both groups showed a reduction in the days of MV, in the days of continuous infusion of opioids and benzodiazepines, and in the total days of benzodiazepine use in the post-intervention stage (*Table 2*). After adjusting for severity and age, the reduction in the days of continuous infusion of opioids ($p = 0.018$) and in the days of continuous infusion of benzodiazepines ($p = 0.001$) persisted in the post-intervention stage. No significant differences were observed in the days of MV ($p = 0.321$) and in the total days of benzodiazepine use ($p = 0.887$).

DISCUSSION

Sedation and analgesia for critically ill patients in the PICU involves taking care of the physical comfort and psychological well-being of children and adolescents. The approach to sedation and analgesia should be comprehensive, correcting environmental and physical factors, optimizing pharmacological agents, aiming at alleviating pain, reducing anxiety and distress, and preventing

Figure 1. Flow chart of patients included in the study

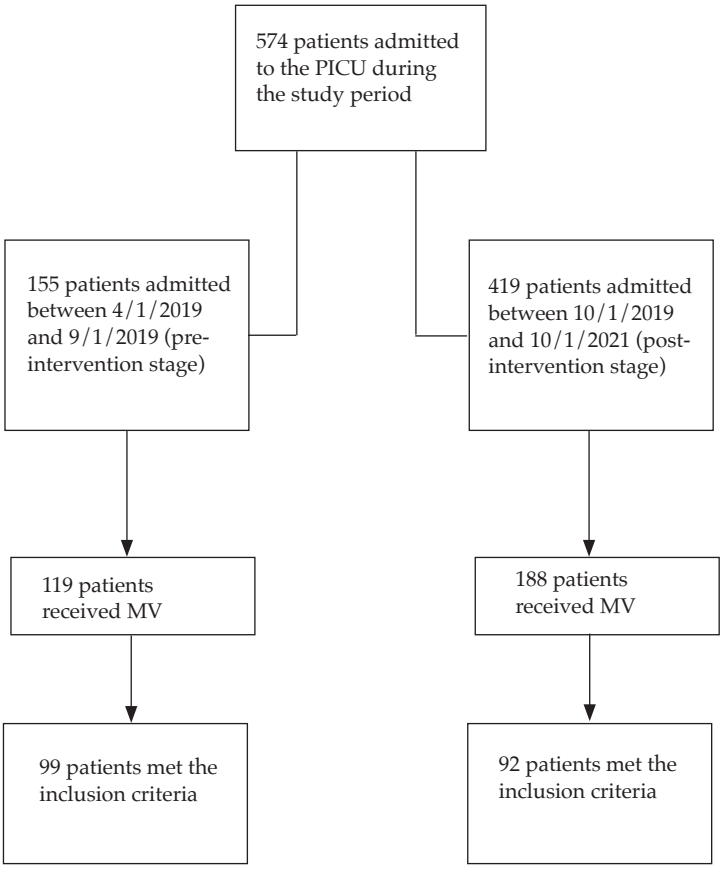

Table 1. Characteristics of patients in both study stages

	Pre-intervention (N = 99)	Post-intervention (N = 92)	*P*
Age (months)*	5.8 (3.1, 17.5)	8.2 (3.1, 50.3)	0.229
Weight (kg)*	6.5 (4.8, 11)	8.8 (5, 18.8)	0.036
Sex (female)+	41 (41.4)	37 (40.2)	0.866
Pediatric Index of Mortality 3**	12.3 ± 1.3	7.3 ± 1.5	0.014
Presence of comorbidity+	35 (35.3)	43 (46.7)	0.110
Reason for admission			
Respiratory+	86 (86.9)	62 (67.4)	
Hemodynamic+	8 (8.1)	15 (16.3)	

N: number of patients.

**Median and range; +N and %; ** Mean and standard deviation.*

adverse events. One way to achieve this is to implement a goal-directed treatment strategy and a validated protocol-driven assessment of the patient's comfort.[4–6]

Our study had no positive impact on the length of stay in the PICU, and this is consistent with the bibliography. Curley et al.,[9] in a large-scale study that compared a sedation protocol versus standard management in pediatric patients with respiratory failure receiving MV, reported no difference in the number of days of MV (6.5 days [$CI_{25–75}$: 4.1–11.2] in the intervention group and 6.5 days [$CI_{25–75}$: 3.7–12.1] in the control group, [p = 0.61]), or in the occurrence

Table 2. Comparison of pre-intervention and post-intervention stages

	Pre-intervention (N = 99)	Post-intervention (N = 92)	*P*	*P* (adjusted for age and PIM 3)
Length of stay in the PICU (days)*	12.3 ± 8.3	11.5 ± 46.8	0.346	0.306
Length of hospital stay (days)*	26.3 ± 27.5	40.9 ± 76.4	0.077	0.087
Days of MV*	9.2 ± 6.8	7.4 ± 4.3	0.034	0.321
Continuous infusion of opioids (days)*	7.6 ± 5.8	6 ± 5.2	0.031	0.018
Total opioids (days)*	13.1 ± 10.4	13.3 ± 13.1	0.893	0.137
Continuous infusion of benzodiazepines (days)*	7.6 ± 6.8	3.3 ± 3.5	0.001	0.001
Total benzodiazepines (days)*	10.5 ± 9.9	7.5 ± 7.7	0.021	0.887
Extubation failure⁺	15 (15.2)	16 (17.4)	0.675	0.398
Unplanned extubations⁺	6 (6.1)	6 (6.5)	0.896	0.854

N: number of patients MV: mechanical ventilation. PIM 3: Pediatric Index of Mortality 3.
**Mean and standard deviation; ⁺N and %.*

of sedation-related adverse events. In the same line, Blackwood et al.,[10] in a multicenter study, implemented a protocol of weaning from sedation and ventilation and established an objective reduction in MV (64.8 hours versus 66.2 hours; median adjusted difference: -6.1 hours [$CI_{25–75}$: -8.2, -5.3], adjusted hazard ratio: 1.11 [95% CI: 1.02, 1.20], $p = 0.020$). Although this is a significant difference, the authors concluded that it is lower than that estimated, and of uncertain clinical impact.

In a single-center study, Sanavia et al.[15] assessed the implementation and efficacy of a sedation and analgesia rotation protocol in critically ill patients, and reported a lower incidence of withdrawal syndrome (34.3% versus 84.6%), a shorter length of stay in PICU (16 versus 25 days), a shorter duration of opioid infusion (5 versus 7 days), benzodiazepine infusion (5 versus 9 days), and propofol infusion (4 versus 8 days) in the protocol adherence cohort ($p < 0.005$). It is worth noting that the sedation and analgesia rotation strategy lacks support in recent guidelines.[6]

Nevertheless, the introduction of sedation and analgesia protocols has provided several benefits, including a reduction in benzodiazepine use, improvements in interprofessional communication in relation to sedation goals and management of sedation goals, and reductions in withdrawal symptoms.[16,17] Our study showed a reduction in the days of continuous infusion of opioids and benzodiazepines and an incidence of WS in the post-intervention period lower than that reported in the bibliography (34–70%).[18]

The objective of our study was to limit the use of benzodiazepines, given their short-term association with delirium[19,20] and the medium-term association with post-traumatic stress.[21] To this end, new sedation protocols, focused on benzodiazepine-sparing strategies, have been implemented in the PICU.[22]

As a benzodiazepine-sparing strategy, this study used a delayed initiation of continuous infusion and an early association of adjuvant therapies. Recent treatment guidelines[5,6] favor the use of dexmedetomidine, leaving benzodiazepines as a second-line option. In this regard, it is worth mentioning that our protocol was developed in 2019 and the evidence supporting the use of dexmedetomidine as a first-line agent was introduced later. Prior to the initiation of our protocol, only Grant et al,[23] had assessed the use of dexmedetomidine in patients requiring MV due to respiratory failure and concluded that the use of dexmedetomidine as a primary sedative in patients with lower severity scores achieved adequate levels of sedation rapidly. The use of dexmedetomidine as a secondary agent did not appear to add benefits, while it favored weaning from MV in the pre-extubation group.

In recent years, several studies have been published which reported evidence supporting the use of dexmedetomidine as a primary agent;[24–26] however, the paradigm shift regarding the use of benzodiazepines as a primary sedative has not occurred. A recent survey of 215 PICUs from 27 European countries showed that midazolam was the first choice in 71% of the responses.[27]

There are no unified criteria for defining refractory sedation and analgesia. Lebet et al.[28] conducted a survey among experts to design a predictive model of complex sedation and analgesia, dividing associated variables into 3 groups: sedation-related, adverse event-related, and demographic/diagnostic variables.

In a scenario of refractory cases, the current guidelines suggest the use of ketamine due to its adequate safety profile[5,6] and/or propofol in doses of less than 4 mg/kg/h for less than 48 hours.[5] In our study, only 2 patients required admission to the protocol for refractory patients, and were treated with ketamine and ketamine together with propofol. No complications were observed.

Our study reported an incidence of WS of 12% in the post-intervention stage. The WS prevention strategy was underpinned by a risk-stratified weaning of opioids,[11] primarily with methadone,[29] and additional doses for symptom management.[5] Regarding the use of methadone to facilitate weaning from continuous infusion of opioids, a meta-analysis of 12 studies and 459 pediatric patients reflected a broad heterogeneity in the dosing strategy and concluded that there was insufficient evidence to recommend any weaning strategy with methadone, or to recommend methadone over other drugs.[30]

In order to alleviate the sequelae of critical illness (post-intensive care syndrome),[31] the Society of Critical Care Medicine introduced the "ICU liberation" initiative, a bundle consisting of interconnected elements aimed at reducing the harmful effects of excessive sedation, prolonged immobilization, sleep disruption, and delirium by allowing awakening, comfort, and spontaneous breathing. Its implementation is effective and impacts clinical outcomes in adult patients.[32] The implementation of the sedation and analgesia protocol in our study shares some of the measures suggested in the ICU liberation bundle, and we consider it is a starting point for introducing multifaceted and related interventions in our hospital.

Due to the presence of the COVID-19 pandemic, there were fewer monthly hospitalizations, and the distribution of baseline patient characteristics in both groups was observed to be non-uniform; severity was greater in the pre-intervention period and the proportion of hospitalizations due to respiratory causes was higher. Such difference was adjusted for in the statistical analysis.

A limitation of this study is that it was a single-center study with a design that did not allow causality to be established. Both cohorts in our study were from 2 different time periods. There is a possibility that other factors within the PICU, that were not controlled for, may have inadvertently affected the post-intervention cohort. We were unable to compare the association of our intervention in relation to the prevalence of delirium and WS between both groups, as scores were not available in the pre-intervention period.

As strengths of our study, it is worth highlighting that the proposed intervention is supported by evidence, posing no risks to patients. All health care providers involved in the department participated in the implementation and development of the protocol. Adherence to the protocol was greater than 90%, and the heterogeneity of health care was reduced.

CONCLUSION

The implementation of a sedation and analgesia protocol was associated with a significant reduction in exposure to continuous infusion of benzodiazepines and opioids; adherence was greater than 90%, but there was no impact on duration of MV, length of stay in the PICU and in the hospital. ■

Supplementary material available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2023/2806_AO_Taffarel_Anexo.pdf

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