Pediatric Ventilation Liberation: Bundled Extubation Readiness and Analgosedation Pathways Decrease Mechanical Ventilation Duration and Benzodiazepine Exposure

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BACKGROUND: Recent studies reported that children on mechanical ventilation who were managed with an analgosedation approach and standardized extubation readiness testing experienced better outcomes, including decreased delirium and invasive mechanical ventilation duration. METHODS: This was a quality improvement project in a 24-bed pediatric ICU within a single center, including subjects ≤ 18 years old who required invasive mechanical ventilation via an oral or nasal endotracheal tube. The aim was to decrease the invasive mechanical ventilation duration for all the subjects by 25% within 9 months through the development and implementation of bundled benzodiazepine-sparing analgosedation and extubation readiness testing clinical pathways. RESULTS: In the pre-implementation cohort, there were 274 encounters, with 253 (92.3%) that met inclusion for ending in an extubation attempt. In the implementation cohort, there were 367 encounters with 332 (90.5%) that ended in an extubation attempt. The mean invasive mechanical ventilation duration decreased by 23% (Pre 3.95 d vs Post 3.1 d; *P* = .039) after the implementation without a change in the mean pediatric ICU length of stay (Pre 7.5 d vs Post 6.5 d; *P* = .42). No difference in unplanned extubation (*P* > .99) or extubation failure rates (*P* = .67) were demonstrated. Sedation levels as evaluated by the mean State Behavioral Scale were similar (Pre −1.0 vs Post −1.1; *P* = .09). The median total benzodiazepine dose administered decreased by 75% (Pre 0.4 vs Post 0.1 mg/kg/ventilated day; *P* < .001). No difference in narcotic withdrawal (Pre 17.8% vs Post 16.4%; *P* = .65) or with delirium treatment (Pre 5.5% vs Post 8.7%; *P* = .14) was demonstrated. CONCLUSIONS: A multidisciplinary, bundled benzodiazepine-sparing analgosedation and extubation readiness testing approach resulted in a reduction in mechanical ventilation duration and benzodiazepine exposure without impacting key balancing measures. External validity needs to be evaluated in similar centers and consensus on best practices developed. *Key words: mechanical ventilation; analgesia; clinical pathways; benzodiazepine; opioid; pediatrics.* [Respir Care 2022;67(11):1385–1395. © 2022 Daedalus Enterprises]

Introduction

Respiratory failure that requires invasive mechanical ventilation is prevalent in the PICU.[1] Although it is an essential supportive care modality, timely weaning and liberation are critical to minimize complications associated with invasive mechanical ventilation.[2,3] Potential complications include, but are not limited to, hospital-acquired infection, airway injury, iatrogenic narcotic withdrawal, diaphragmatic atrophy, and deconditioning. Patients who require such support often require pain and anxiety control, but optimally balancing the risks and benefits of analgosedation remains a challenge.[4-6] Inadequate analgosedation may impose undue physiologic and psychological stress on the patient.[7-9] Conversely, excessive analgosedation may promote deconditioning and delirium, which results in an increased invasive mechanical ventilation duration, PICU and hospital lengths of stay, and hospital costs.[5,7,9-13] Therefore, developing and implementing an evidence-based guideline for optimal analgosedation practice may improve outcomes and intensive care experience while decreasing invasive mechanical ventilation duration.

The RESTORE trial[14] aimed to address this need by evaluating if a nurse-implemented, goal-directed sedation protocol decreased the invasive mechanical ventilation duration in children who were critically ill compared with non-protocolized care. Although opioid exposure was lower in the intervention group, there was not a significant change in invasive mechanical ventilation duration. Moreover, benzodiazepines were used as a first-line sedative agent. A similar goal-directed benzodiazepine-sparing sedation algorithm may reduce the invasive mechanical ventilation duration. Frequent assessment of a patient's extubation readiness limits the invasive mechanical ventilation duration and improves outcomes.[15-19] The RESTORE trial[14] incorporated a daily extubation readiness test. Although the study did not demonstrate a change in invasive mechanical ventilation duration, it demonstrated that a pathway that incorporates extubation readiness tests with regimented sedation management is feasible. Further, the trial's extubation readiness test process assessed subjects only once daily, with the decision to extubate made during multidisciplinary rounds. It is reasonable to conclude that more-frequent extubation readiness evaluations may trigger earlier consideration for ventilator liberation. Informed by the RESTORE trial,[14] recent attention to limit benzodiazepine exposure, and the potential benefit of frequent extubation readiness assessment, we implemented a respiratory therapist (RT)-driven extubation readiness test clinical pathway in combination with bundled prescriber-driven, benzodiazepine-sparing analgosedation as a quality initiative in our PICU.[20] The aim of the project was to decrease the invasive mechanical ventilation duration for subjects ≤ 18 years old by 25% from a baseline of 3.95 d by July 31, 2020.

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QUICK LOOK

Current knowledge

Results of recent studies suggest that children on mechanical ventilation who are managed with an analgosedation approach and standardized extubation readiness testing may have improved outcomes. In the landmark RESTORE trial,[14] benzodiazepines use was prevalent. Since its publication, evidence has emerged that demonstrates morbidity and mortality associated with the use of benzodiazepines in children on mechanical ventilation.

What this paper contributes to our knowledge

The implementation of a bundled, prescriber-driven benzodiazepine-sparing analgosedation clinical pathway and a respiratory therapist–driven extubation readiness test pathway decreased the duration of mechanical ventilation. The subjects received significantly less benzodiazepine without changing the perceived level of comfort during invasive mechanical ventilation. Such an approach was feasible, safe, and may improve outcomes in similar academic pediatric ICUs.

Methods

Design, Setting, and Ethics

A quality initiative was performed in the Children's of Alabama PICU by instituting a prescriber-driven, benzodiazepine-sparing analgosedation algorithm in conjunction with an RT-driven extubation readiness test clinical pathway. The Children's of Alabama PICU is a 24-bed, quaternary medical-surgical unit. In 2020, there were 1,585 PICU admissions, with 43.9% of children who required invasive mechanical ventilation for a mean duration of 4.3 d (internal data). There is a separate cardiovascular ICU and a 26-bed step-down unit. Neither of those units were included in this project. The nurse-to-patient ratio is usually 1:2 except in cases of higher acuity when the ratio is 1:1 (eg, critical airways, continuous renal replacement therapy, and extracorporeal membrane oxygenation support). Four RTs staff the PICU per shift, and there is 24 hours/day, 7 days/week in-house critical care fellow and/or attending physician coverage. Intubations are performed by physicians or nurse practitioners, and our diurnal extubation practices were previously published.[21] The need for informed consent was waived after review by the University of Alabama at Birmingham Institutional Review Board (IRB 300001303).

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The location of the research was the Pediatric Intensive Care Unit, Children's of Alabama, Birmingham, AL.

The authors have disclosed no conflicts of interest.

Supplementary material related to this paper is available at http://www.rcjournal.com.

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Subjects

The pre-implementation cohort included all invasive mechanical ventilation encounters that used an oral or nasal endotracheal tube between July 1, 2018, and December 31, 2018. The only patients excluded were those with a tracheostomy at the time of the PICU admission or age ≥ 19 years. The implementation cohort included invasive mechanical ventilation encounters by using the same criteria from November 4, 2019, to July 31, 2020. These time periods ensured capturing seasonal variation. January–October 2019 was avoided to mitigate bias created by implementation planning. During this planning period, the extubation readiness test pathway was piloted in small subsets of subjects who required invasive mechanical ventilation for respiratory failure due to a primary pulmonary pathology. This subpopulation was chosen due to the prevalence and perceived potential benefit of an extubation readiness test. These subjects were not included in the pre-implementation cohort. Furthermore, planning for an encompassing PICU liberation project was underway. During the planning and implementation phases, longstanding delirium screening and/or management and early mobility pathways were already in place. The only new implementations were the bundled pathways described herein.

Baseline Practice

During the baseline period, there were no standardized processes about analgosedation or extubation readiness assessment and testing. Approaches were at the discretion of the attending intensivist. Generally, the subjects who were mechanically ventilated were managed with an opioid and benzodiazepine as needed every hour, with administration guided by the bedside nurse. Some subjects also received continuous opioid, benzodiazepine, and/or dexmedetomidine infusions at the prescriber's discretion. Nursing practices and perspectives with regard to analgesia and sedation administration to the subjects on ventilation in our PICU have been previously described.[22] An extubation readiness test most often involved a spontaneous breathing trial (SBT) that used the pressure support ventilation mode with a PEEP of 5 cm H_2O, with pressure support of 5–10 cm H_2O above PEEP. Extubation readiness test eligibility, timing, frequency, duration, and pass/fail criteria varied according to the discretion of the intensivist. In some instances, the subjects were extubated without an SBT.

Analgosedation Clinical Pathway Development and Implementation

The analgosedation clinical pathway (Fig. 1) was developed through a literature review, multidisciplinary collaboration (physicians, nurses, RTs, and a pharmacist), and prescriber consensus. The pathway used the State Behavioral Scale (SBS) to evaluate subject alertness with the goal of targeting a score between -2 and 0, depending on clinical context.[14] The Individualized Number, Faces, and Face Legs Activity Cry Consolability pain scales were used to assess pain intensity, depending on subject age, developmental status, and clinical situation.[23,24] Nurses notified prescribers if the SBS score was higher than the goal for 2 consecutive assessments if the SBS value was > 2 values higher than the prescribed goal or based on an elevated pain score. The pathway consisted of 3 phases for analgosedation escalation informed by SBS and pain scores. It was posted outside of each room. Because medication administration data would serve as surrogate compliance assessments (specifically with regard to benzodiazepine use), interval compliance audits were not undertaken for the analgosedation clinical pathway.

Extubation Readiness Test Clinical Pathway Development and Implementation

The RT-driven extubation readiness test clinical pathway (Supplementary Fig. 1, see the supplementary materials at http://www.rcjournal.com) was developed in a similar fashion to the analgosedation clinical pathway.[17,18,25-27] Eligible subjects undergoing invasive mechanical ventilation were screened for extubation readiness test eligibility every 3 h, which coincided with institutional ventilator assessment protocols. The screening criteria for extubation readiness test eligibility represented generally accepted minimal ventilator settings and clinical safety criteria (Table 1). If a patient met all eligibility criteria, then the RT notified the prescriber for SBT approval. The test was terminated at 2 h or sooner if the subject had a failed SBT according to standardized pass/fail criteria, followed by prescriber notification (Table 1). After a passed SBT, additional components of an extubation readiness test (eg, cuff leak pressure assessment) were performed, and extubation preparation began at the prescriber's discretion regardless of the time of day. After a failed SBT, extubation readiness test eligibility screening would begin again 6 h after the start of the previous SBT.

Before unit-wide implementation, all the staff received didactic training and the pathway was posted outside subjects' rooms and in work areas. As mentioned, to determine operational feasibility, the extubation readiness test pathway was deployed in a limited group of subjects with primary pulmonary disease.[19] The principal investigator (JML) performed weekly extubation readiness test compliance reviews through electronic medical records review in an effort to maximize compliance with the pathway. In accordance with the Pareto principle, 20% of the encounters were audited weekly for process compliance.[28] The first 20% of the ventilator encounters, which included an extubation readiness test, were selected weekly for audits that evaluated eligibility screening, testing, and documentation.

- To be used for ventilated, unparalyzed patients to target a goal SBS as determined by PICU MD/NP.
- SBS will be documented Q2h.
- MD/NP to be notified if out of goal for 2 consecutive exams OR if SBS is >2 values away from goal.
- Some interventions may be prescribed simultaneously.

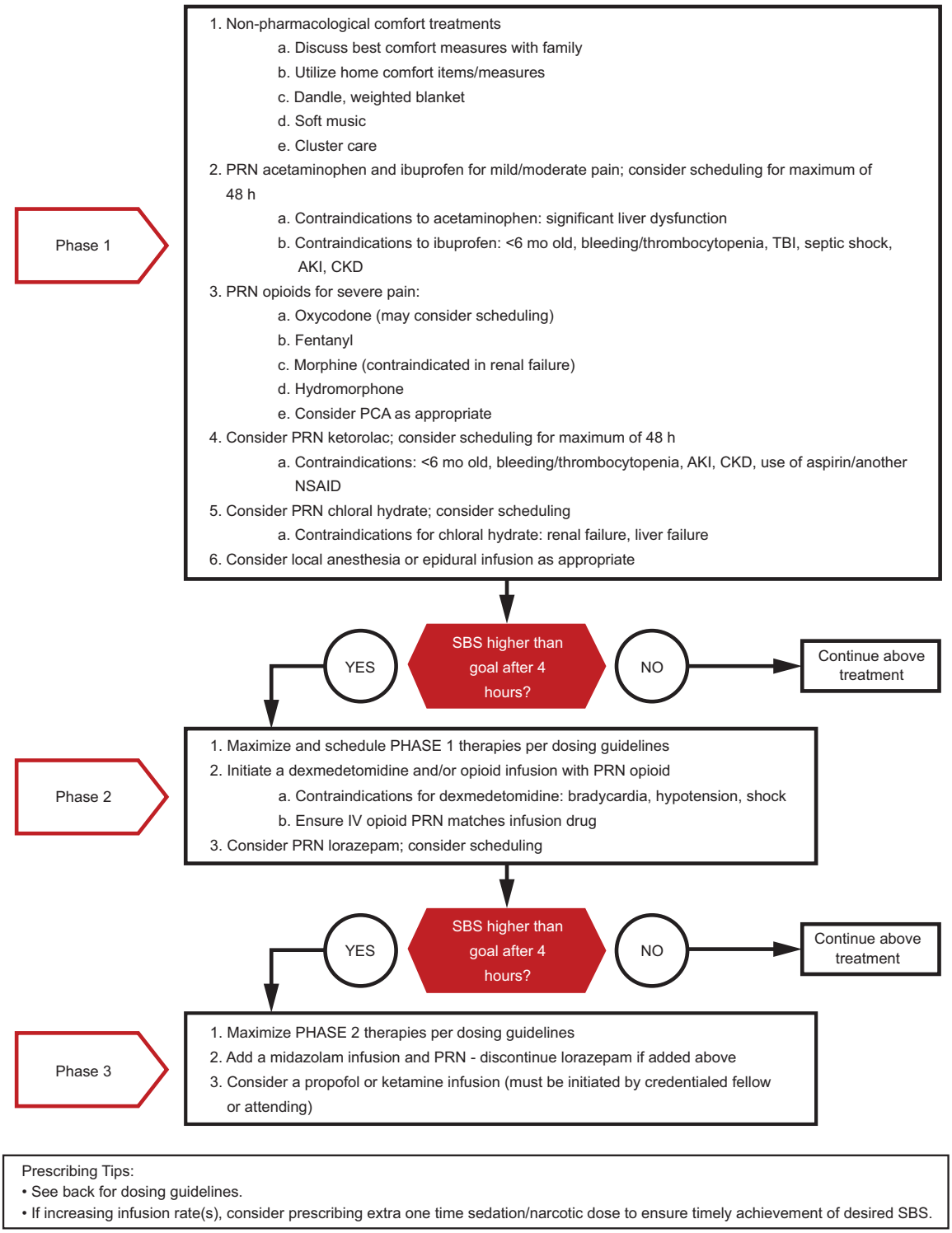

Fig. 1. PICU sedation algorithm. AKI = acute kidney injury; CKD = chronic kidney disease; IV = intravenous; MD = medical doctor; NSAID = non-steroidal anti-inflammatory drug; NP = nurse practitioner; PCA = patient controlled analgesia; PICU = pediatric ICU; PRN = as needed; SBS = State Behavioral Scale; TBI = traumatic brain injury.

Table 1. Screening Criteria for Extubation Readiness Test Eligibility and Pass Criteria for Spontaneous Breathing Trials

Extubation Readiness Test Screening Criteria*	Spontaneous Breathing Trial Pass Criteria*
1. Oral or nasal endotracheal tube	1. Exhaled $V_T \geq 5$ mL/kg ($\geq$300 mL if $\geq$ 60 kg ideal body weight/dosing weight)
2. Intubated $\geq$ 12 h	2. Temporary decline (<15 min) in exhaled V_T may be disregarded at the discretion of the RT, bedside RN, and/or prescriber (attending physician, fellow, or NP)
3. No current neuromuscular blockade	3. $S_{pO_2} \geq 92\%$; different limits may be considered for patients with cyanotic heart disease or at the discretion of the prescriber team; a temporary decline (<15 min) in S_{pO_2} may be disregarded at the discretion of the RT, the bedside RN, and/or prescriber (attending physician, fellow, NP)
4. An SBS score of −1 to 2 and GCS score of 8 to 15 as scored by the bedside RN; lower thresholds may be considered for patients with abnormal neurologic status at baseline	4. No increase in breathing frequency > 30% from the pretest value sustained for $\geq$ 15 min
5. $F_{IO_2} \leq 0.5$, PEEP $\leq$ 6 cm H_2O, pressure support $\leq$ 10 cm H_2O, and saturations within the patient-specific target range	5. No increase in heart rate > 30% from the pretest value sustained for $\geq$ 15 min
6. No planned sedated and/or surgical procedures < 24 h	6. Hemodynamic stability is maintained throughout the test
7. $\leq$1 vasoactive infusions and no significant changes $\leq$ 12 h (exclude milrinone infusion)	7. No increase in $ETCO_2$ > 10 mm Hg from pretest value sustained for $\geq$ 15 min (if an $ETCO_2$ is present)
8. No sustained increases in ventilator settings $\leq$ 12 h; "sustained" is at the discretion of the RT	8. No subjective signs of significant respiratory distress at the discretion of the RT, bedside RN, and/or prescriber; consider whether the distress is any different on an extubation readiness test compared with SIMV
9. PIP $\leq$ 30 for $V_T \geq 5$ mL/kg ideal body weight (use dosing weight)	
10. No inhaled nitric oxide (unless otherwise ordered by the prescriber to continue with extubation readiness test regardless)	
11. Not on HFOV, APRV, or ECMO	
12. No extubation readiness test started < 6 h	

*All criteria must be met.
V_T = tidal volume
RT = respiratory therapist
RN = registered nurse
NP = nurse practitioner
SBS = State Behavioral Scale
GCS = Glasgow coma scale
$ETCO_2$ = end-tidal carbon dioxide
SIMV = synchronized intermittent mandatory ventilation
PIP = peak inspiratory pressure
HFOV = high frequency oscillatory ventilation
APRV = airway pressure release ventilation
ECMO = extracorporeal membrane oxygenation

The RT supervisor (RMJ) addressed individual opportunities for improved compliance or documentation discrepancies. There was no independent observation process during SBT performance to limit the potential impact from the Hawthorne effect on process compliance.

Data Collection and Definitions

The primary outcome was the duration of invasive mechanical ventilation. Secondary outcomes included extubation failure, PICU length of stay, analgesic and/or sedation medication administration, delirium treatment, treatment of iatrogenic narcotic withdrawal, and the average daily SBS score. Demographic (eg, age, sex, and race) and clinical data were collected, including the primary indication for intubation and extubation failure risk factors. The principal investigator (JML) reviewed the attending physician notes to determine the subjects' indication for intubation. Extubation failure risk factors included age $\leq$ 24 months, dysgenetic/syndrome co-morbidity, chronic neurologic disorder, chronic respiratory disorder, surgical or medical airway condition, and chronic noninvasive positive pressure use.[29] These risk factors were used to describe and compare both cohorts in the event that extubation failure rates differed significantly. Baseline cohort extubation data were collected retrospectively, whereas implementation cohort data were collected prospectively.

The invasive mechanical ventilation duration for the interim planning phase was abstracted from the Virtual Pediatric Systems, (Los Angeles, CA) site-specific database. Extubations were categorized as planned or unplanned. Extubation failure was defined as re-intubation

within 48 h of extubation for any reason other than a planned procedure. Extubation to noninvasive ventilation was defined as the planned or unplanned use of CPAP or bi-level positive airway pressure within 48 h of extubation. The subjects on chronic noninvasive ventilation were not included in that measure. Delirium treatment was defined by a new order for an anti-psychotic treatment during the PICU length of stay. Iatrogenic narcotic withdrawal was defined as the initiation of methadone and/or lorazepam concurrent with Withdrawal Assessment Tool Version 1 scoring per institutional policy.[30] The average daily SBS score was determined by calculating the sum of all SBS scores documented on a calendar day and dividing by the total number of documented scores.

Analgosedation administration data were collected retrospectively from the electronic medical records. Total doses of opioid, benzodiazepine, dexmedetomidine, and propofol administrated for each invasive mechanical ventilation day were calculated. For infusions, the maximum dose was also collected. Opioid dosages were converted to fentanyl equivalents (1 μg fentanyl = 0.02 mg hydromorphone, 0.1 mg morphine, 0.02 mg methadone, and 0.25 mg oxycodone) and benzodiazepine doses converted to midazolam equivalents (1 mg midazolam = 0.5 mg lorazepam). Total dosages were normalized to dosing weight. Dosages of medications given for intubation, those given after extubation, and methadone-lorazepam started for withdrawal treatment were not included in the analgosedation totals. Rigorous controlled substance monitoring process layers at this institution limited the possibility of registration bias from impacting this data collection method.

Statistical Methods

Results are presented as sums with percentages for categorical variables and means ± SDs or medians (interquartile ranges) for continuous variables. In accordance with quality-improvement methodology, the means ± SDs were evaluated for the primary outcome measures. Statistical comparisons between the pre-implementation and implementation cohorts were performed by using the Fisher exact test, chi-square test, independent sample *t* test (when assuming unequal variances), and the Mann-Whitney U test as appropriate. A 2-sided hypothesis test with a $P < .05$ was considered significant. Analyses were performed by using SPSS, version 25 (IBM, Armonk, New York). The invasive mechanical ventilation duration was presented in an individual's statistical process control chart, along with the corresponded moving range chart. The control chart was prepared by using QI Macros (KnowWare International, Denver, Colorado) for Excel (Microsoft, Redmond, Washington). Upper and lower control limits were calculated as 3 SDs (σ) above and below the center line (mean). However, the lower control limit was excluded due to a negative value (not clinically possible). The center line represents the mean.

Results

The timeline and key events for the project are presented in Supplementary Figure 2 (see the supplementary materials at http://www.rcjournal.com). The final analysis cohort ($n = 254$ baseline and $n = 332$ implementation) was yielded by excluding all invasive mechanical ventilation encounters that did not end in an extubation attempt. The implementation cohort was evaluated for the key outcome measures because they were exposed to the entire bundled implementation by virtue of an extubation attempt. The descriptive statistics for the baseline and implementation cohorts are presented in Table 2. In the implementation cohort, there were significantly fewer male subjects ($P = .01$) and significant differences in race distribution ($P = .030$). With regard to extubation failure risk factors, there also were significantly fewer subjects with a respiratory ($P < .001$) or dysgenetic/syndrome comorbidity ($P = .01$). Analgosedation medication administration outcomes are presented in Table 3. Cumulative benzodiazepine administration significantly decreased after the implementation. When considering encounters in which a continuous opioid was administered, the mean ± SD maximum dose in fentanyl equivalents was 1.75 ± 0.89 μg/kg/h at baseline versus 1.65 ± 0.7 μg/kg/h after implementation ($P = .28$). When considering encounters in which a continuous benzodiazepine was administered, the median (IQR) maximum dose in midazolam equivalents was 0.1 (0.05–0.2) at baseline versus 0.1 mg/kg/h (0.05–0.15) after implementation ($P = .27$).

Clinical and extubation outcomes for this group are presented in Table 4. There was a significant decrease in the mean ventilation duration (Pre 3.95 d vs Post 3.1 d; $P = .039$) without a concomitant decrease in PICU length of stay (Pre 7.5 d vs Post 6.5 d; $P = .42$). The mean ventilation duration is presented in an individual's statistical process control chart in Figure 2. Subjects were extubated to noninvasive ventilation 7.6% of the time in the baseline cohort versus 9.8% in the implementation cohort ($P = .35$). A total of 74 invasive mechanical ventilation encounters in the implementation cohort (22.3%) were audited for extubation readiness test process compliance. The median (IQR) time between when a subject met the screening criteria for an SBT and when the first SBT started was 1.83 (0.13–4.25) h. The process goal was ≤ 3 h, which was met in 63.5% ($n = 47$) of audited encounters. There were 121 total SBTs expected in the audited encounters with 75.2% ($n = 91$) being performed and documented correctly in the electronic medical records. The process goal was ≥ 90%, which was met in 73% ($n = 54$) of the audited encounters. Both goals were met

Table 2. Descriptive Statistics for Baseline and Implementation Cohorts

Descriptive Variable	Baseline Cohort	Implementation Cohort	*P*
No. ventilation encounters	253	332	NA
Median age, median (IQR) mo	43 (12–122.5)	57 (15–143)	.20
Boys, *n* (%)	159 (62.8)	170 (51.2)	.01
Race, *n* (%)			.030
White	116 (45.8)	163 (49.1)	
Black	111 (43.9)	151 (45.5)	
Hispanic	18 (7.1)	17 (5.1)	
Other	9 (3.2)	1 (0.3)	
PIM-3 risk of mortality, median (IQR)*	1.3 (0.9–3.1)	1.6 (0.8–3.1)	.84
Weight, median (IQR) kg	15 (9–32)	18 (10–45.2)	.09
Neurologic intubation indication, *n* (%)	79 (31.2)	124 (37.3)	.29†
Intracranial injury	13 (5.1)	30 (9)	
Encephalopathy	64 (25.3)	89 (26.8)	
Neuromuscular weakness	2 (0.8)	5 (1.5)	
Circulatory intubation indication, *n* (%)	32 (12.6)	33 (9.9)	
Shock (all types)	27 (10.7)	23 (6.9)	
Cardiac arrest	5 (2)	10 (3)	
Respiratory intubation indication, *n* (%)	88 (34.8)	99 (29.8)	
Lower respiratory tract infection	68 (26.9)	71 (21.4)	
Pulmonary (non-infectious)	10 (4)	18 (5.4)	
Upper airway obstruction	10 (4)	10 (3)	
Procedure and/or operative intubation indication, *n* (%)	43 (17)	54 (16.3)	
Other intubation indication, *n* (%)	11 (4.3)	22 (6.8)	
Extubation failure risk co-morbidity, *n* (%)			
Age ≤ 24 mo	91 (36)	106 (31.9)	.31
Dysgenetic or syndromic condition	47 (18.6)	35 (10.5)	.01
Chronic neurologic condition	77 (30.4)	78 (23.5)	.059
Chronic respiratory condition	99 (39.1)	61 (18.4)	<.001
Acute surgical airway condition	18 (7.1)	15 (4.5)	.18
Acute or chronic medical airway condition	11 (4.3)	23 (6.9)	.19
Chronic NIV use	15 (5.9)	9 (2.7)	.052
Cumulative extubation failure risk co-morbidity per ventilation encounter, *n* (%)			<.001
0	59 (23.3)	111 (33.4)	
1–2	138 (54.5)	194 (58.4)	
>2	56 (22.1)	27 (8.1)	

*$n = 6$ (baseline) and $n = 1$ (implementation) encounters were excluded from analysis (repeated encounters during the same pediatric ICU stay).
†Chi-square test performed at the primary category level (neurologic, circulatory, respiratory, procedure and/or operative, and other).
NA = not applicable
IQR = interquartile range
PIM-3 = Pediatric Index of Mortality-3
NIV = noninvasive ventilation

simultaneously, which indicated complete extubation readiness test bundle compliance, in 58% ($n = 43$) of audited encounters.

Discussion

This quality-improvement project aimed to decrease the mean invasive mechanical ventilation duration in our PICU by 25% through implementing a bundled prescriber-driven analgosedation algorithm combined with an RT-driven extubation readiness test pathway. The post-implementation mean invasive mechanical ventilation duration decreased by 0.9 d (23%), although the PICU length of stay did not change. Balancing measures, including extubation failure, unplanned extubations, iatrogenic withdrawal, and delirium, were unchanged.

The results of our implementation are in contrast to the landmark RESTORE trial.[14] More-frequent assessment of extubation readiness facilitated by an analgosedation approach likely translated into a decreased invasive mechanical ventilation duration. Recently, a similar bundled approach by the SANDWICH collaborators[31]

Table 3. Pain and Sedation Medication Administration Outcomes

Outcome Measure	Baseline Cohort	Intervention Cohort	*P*
No. ventilation encounters	253	332	NA
Opioid administration (fentanyl equivalents)			
Total cumulative, μg/kg/ventilated day	14.2 (4.6–33.8)	11.7 (3–29.6)	.07
Total continuous, μg/kg/ventilated day	7.6 (0–22.8)	0 (0–21.1)	.051
Calendar ventilated days + infusion, %	48 (0–100)	0 (0–81.4)	.049
Total PRN IV, μg/kg/ventilated day	5.6 (2.6–10.9)	5.8 (2.1–10.4)	.58
Benzodiazepine administration (midazolam equivalents)			
Total cumulative, mg/kg/ventilated day	0.4 (0.1–1.4)	0.1 (0–0.5)	<.001
Total continuous, mg/kg/ventilated day	0 (0–0.9)	0 (0–0)	<.001
Calendar ventilated days + infusion, %	0 (0-58.6)	0 (0–0)	<.001
Total PRN IV, mg/kg/ventilated day	0.2 (0.1–0.6)	0 (0–0.2)	<.001
Dexmedetomidine administration			
Total cumulative, μg/kg/ventilated day	1.5 (0–7.3)	0 (0–8.5)	.44
Calendar ventilated days + infusion, %	38.9 (0–96.4)	0 (0–92)	.11
Propofol administration			
Total cumulative, mg/kg/ventilated day	0 (0–0)	0 (0–0)	.29
Calendar ventilated days + infusion, %	0 (0–0)	0 (0–0)	.22
Calendar ventilated days + neuromuscular blockade infusion, %	0 (0–5.3)	0 (0–0)	.18

Values are presented as median (interquartile) unless otherwise noted.
NA = not applicable
PRN = as needed
IV = intravenous

Table 4. Clinical Outcomes for Baseline and Implementation Cohorts

Clinical Outcome Variable	Baseline Cohort	Implementation Cohort	*P*
No. ventilation encounters	253	332	NA
Mechanical ventilation, mean ± SD d	3.95 ± 5.6	3.1 ± 4	.039
Pediatric ICU length of stay, mean ± SD d*	7.5 ± 16.1	6.5 ± 9	.42
Planned extubation failures, *n* (%)†	24 (9.6)	35 (10.7)	.67
Unplanned extubations, *n* (%)	4 (1.6)	6 (1.8)	>.99
Nocturnal extubation (23:00–06:59), *n* (%)	55 (21.7)	85 (25.6)	.28
Iatrogenic narcotic withdrawal treatment, *n* (%)	45 (17.8)	54 (16.4)‡	.65
Anti-psychotic treatment for delirium, *n* (%)	14 (5.5)	29 (8.7)	.14
State Behavioral Scale Score, mean ± SD§	–1.0 ± 0.7	–1.1 ± 0.7	.09

*$n = 8$ baseline and $n = 9$ implementation encounters were excluded due to multiple courses during the same pediatric ICU stay.
†$n = 4$ baseline and $n = 6$ implementation encounters were excluded as unplanned extubations.
‡$n = 2$ encounters were excluded (treatment for withdrawal before the ventilator course).
§$n = 53$ baseline and $n = 60$ implementation encounters excluded due to no State Behavioral Score indicated.
NA = not applicable

also showed a decrease in invasive mechanical ventilation duration. That study used sedation and ventilator liberation protocols that focused on daily assessment of extubation readiness. The effect size was much smaller, at 2.2 h.[31] Importantly, there was no change in the extubation failure rate, a key balancing measure for assessment of the invasive mechanical ventilation duration. Co-morbid respiratory and dysgenetic/syndromic extubation failure risk factors were more prevalent in the baseline cohort. This limitation may have resulted in more extubation failures with the newly implemented strategy in a lower-risk implementation cohort. The optimal extubation failure rate and its balance with the invasive mechanical ventilation duration are unknown but are inversely related. Multi-center benchmark data are needed on this important balance for ventilation liberation strategies.

There is a complex relationship with a patient's comfort, wakefulness, and spontaneous breathing during invasive mechanical ventilation that impacts extubation outcomes. Through a multidisciplinary focus on optimizing patient

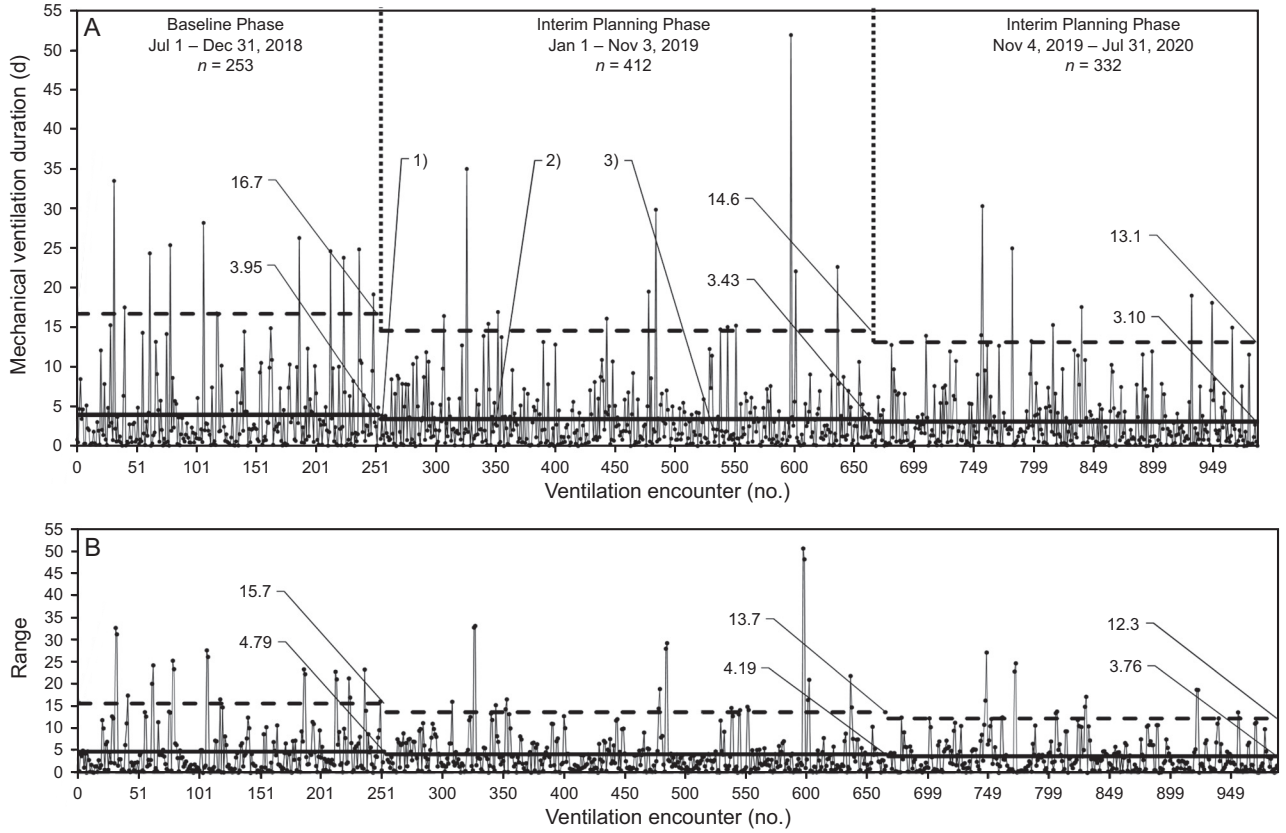

Fig. 2. A: Statistical process control chart (individuals) and B: corresponding moving range chart, depicting mechanical ventilation duration (in days) for each ventilation encounter across the continuous baseline, planning, and intervention phases. The dashed horizontal lines denote the upper control limit. Note that the lower control limit was omitted due to a negative value, which is not clinically possible. 1) Pulmonary disease cohort ERT pilot #1 (January 2019), 2) PICU liberation project planning begins (February 2019), C) PICU liberation project launch (July 2019) and pulmonary disease cohort ERT pilot #2 (July 2019–October 2019).

comfort in a standardized fashion, the subjects received more intentional analgosedation, which resulted in a decline in benzodiazepine use. Despite this practice change, the average post-implementation SBS scores were not different, which suggests that subject comfort was not compromised. Importantly, this also suggests that the method (less benzodiazepine or polypharmacy) rather than the sedation level is more important, as demonstrated in one adult study.[32]It is also reasonable to conclude that the subjects experienced a higher spontaneous breathing fraction, which may attenuate respiratory muscular atrophy.[33,34] Diaphragmatic atrophy may occur within 18 h after initiation of invasive mechanical ventilation, with 2%–7% daily progression.[3,35] Increasing spontaneous breathing and limiting diaphragmatic atrophy may have contributed to a shorter duration of invasive mechanical ventilation. Although our data do not directly support this conclusion, future studies may incorporate the evaluation of diaphragmatic thickness to more conclusively demonstrate the physiologic effects of our implementations.

Although the invasive mechanical ventilation duration was decreased in the implementation cohort, PICU length of stay was decreased but did not reach statistical significance. This may be related to a host of factors. Earlier extubation may have impacted post-extubation practice such as noninvasive ventilation use (baseline [7.6%] vs implementation [9.8%]), although not significant ($P = .35$). Data on high-flow nasal cannula use were not collected and stands as a limitation. It is possible that, over time, noninvasive ventilation use after extubation will increase within our unit. This trade-off may be acceptable to decrease invasive mechanical ventilation duration but will require ongoing outcomes monitoring. Additional factors that influence a subject's candidacy for transfer from the PICU may have been present. This is an additional limitation because we were unable to evaluate these factors retrospectively. In addition to those described previously, there are several important limitations.

First, the implementation was performed at a single-center PICU with a separate cardiac ICU and step-down unit. This limits external validity to similar centers and non-

cardiac populations. Second, the implementation was designed as a quality initiative without strict adherence to a study protocol and is prone to decision and selection biases. The invasive mechanical ventilation duration did downtrend during the planning period rather than acutely decrease at implementation. This may reflect early adoption of implementations in the planning stages as well as the influence of extubation readiness test pilot implementations. Third, at the time of implementation, the analgosedation clinical pathway did not prompt for de-escalation of therapies for the subjects whose SBS scores were below the goal and who were oversedated. The management of these situations was left to the prescriber's discretion, which may have had limited implementation effect. Although the specific results we observed from the implementation had limited external validity, the general management of analgosedation and frequent evaluation for extubation readiness in children who were critically ill and receiving invasive mechanical ventilation is applicable to pediatric ICUs worldwide. Importantly, it is possible that the introduction of standardized protocols and the focus on quality improvement may yield improvements independent of the specific granular details of the protocols themselves.

Future multi-center studies that evaluate the effect of a benzodiazepine-sparing analgosedation clinical pathway coupled with frequent RT-led extubation readiness tests are still needed. Results from such studies may translate into consensus practice recommendations that will inform and shape clinical practice. Locally, we aim to evaluate the outcomes of this implementation in a population-specific subanalysis. It is likely that there are subpopulations in which the bundled analgosedation and RT-driven extubation readiness test approach would have the most significant impact.

Conclusions

The development and implementation of a bundled, prescriber-driven benzodiazepine-sparing analgosedation clinical pathway coupled with an RT-driven extubation readiness test pathway decreased the invasive mechanical ventilation duration by 0.85 d for our center's PICU population. The subjects received significantly less benzodiazepine without changing the perceived level of comfort during invasive mechanical ventilation. Further multi-center randomized trials, followed by systematic reviews, are needed to verify our findings.

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