



Effect of Target-Driven Sedation Protocol to Ventilator Liberation in Pediatric Intensive Care Unit: Pre- and Postimplementation Single-Center Study

Abdulla Alfraj^{1,2}  Ahmed Abdelmoniem¹ Mohammad Surour¹ Mohamed Basuni¹
Mohamed Elseadawy¹

¹ Pediatric Intensive Care Unit, Department of Pediatrics, Farwaniya Hospital, Sabah Al-Nasser, Al Farwaniya Governorate, Kuwait

² Pediatric Intensive Care Unit, Department of Pediatrics, Ahmadi Hospital, Kuwait Oil Company, Al Ahmadi, Kuwait

Address for correspondence Abdulla Alfraj, MD, Pediatric Intensive Care Unit, Department of Pediatrics, Ahmadi Hospital, Kuwait Oil Company, Al Ahmadi, P.O. Box 9758 Ahmadi 61008, Kuwait (e-mail: alfraj.abdulla@gmail.com).

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Abstract

Oversedation of mechanically ventilated children is common in many pediatric intensive care units (PICUs). This practice is driven by the challenges of dealing with children of different ages as they have different behavioral, mental, and emotional statuses. We aimed to evaluate the effect of implementing a target-driven sedation protocol in the PICU on ventilator-free days (VFDs), PICU stays, and hospitalization. A 2-year retrospective cohort study was performed in our PICU between October 1, 2018, and October 1, 2020. All intubated children up to 12 years of age were included. Descriptive analyses and a pre- and postintervention comparison of VFDs and length of stay were used to assess the protocol's effectiveness. A total of 134 patients were studied. There was a significant increase in VFDs in cases with respiratory illness requiring mechanical ventilation after implementing this protocol (19.9 vs. 22.3, respectively, with a p -value of 0.031). Also, there was a trend of reduction in the length of PICU stay (median of 9 vs. 8 days, $p = 0.816$), post-PICU length of stay (median of 4 vs. 3 days, $p = 0.055$), and hospitalization duration (median of 16 vs. 13 days, $p = 0.062$) though not statistically significant. Implementing a target-driven sedation protocol in the PICU significantly affects VFDs in mechanically ventilated respiratory cases. Though inconclusive in our study, implementing such a protocol will influence patients' care and reduce unnecessary sedation uses that will reduce sedation hazards.

Keywords

- ▶ ventilator liberation
- ▶ target-driven sedation
- ▶ sedation during mechanical ventilation
- ▶ pediatric
- ▶ intensive care unit

Introduction

Intensive care units (ICUs) are very stressful environments, especially for children and their parents. In most centers, a daily goal is set to provide comfort and reduce anxiety and agitation for their patients. This goal can be achieved using many methods, including controlling sedation and analgesia

during mechanical ventilation, which is the most used method.¹ Agitation and anxiety in mechanically ventilated children sometimes cause patient-ventilator asynchrony that needs to be addressed, assessed, and managed properly. One of the common practices to control this asynchrony is using sedative agents. However, this kind of practice leads

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physicians to overuse sedation in mechanically ventilated children. Those who use this type of practice usually believe that reaching the level of deep sedation will have better control over children, and they never count the worse outcome of such a practice. Aragón et al's study confirmed that most mechanically ventilated patients were deeply sedated using opioids and benzodiazepines during their pediatric intensive care unit (PICU) stay.²

Nowadays, it is clear that deep sedation, especially with the use of benzodiazepine, is associated with unwanted ICU outcomes, including delirium.^{3,4} On the other hand, delirium, which is a preventable complication, is considered an independent predictor of mortality and impacts long-term cognitive impairment and disability.⁵⁻⁸ So, indirectly, we might speculate that deep sedation has some influence on ICU mortality and long-term sequelae. Target-driven sedation protocols control unnecessary sedative use, reducing its negative impact on mechanically ventilated patients.⁹ Furthermore, oversedation was found to be associated with developing ICU-acquired weakness, increased mechanical ventilation days, prolonged ICU and hospital stay, and causing iatrogenic withdrawal syndrome (IWS).¹⁰⁻¹³

Currently, many PICUs changed their sedation practices. They moved toward more target-driven protocols to minimize medication side effects and improve patient outcomes, as recent evidence shows. This practice was clearly supported by the position statement of the European Society of Paediatric and Neonatal Intensive Care in 2016 to help guide physicians in using analgesia and sedation in children to better control pain, inadequate sedation, withdrawal syndrome, and delirium.¹⁰ However, despite that evidence and expert recommendations, there is still a significant gap in units' practices from center to center and physician to another regarding sedation for mechanically ventilated children.^{9,14,15} Therefore, a target-driven sedation protocol was implemented in Farwaniya PICU in October 2019. We hypothesized that implementing this strategy might decrease the days of ventilation and PICU stay, which indirectly influences less sedation and ventilation side effects such as ventilator-associated pneumonia, hemodynamic instability, and the risk of withdrawal, besides a reduction in the cost of these medications.

Materials and Methods

Study Population and Setting

A retrospective cohort study was performed in the PICU of the Farwaniya Hospital, an urban governmental hospital in Kuwait, between October 1, 2018, and October 1, 2020. The hospital covers a population of 1,256,000 inhabitants (2020), and the PICU has a 20-bed capacity.¹⁶ Patients included in this study were all intubated and mechanically ventilated children (aged 0–12 years) in the PICU. Exclusion criteria were: patients admitted to PICU outside the defined study period, patients transferred out the PICU on a mechanical ventilator to continue management in another hospital, or patients known for palliative (terminal care)/chronic care.

Data Collection

Patients were identified using the admission and discharge records available at the unit and medical archives. Medical records were reviewed to obtain clinical and demographic data. Daily progress notes, order sheets, and medication prescriptions were also reviewed to describe the patient's clinical condition trajectories. The period of patient follow-up was limited to hospitalization. Patients admitted to the PICU prior to the study period but were still receiving intensive care within the study period were excluded.

Sedation Protocol Settings

The protocol goal was to achieve a calm/awake state for children on a mechanical ventilator. This target is challenging to be achieved in pediatrics due to many factors, including the child's developmental age, clinical condition, disturbance of the day–night cycle, and psychological effects. An objective scoring tool was adopted, the Bloomsbury score (BBS), with a standard target of 0 to +1 (arousal/awake sedation target). This was generalized to all intubated children during the implementation period unless the PICU team specified another target with a clear evidenced-based justification mentioned in the patient chart and the duration validity for their decision.

The sedation protocol was categorized into four levels. Level 1 includes as-needed doses of primarily opioids with restricted use of a benzodiazepine for anxiety relief as PRN frequency also. The next level (Level 2) is where regular intermittent opioids with/without benzodiazepine are used. The third level is when infusions are required to achieve the sedation target. And finally (Level 4), once paralytic agent, with other sedative infusions, is necessary. Daily revision of the sedation score target regulates movements from one level to another. Any deviation from the protocol required both specifying its rationale and the safe time to return to the protocol. Pain and discomfort were well monitored, addressed, and controlled during implementation to minimize the overlap between sedation and analgesia agent needs. This was maintained by closely and objectively monitoring pain and discomfort using a pain and discomfort scoring system. Nonpharmacological and nonopioids analgesics were used as situations required.

Protocol Implementation and Setting

On October 1, 2019, the protocol was implemented, including formal assessment using a BBS with a standard target of awake/calm child while on the mechanical ventilator. Some exception was made for neurocritical, cardiac, and airway disease conditions where deeper targets were initially required to control the pathophysiology of the disease.

Before the implementation, there was no formal protocol for such a target in our PICU. In fact, deep sedation was aimed with every mechanically ventilated case to have more control condition with the fears of unplanned extubation. Therefore, all health care workers in the unit were provided intensive educational sessions 1 month prior to implementation to ensure team awareness of such a change. These

sessions aimed to introduce the BBS scoring system, familiarize the PICU physicians with the protocol, and do non-pharmacological troubleshooting of patient anxiety or ventilator asynchronies.

Statistical Analysis

Statistical analysis was performed using R v 3.6.3. Counts and percentages were used to summarize the distribution of categorical variables. The mean \pm standard deviation of the median/interquartile range were used to summarize the distribution of normal and nonnormal continuous variables, respectively. The chi-square test of independence was used to compare the distribution of categorical variables before and after the protocol implementation. Unpaired *t*-test or Mann-Whitney's test was used to compare the distribution of continuous variables. Hypothesis testing was performed at a 5% level of significance. For ventilator-free days (VFDs), we used the standard equation based on 28 days (VFDs = 28 – intubation days).¹⁷ If intubation days exceed 28 or the patient dies, VFDs will be considered zero as per calculation guidelines.¹⁷

Results

A total of 562 patients were admitted to the PICU during the study period, with 134 patients matching the study inclusion criteria (73 patients in preimplementation vs. 61 patients in the postimplementation period). The intubation rate in the unit was around 23 versus 24% of the total admissions before and after implementation, respectively. The same intubation rate among PICUs was reported by Khemani et al.¹⁸ Median age in years for patients in the pre- and postimplementation periods was similar, 3.07 and 2.00 years, respectively (*p*-value 0.374) (► **Table 1**). There was no difference in sex distribution; 46.6% were males in the pre group and 52.5% in the post group (*p*-value 0.614). No significant differences between the two groups on discharge diagnoses or type of viral infection for respiratory cases could be found. The most common reason for PICU admission was respiratory diseases, followed by cardiovascular/shock conditions. Also, no statistical differences could be detected between the two groups in terms of the need for vasoactive drug support, 58.6 versus 40.4%, respectively, with a lower trend in the postimplementation group.

Though the two groups had no significant differences in length of PICU stay (median of 9 vs. 8 days, *p* = 0.816), post-PICU length of stay (median of 4 vs. 3 days, *p* = 0.055), which also reflects on hospitalization duration (median of 16 vs. 13 days, *p* = 0.062); however, it showed a trend of reduction in the results (► **Table 2**, ► **Fig. 1**). This trend of decline was evident in the post-PICU length of stay after implementing the protocol. VFDs with a duration frame of 28 days were similar in both groups, 18.5 versus 18.1 (*p*-value 0.809), but with perfuming subgroup analysis (► **Table 3**), there was a significant increase in VFDs in the postimplementation group (19.9 vs. 22.3, respectively, with *p*-value 0.031) (► **Fig. 2**). There were no unplanned extubation events reported in both pre and post phases.

Discussion

Oversedating ventilated children have its own hazards. Many oversedation-related sequelae affect the patients and contribute to more extended hospitalization for PICU patients. These main sequelae include IWS, delirium, and neuromuscular weakness.^{19,20} The prolongation of ventilation could also be due to the effect of oversedation on patients' wakefulness in the recovery phase and the readiness for extubation.²¹ Thus, despite fulfilling the rest of the extubation readiness criteria, which are resolving the original cause for intubation, intact airway reflexes, hemodynamic stability, and manageable secretions, the patient will not be extubated due to the effect of oversedation on wakefulness.²¹ This was clear and evident in our unit before implementing this protocol, as patients remained ventilated for a few days after the disease's recovery because they were not appropriately wakeful for extubation.

Implementing a sedation protocol in our PICU was a successful quality improvement project associated with increased VFDs and reduced hospitalization duration. Though the post-PICU length of stay differences were not statistically significant, we noticed a reduction trend in the postimplementation phase. This reduction is mainly due to minimizing the ICU sequelae such as IWS, delirium, and neuromuscular weakness from sedatives, especially benzodiazepines. PICU-recovered children in our facility stay in the pediatric ward to complete their management of IWS which increases the hospitalization period. This sequela can be prevented to some degree by avoiding unnecessary sedation use and avoiding keeping the patient oversedated during mechanical ventilation. To assess sedation level, we adapt the BBS scale to facilitate objective measurement of our patients. The protocol was friendly user, and we think it can be translated into a nurse-driven practice. This kind of practice was demonstrated in some studies to be safe and feasible with its effect on reducing the duration of mechanical ventilation.²²

Our PICU mainly receives nonsurgical cases as our center lacks an in-house pediatric surgical/neurosurgical team. This was reflected in the patients' diagnoses that were admitted to our unit. The overall VFDs were similar in both phases, but due to the fact that our sedation protocol targeted mainly the respiratory and sepsis/septic shock cases with no changes in sedation input for other cases such as neurocritical, upper airway, foreign body aspiration, cardiac cases as awake sedation targets was not part of management strategy initially for those cases to avoid complications and possible poor outcomes. Therefore, further subgroup analysis was performed to determine the effect of the use of sedation protocol for sepsis/septic shock and respiratory cases separately. There was a significant increase in mean VFDs from 19.9 to 22.3 (i.e., by 2.4 days) in the postimplementation phase. We speculate that this increase in VFDs impacts patients' care, family perception, and the total PICU cost, though it was not measured or studied precisely in our research. Moreover, no unplanned extubation events were reported in both phases. Still, we cannot conclude any association as the nature of the study design is not the best method to do so.

Table 1 Demographic and clinical characteristics of the study population, according to study period

Variable	Preimplementation N = 73	Postimplementation N = 61	p-Value
Period	October 1, 2018–September 31, 2019	October 1, 2019–October 1, 2020	
Months	12	12	
Age (y) Median (IQR)	3.07 (1.20–8.60)	2.00 (1.07–6.67)	0.374
Male	34 (46.6%)	32 (52.5%)	0.614
Discharge diagnosis			
Respiratory disease	50 (68.5%)	31 (50.8%)	0.057
Cardiovascular disease/shock	15 (20.5%)	20 (32.8%)	0.159
Central nervous system disease	4 (5.48%)	10 (16.4%)	0.076
GI/renal disease	2 (2.74%)	0 (0.00%)	0.5
Trauma/injuries	2 (2.74%)	0 (0.00%)	0.5
NPA			
Adenovirus	3 (4.11%)	0 (0.00%)	0.250
Rhinovirus	18 (24.7%)	12 (19.7%)	0.630
Bordetella pertussis	0 (0.00%)	1 (1.64%)	0.455
Enterovirus	3 (4.11%)	3 (4.92%)	1.000
Human bocavirus	7 (9.59%)	0 (0.00%)	0.016
Human metapneumovirus	1 (1.37%)	1 (1.64%)	1.000
Influenza A	7 (9.59%)	5 (8.20%)	1.000
RSV	20 (27.4%)	27 (44.3%)	0.064
Para influenza type 4	1 (1.37%)	0 (0.00%)	1.000
Parainfluenza virus	1 (1.37%)	0 (0.00%)	1.000
Seasonal coronavirus	3 (4.11%)	0 (0.00%)	0.250
Need of vasoactive drug support (overall)	34 (58.6%)	23 (40.4%)	0.076

Abbreviations: GI, gastrointestinal; IQR, interquartile range; NPA, nasopharyngeal aspirate; RSV, respiratory syncytial virus.

Notes: NPA and discharge diagnosis were dummy coded.

Analysis was performed using chi-square test of independence for categorical variables.

Continuous nonnormal variables were compared using Mann–Whitney's test.

Table 2 Changes in length of stay after implementation of the sedation protocol

Variable	Preimplementation N = 73	Postimplementation N = 61	p-Value
Length of PICU stay, median (IQR)	9.00 (5.00–14.0)	8.00 (6.00–13.0)	0.816
Post-PICU length of stay, median (IQR)	4.00 (1.00–6.00)	3.00 (1.00–4.00)	0.055
Length of hospitalization, median (IQR)	16.0 (12.0–20.0)	13.0 (9.00–18.0)	0.062
Hospital-free days “duration frame 28 d” Mean (CI)	11.4 (9.44–13.4)	13.2 (10.9–15.4)	0.238

Abbreviations: CI, confidence interval; IQR, interquartile range; PICU, pediatric intensive care unit.

Most of the sedative agents, especially on higher doses, affect patients' blood pressure and hemodynamics. We could not get a statistically significant difference between the two groups; however, we noticed a reduction in vasoactive medication use after implementing the protocol despite more cases having cardiovascular/shock on their discharge diagnoses. We explained that indirectly as deep sedation was

used in the preimplementation era requiring high doses of sedatives which affect the hemodynamics of mechanically ventilated children. Further researches may be necessary to study this association better in the future.

Our study carries some limitations. Given that it is a single-center study which was reflected by a small sample size that was insufficient to detect significant values. Also,

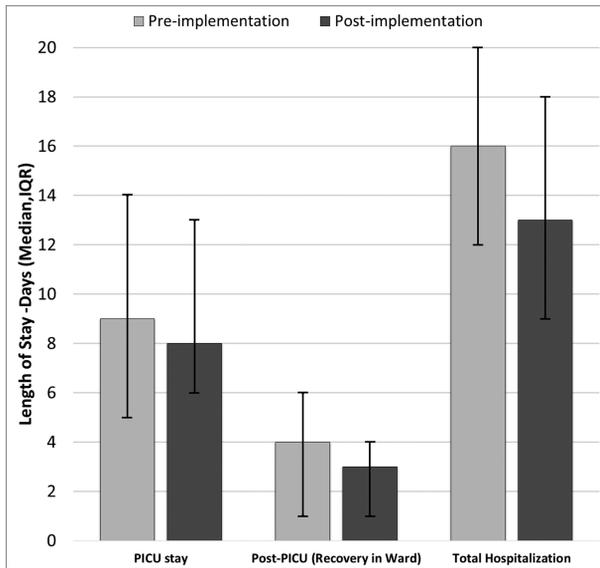


Fig. 1 Differences between the length of stay in PICU, post-PICU, and hospitalization period pre-and postimplementation of the protocol. PICU, pediatric intensive care unit.

being a retrospective type study, this limits us to be dependent on patients' medical records, which impacts the studying of essential elements such as nurses' contribution, IWS scores, the prevalence of delirium, and side effects of using such a protocol in ventilated children which was not mentioned in patients' charts. The second limitation was related to measuring the severity and acuity of the admitted cases using evidence-approved scores such as the Pediatric Risk of Mortality or Pediatric Index of Mortality, which are widely used for admitted patients to a PICU.^{23,24} Unfortunately, those scores were unavailable in our patients' records and could not be measured retrospectively. Objective measurement of the team's compliance with the protocol is another main limitation of our study; however, being conducted in one center with the assistant of reviewing daily sedation prescriptions and daily checking of the targets from the charts could indicate good compliance subjectively. Finally, oversedation sequelae such as IWS, delirium, and neuromuscular weakness were not objectively assessed and documented in patients' records. Thus, it could not be overcome

Table 3 Changes of VFDs after implementation of the sedation protocol

Variable	Preimplementation Mean (CI)	Postimplementation Mean (CI)	p-Value
Overall VFDs (duration frame 28 d)	18.5 (16.5–20.6)	18.1 (15.7–20.6)	0.809
VFDs per discharge diagnosis			
Respiratory infections N = (45, 26)	19.9 (17.8–22.0)	22.3 (20.2–24.4)	0.031
Sepsis/septic shock N = (13, 14)	13.1 (6.22–19.9)	15.0 (9.22–20.8)	0.646
Others N = (15, 21)	19.2 (13.3–25.1)	15.1 (9.92–20.3)	0.277

Abbreviations: CI, confidence interval; VFDs, ventilator-free days.

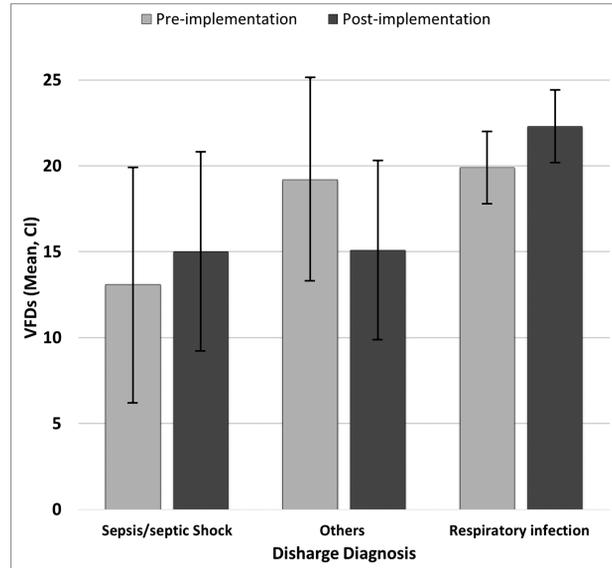


Fig. 2 Differences between ventilator-free days (VFDs) per discharge diagnosis in pre- and postimplementation of the protocol.

due to the study's retrospective nature. Given all these limitations, further studies are required to get better answers to the studied outcomes.

Conclusion

Our study highlights the importance of implementing a target-driven sedation protocol in PICUs. There was a significant increase in mean VFDs in sepsis/septic shock and respiratory cases after using the protocol. Implementing such a protocol will influence patients' care and reduces the unwanted effects of unnecessary sedation use. These protocols can be translated into a nurse-driven practice that facilitates a safe approach with its impact on reducing the duration of mechanical ventilation in pediatric patients.

Authors' Contribution

A.A. contributed to conceptualization, methodology, investigation, data curation, writing—original draft, and supervision. A.A., M.S., M.B., and M.E. helped in investigation—data collection, writing—review and editing.

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Conflict of Interest

None declared.

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