Effect of Protocolized Weaning and Spontaneous Breathing Trial vs Conventional Weaning on Duration of Mechanical Ventilation: A Randomized Controlled Trial

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ABSTRACT

Background: Identifying ventilated patients ready for extubation is a challenge for clinicians. Premature extubation increases risks of reintubation while delayed weaning increases complications of prolonged ventilation. We compared the duration of mechanical ventilation (MV) and extubation failure in children extubated using a weaning protocol based on pressure support spontaneous breathing trial (PS SBT) vs those extubated after nonprotocolized physician-directed weaning.

Patients and methods: A prospective randomized controlled trial was conducted in the pediatric intensive care unit of a tertiary care hospital in children ventilated for ≥24 hours. All eligible patients underwent daily screening and were randomized once found fit. The intervention group underwent PS SBT of 2 hours duration followed by a T-piece trial and extubation. Controls underwent conventional weaning with synchronized intermittent mandatory ventilation mode and a T-piece trial before extubation.

Results: Eighty patients were randomized into two groups of 40 each. About 77.5% of patients passed the PS SBT on the first attempt. No statistical difference was found either in the duration of MV between the two groups [median (interquartile range) in days: 4.77 (2.89, 9.46) in controls and 4.94 (2.23, 6.35) in cases, $p = 0.62$] or in the rate of extubation failure (13% and 10.5%, $p = 1$). Mortality was found to be significantly higher in the reintubated patients compared to those not reintubated in both groups ($p = 0.002$ in cases and 0.005 in controls).

Conclusion: Weaning using PS SBT-based protocol though did not shorten the duration of MV, it was found to be safe for assessing extubation readiness and did not increase extubation failure (CTRI no—CTRI/2018/04/013270).

Keywords: Extubation failure, Extubation readiness trial, Mechanical ventilation, Spontaneous breathing trial, Weaning.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23944

HIGHLIGHTS

- Protocolized weaning using daily screening and pressure support spontaneous breathing trial (PS SBT) did not shorten the duration of ventilation.
- The majority of the patients (77.5%) passed the PS SBT on the first attempt and could be safely extubated without increasing extubation failure.

INTRODUCTION

Mechanical ventilation (MV) is an important lifesaving intervention frequently used in critically ill children but identifying ventilated patients ready for extubation still remains a challenge for clinicians. Premature extubation increases risks of reintubation, associated with a poorer prognosis, while delayed weaning and extended period of MV increases complications of prolonged ventilation.[1–3]

A significant proportion of patients being evaluated for weaning are ready for extubation.[4–6] The process of weaning or reduction in the ventilatory support could be empirical, based on clinical judgment, or protocolized using spontaneous breathing trial (SBT). SBT, also referred to as extubation readiness trial (ERT), is performed on a patient while still intubated and evaluates the patient's cardiorespiratory tolerance to maintain spontaneous breathing with minimal or no support.[6,7] Pressure support (PS), continuous positive airway pressure (CPAP), and T-piece are three of the commonly used SBTs.[7,8] Studies in adults

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have shown that weaning protocol with daily evaluation and use of SBT leads to a reduction in MV duration, treatment costs, and treatment-associated complications.[6,9–11] However a few studies done in pediatric population have shown variable results, and their applicability in resource-limited countries still needs evaluation.[12,13]

In our study, we evaluated if protocolized weaning using daily screening of patients and use of pressure support spontaneous breathing trial (PS SBT) for assessing extubation readiness could lead to any reduction in ventilation duration compared to conventional weaning without increasing risks of premature extubation.

MATERIALS AND METHODS

Design: A single-center, open-labeled randomized controlled trial.
Setting: Pediatric intensive care unit (PICU) of a tertiary care hospital in Delhi, India.
Study period: From April 2015 to March 2016.

Participants and sample size: Eligible patients were children, 1 month to 12 years of age, ventilated for >24 hours in PICU. Exclusion criteria were neuromuscular disorders, spinal cord injury above lumbar region, upper airway obstruction, tracheostomy, anatomical obstruction of lower airways, diaphragmatic hernia or palsy, congenital cyanotic heart disease, chronically ventilated patients (>3 weeks), primary pulmonary hypertension, and significantly decreased lung capacity. A sample size of 80 patients with 40 in each group was taken for the study.

Recruitment and randomization: Patients were randomized into two groups by block randomization with each block of eight, using a computer-generated randomization list.

- **Group A (control group):** Received conventional physician-directed weaning (No PS SBT).
- **Group B (intervention group):** Intervention, PS SBT, was given on fulfillment of eligibility criteria.

Allocation concealment: Sequentially arranged sealed opaque envelopes, prepared by a person who was not involved in the study, were used for allocation concealment.

Outcomes: Primary outcome—duration of MV. Secondary outcome—extubation failure (reintubation or unplanned noninvasive ventilation within 48 hours of extubation).

Methodology: All patients meeting the eligibility criteria were assessed daily for SBT eligibility. Once fit, they were enrolled in the study and randomized. Eligibility criteria for performing SBT were (i) hemodynamically stable patients with no or minimal inotropic support (dopamine/dobutamine ≤10 μg/kg/minute), (ii) basic disease pathology significantly improved/ resolved, (iii) presence of spontaneous breathing efforts, (iv) presence of gag or cough reflex on suctioning, (v) acceptable level of consciousness, (vi) pH 7.32 to 7.47 on recent blood-gas analysis done in last 12 hours, (vii) positive end expiratory pressure ≤5 cm H_2O, fraction of oxygen in inspired air (FiO_2) ≤0.5, peak inspiratory pressure (PIP) ≤25, (viii) absence of new infiltrates on the chest radiograph, (ix) no clinical need to increase ventilator support in the last 12 hours, (x) no planned operative procedures requiring heavy sedation in the next 48 hours, and (xi) not on paralysis in the past 24 hours and minimal sedation (≤midazolam 1 μg/kg/minute). These criteria provided a check sheet to see if factors contributing to ventilator dependence were reversed and to ensure objective and subjective measurement of patient's clinical stability, oxygenation, pulmonary function, and mental status, to assess suitability for weaning and extubation.[12–14]

In the control group, weaning was done as per the treating team's discretion without any written protocol. Most of our patients were ventilated using pressure control synchronized intermittent mandatory ventilation (SIMV) mode with pressure support. In the control arm, first the FiO_2 was reduced up to 35 to 45%, and PIP was reduced to <20, while maintaining oxygen saturation (93–99%). Respiratory frequency was reduced slowly up to 8 to 10 in infants and 5 to 6 in older children, and finally reducing and stopping PS while maintaining O_2 saturation, MV, total respiratory rate (RR) and end tidal CO_2 ($ETCO_2$). Prior to extubation, all patients were given a T-piece trial of 2 hours duration which was the standard of care in our PICU.

Sedation with midazolam and fentanyl was commonly used in our ICU for the initial few days followed by midazolam alone. The usual practice was to give sedation holiday daily in the morning. If the patient was on any midazolam infusion, it was stopped before attempting T-piece trial and extubation.

In the intervention group, PS SBT was given by changing the ventilator mode to pressure support ventilation (PSV) with PS adjusted for increasing ET size—3 to 3.5: 10 cm H_2O, 4 to 4.5: 8 cm H_2O and ≥5: 6 cm H_2O, similar to study by PALISI network.[12] If the patient was able to maintain a tidal volume >5 mL/kg for 10 minutes, trial was continued for the next 2 hours or else the patient was removed from the test and placed back on previous ventilator settings.

The patient was classified as failing the test if anytime during the 2-hour period any of the following criteria was met—(i) RR outside the normal for the given age-group (<1 year: 30–60/minute, 1–3 years: 24–40/minute, 4–5 years: 22–34/minute, 6–12 years: 18–30/minute), (ii) increase in heart rate (HR) >20% over baseline, (iii) increase in work of breathing/accessory muscle use, (iv) tidal volume ≤5 mL/kg, (v) blood pressure falls to <5th centile for age, (vi) saturation decrease ≤92%, and (vii) $ETCO_2$ rises >10 mm Hg/hour.

Patients passing the SBT were subjected to a second T-piece trial as we were not confident about the predictability of PS SBT for safe extubation. The patient was disconnected from the ventilator and allowed to breathe through a T-piece connected to ET tube (with added oxygen if required) and was monitored for the same criteria for 2 hours. If the patient passed both the tests, they were extubated. On failure of either of the test, the patient was put back on the ventilator with previous settings and reassessed again for SBT every day.

Extubated patients were monitored for any complications or need for reintubation. Reintubation was done in cases of extubation failure indicated by (i) marked increase in RR with severe retractions/desaturation <90%/apnea >20 seconds, (ii) blood-gas criteria (PaO_2/FiO_2 ratio <200 or $PaCO_2$ >50 mm Hg with pH <7.3), and (iii) inadequate respiratory effort with decreased consciousness or cardiovascular insufficiency.

Patients were enrolled only once during their hospital stay and only the first intubation was considered for analysis. Both groups were managed by the same medical team and weaning prior to randomization was similar in the groups. Daily screening of patients, randomization, and SBT in the intervention group was performed by a designated resident involved in the study, while extubation/reintubation and further management were done by the managing team.

Data collection: For all patients, the following variables were collected—age, sex, date of admission, primary diagnosis, comorbidities, indication for MV, date of intubation and start of MV, ET size, total duration of MV, ventilatory parameters, weaning time, SBT outcome (failure or success), T-piece outcome, patient outcome (extubation/death), and extubation failure, if therewith reason.

Data analysis: Data entry was done using a Microsoft Excel spreadsheet and analyzed using descriptive statistics/SPSS version 22. Results were expressed as proportions for categorical data and for continuous data as mean ± SD for normally distributed variables or median [interquartile range (IQR)] for non-normally distributed variables. For categorical data, chi-square tests or Fisher's exact tests were used if the expected values in any single cell were <5. For continuous variables, Mann–Whitney U test (for non-normal

distribution) or Student's *t*-test (for normal distribution) was used. *p*-value <0.05 was considered significant.

Ethical considerations: The study was approved by the Institutional Ethics Committee. The details of the study were communicated to parents verbally and by a patient information sheet. Written informed consent was taken from parents/guardians of children before inclusion into the study. Parents were able to withdraw their child from the study at any time.

Results

A total of 80 patients were enrolled in the study with 40 in each group (Flowchart 1). The two groups were comparable in their characteristics except for median age and weight, which was significantly lower in the intervention group, and subsequently also differed in the ET tube sizes (Table 1).

A total of 37 out of 40 patients (92.5%) in the intervention group passed PS SBT on one or more attempts. Thirty-one cases (77.5%) passed the PS SBT in the first attempt, out of which 30 passed the consecutive T-piece trial and 29 of them got extubated (Supplementary file available on IJCCM journal website). One patient who was a case of postdiphtheritic palatal palsy with pneumonia could not be extubated despite passing both the trials as there was pooling of secretions and this patient had to be tracheostomized. One patient who only failed the T-piece trial passed both PS and T-piece trial the next day and was extubated.

Of the remaining nine patients who failed the first trial, one expired before the trial could be repeated. Six successfully passed both the trials on successive attempts and were extubated (four after second and one each after third and fifth attempt). Two cases failed PS SBT repeatedly. One was a case of meningitis with intracranial infarct, failed four PS trials, but extubation attempted as per physician's decision was successful. Second was a case of empyema thoracis, who passed the fourth and fifth PS SBT but failed the subsequent T-piece trial, got self-extubated and was

successfully managed on oxygen support. A total of 58 PS SBT was given to 39 patients, out of which 39 (67%) were successful and 19 (33%) failed. The median number of days for which the patient had been ventilated before giving PS SBT was 2.71 (1.56–5.35) in those who passed the trial in the first attempt and 4.29 (2.58–5.67) in those who did not ($p = 0.39$). The mean duration after which the PS SBT trial failed was 23 minutes while the maximum was 1 hour, with tachypnea being the most common cause of failure.

In the control group, a case of postdiphtheritic polyneuropathy had difficult weaning attributed to neuromuscular weakness and required elective tracheostomy. Rest of the 39 patients were conventionally weaned and given T-piece trial which was passed by 36 patients on the first attempt (92.3%), by two on the second attempt, and one failed the trial and expired before becoming eligible for a repeat trial. The median number of days for which the patient had been ventilated before taking on T piece was 3.79 (1.90–8.27) in those who passed the trial and 1.29 (1.18–2.14) in those who did not, which was not significantly different ($p = 0.34$). The clinical profile of patients failing various extubation trials is given in Table 2.

There was no difference in total extubation rates in the two groups, with 38 getting extubated in both. The mean duration of ventilation was similar in both groups (Table 3, Figure 2). They also did not differ with respect to weaning time (time from the beginning of weaning to extubation), duration of PICU stay, and duration of hospital stay. However total reintubation rate was lower in the intervention group as compared to controls but was not statistically significant [15.78% (6/38) vs 26.3% (10/38), $p = 0.4$]. The rate of extubation failure, as defined by patients reintubated within 48 hours was 10.5% (4/38) and 13% (5/38) in the intervention and control groups, respectively, and was not significantly different. Reintubation rate was lower, i.e., 13.8% (4/29) in those extubated after passing the PS SBT on the first attempt as compared to 40% (2/5) in those who were extubated after the second attempt. There were however no reintubations in those four who passed the trial

Flowchart 1: Flowchart depicting the outcome of PS SBT in the intervention group
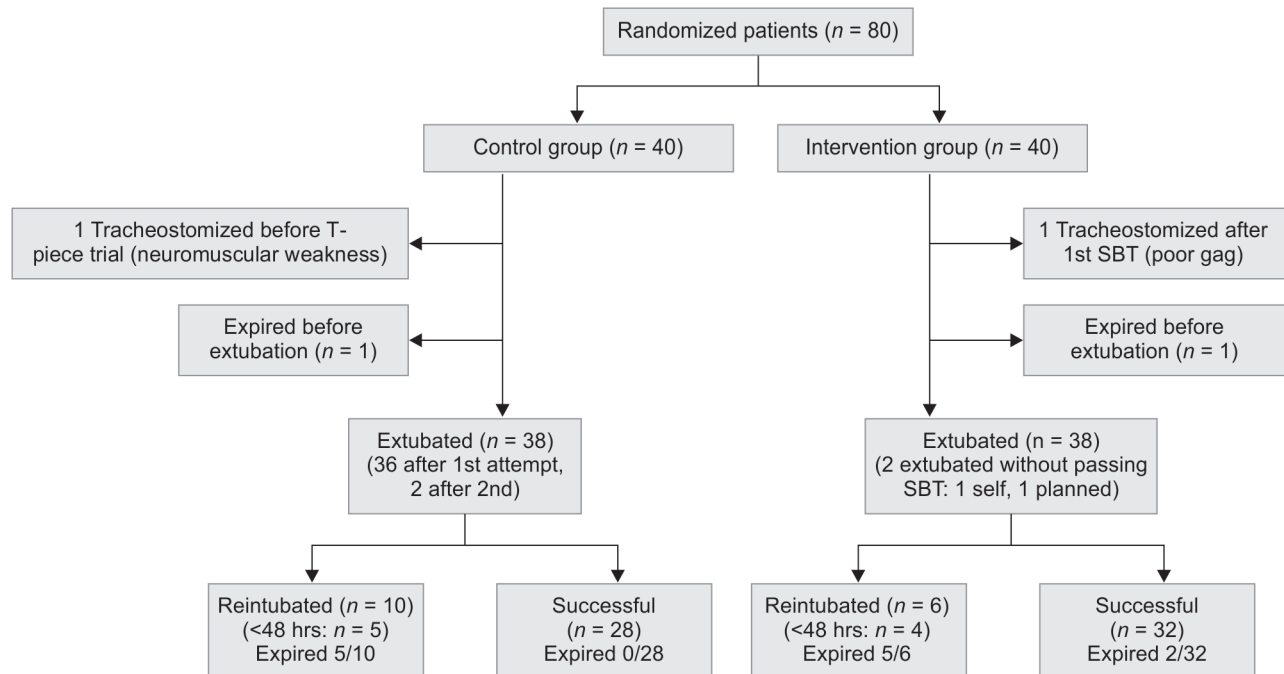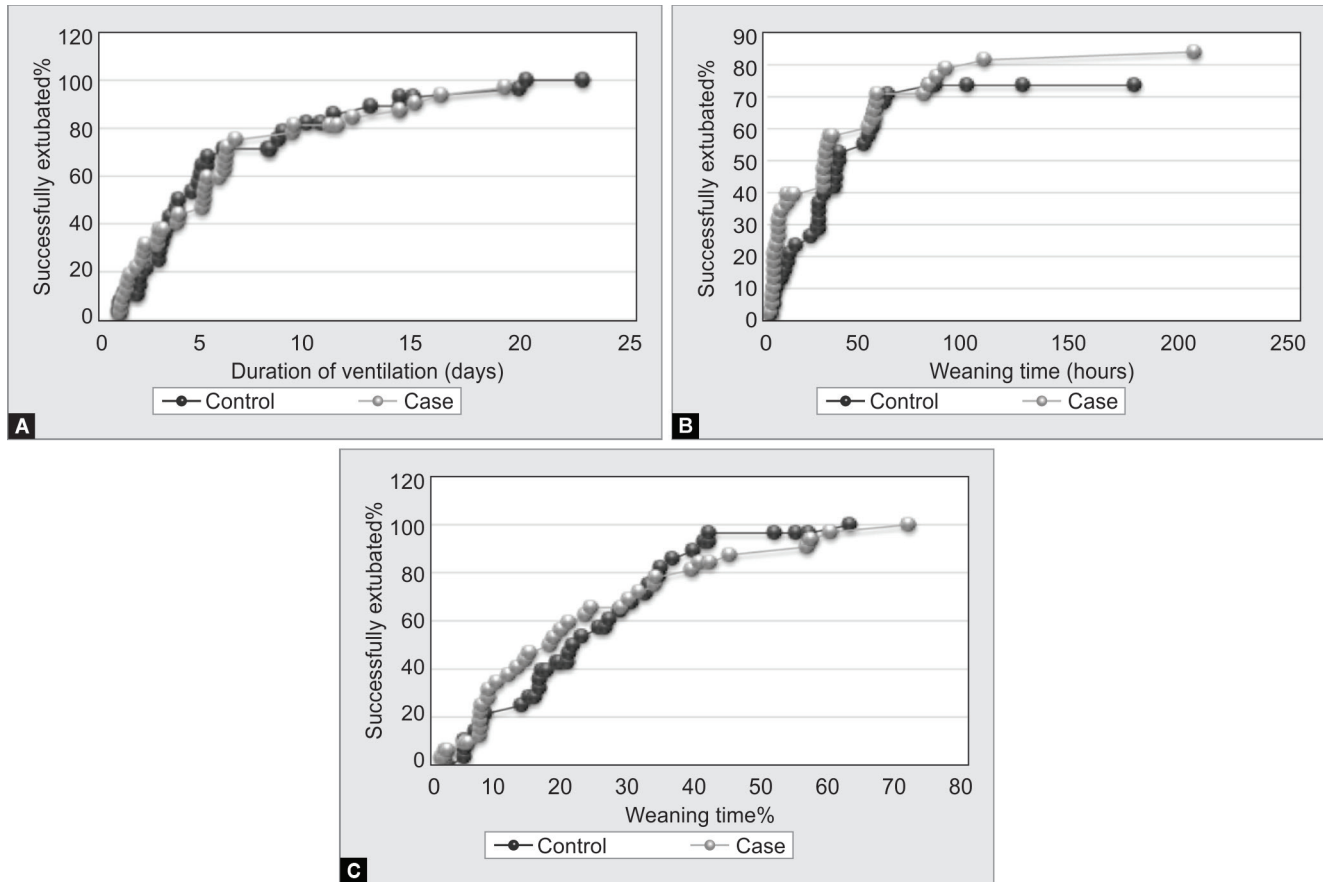
Figs 2A to C: Kaplan–Meier curve comparing (A) duration of mechanical ventilation; (B) weaning time; and (C) weaning time as percentage of total MV duration between the two groups

later with more attempts. The number of patients in subsequent attempts of SBTs was so small that it is difficult to conclude whether the need for more attempts of SBTs is associated with more extubation failures.

The mean time to reintubation in extubation failures was 5.6 hours for controls and 17.5 hours for the intervention group, with the earliest being 1 hour in both groups. Of the reintubated patients, four in the control group needed tracheostomy, three for upper airway obstruction (all ventilated for >10 days), and one due to vocal cord palsy (an operated case of brain stem glioma). In the intervention group, two reintubated patients were tracheostomized for prolonged ventilation with difficult weaning. Noninvasive ventilation was not used after extubation in any patient.

There was no statistically significant difference in the duration of ventilation prior to extubation in reintubated patients compared to those who were not, in both groups. However, there was a significant difference in mortality between the patients successfully extubated vs those requiring reintubations (intervention group: 2/32 expired in successfully extubated vs 5/6 in reintubated, $p = 0.0002$, controls: 0/28 in successfully extubated vs 5/10 in reintubated patients, $p = 0.0005$).

DISCUSSION

There is no clear consensus on the ideal PS to be used for PS SBT. Adult studies have used a uniform pressure of 7 cm H_2O while pediatric studies have used variable support.[12–19] Studies have

shown that PS of 3 to 4 cm may be sufficient to alleviate any increased resistance due to ET tube at physiological flow rates.[20–22] Khemani et al. found very low work of breathing in children while on PS of 10 cm H_2O measured by an esophageal manometer and concluded that it underestimates work of breathing and hence should not be used as an ERT.[23] Ferguson et al. found that PS SBT given according to ET size may overestimate extubation readiness.[24] We used PS levels as per ET tube size like Randolph et al. and Gaffari et al., whereas Foronda et al. and Farias et al. used a uniform level of 10 cm H_2O.[12–14,19]

Previous studies have shown that the majority of the ventilated patients do not require gradual weaning and can be extubated after an SBT, with 76 to 89% of patients passing it at first attempt.[25–28] About 77.5% (31/40) passed the PS SBT in the first attempt in our study and 93.5% (29/31) of these were extubated. Faustino et al. in a study on 1,042 children ventilated for lower respiratory tract diseases found that 43% passed their first PS SBT of which 66% got extubated within the next 10 hours and 92.2% of them were successful.[27] They found that PS SBT had a positive predictive value of 92% for successful extubation. The average duration at which PS SBT trial failed in our study was 23 minutes. Other studies have reported 20–45 minutes trial duration before failing.[15,28]

Our study found that protocol-guided daily screening, combined with a 2-hour PS SBT, did not significantly shorten the duration of MV or weaning time compared to conventional weaning.

Some adults studies have shown that identification of difficult to wean patients by use of a 2-hour T-piece SBT and then gradual

Table 1: Characteristics of the study population

	Group A (control)	Group B (intervention)	p value
Males/females, N (%)	30/10 (75%, 25%)	25/15 (62.5%, 37.5%)	0.23[a]
Age in months, median (IQR)	45 (6.5–102)	11.5 (3–54)	0.02[b]
Weight in kg median (IQR)	12 (5.25–24.25)	7 (4–11.38)	0.02[b]
Problem—medical/surgical (%)	30/10 (75%, 25%)	26/14 (65%, 35%)	0.33[a]
Primary disease			0.29[c]
• Respiratory	11 (27.5%)	14 (35%)	
• CNS	12 (30%)	11 (27.5%)	
• GIT	6 (15%)	8 (20%)	
• CVS	2 (5%)	5 (12.5%)	
• Others	9 (22.5%)	3 (7.5%)	
ET tube size			0.03[c]
• 2.5–3.5	7	8	
• 4–4.5	12	22	
• 5–5.5	14	9	
• 6–8	7	1	
Days intubated prior to randomization, median (IQR)	3.58 (1.84–9.48)	3.19 (1.72–6.25)	0.50[b]
Indications for MV	N = 40	N = 40	0.66[c]
• Acute respiratory failure due to pulmonary disease	14 (35%)	16 (40%)	
• Acute respiratory failure due to neurological disease	7 (17.5%)	5 (12.5%)	
• Altered mental state GCS<8	7 (17.5%)	3 (7.5%)	
• Cardiovascular disease	1 (2.5%)	3 (7.5%)	
• Shock	1 (2.5%)	1 (2.5%)	
• Elective ventilation (postoperatively)	10 (25%)	12 (30%)	

[a]Chi-square test, [b]Mann–Whitney U test, [c]Fisher's exact test; ET, endotracheal tube; GCS, glasgow coma scale; IQR, interquartile range; MV, mechanical ventilation

Table 2: Clinical profile of patients failing breathing trials

Sl. No.	Diagnosis	Failed attempts	Duration after which trial failed	Cause for failure	Days ventilated prior to trial
PS SBT failure in the intervention group (N = 9)					
1	Sepsis/pneumonia/pneumothorax	1	15 min	Tachypnea	2.58
2	Corrosive poisoning/postgastrectomy	1	15 min	Tachypnea	3.00
3	Sepsis/pneumonia/perforation peritonitis (operated)	1	1 hr	Low TV and Tachypnea	4.75
4	ACHD/VSD/CHF	1	1 hr	Tachypnea	5.83
5	Coarctation of aorta (operated)	1	15 min	Tachypnea	8.00
6	Empyema	2	10 min, 30 min	Tachypnea	4.29
7	Posterior fossa mass/operated case	4	15 min, 10 min, 30 min, 15 min	Low RR with apnea (on two attempts) Tachypnea and low TV (on two attempts)	1.75
8	Post-traumatic meningitis with intracranial infarcts	4	10 min	Low RR	2.50
9	Sepsis/empyema/shock	4	15 min	Tachypnea	5.67
T-piece trial failure in the control group (N = 3)					
1	ACHD/VSD/PDA/CHF	1	90 min	Severe chest retractions and CO_2 build-up	1.08
2	Seizure disorder/aspiration pneumonia	1	120 min	Seizure on T-piece	1.29
3	Esophageal atresia (operated)	1	120 min	Increased chest retractions	3.00

ACHD, acyanotic congenital heart disease; CHF, congestive heart failure; PDA, patent ductus arteriosus; RR, respiratory rate; TV, tidal volume; CO_2, carbon dioxide; VSD, ventricular septal defect

Table 3: Comparison of outcome of two groups

	Group A (control)	Group B (intervention)	p value[a]
Duration of mechanical ventilation in days	$N = 38$[b]	$N = 38$[b]	0.62
• Mean $\pm$ SD	6.78 ± 5.7	5.72 ± 4.6	
• Median (interquartile range)	4.77 (2.89, 9.46)	4.94 (2.23–6.35)	
Weaning time in hours	$N = 38$[b]	$N = 38$[b]	0.23
• Mean $\pm$ SD	36.98 ± 35.02	32.68 ± 39.27	
• Median (interquartile range)	29.5 (10.62–50)	27 (4.25–50.75)	
Weaning time as percentage of total MV duration	25.4%	23.27%	0.33
Duration of PICU stay in days	$N = 32$[c]	$N = 30$[c]	0.64
• Mean $\pm$ S.D	16.87 ± 11.91	19.77 ± 18.78	
• Median (interquartile range)	14 (7.75, 23.25)	19.5 (8.25, 23)	
Duration of hospital stay in days	$N = 31$[d]	$N = 30$[d]	0.67
• Mean $\pm$ S.D	27.77 ± 23.56	26.83 ± 19.75	
• Median (interquartile range)	22 (15, 33.5)	23.5 (16.5, 27.75)	

[a]Mann–Whitney U test; [b]extubated patients; [c]patients transferred out of PICU, [d]discharged patients

protocolized weaning in them using different methods—SIMV, PSV, T piece, or daily T-piece SBT—did lead to a reduction in the duration of MV.[9,11,27,29] In children, two large studies have been conducted that showed opposite results.[12,13] Randolph et al. used a PS SBT as a screening tool to either extubate children who passed the trial or randomize the one failing it to one of the three groups for protocolized weaning—PSV, volume support ventilation (VSV), or no protocol.[12] They found that protocolized weaning did not shorten the ventilation duration. In contrast, Foronda et al. conducted daily screening to assess eligibility to give PS SBT, which was given only to the intervention group, like our study.[13] They found that there was a reduction in the duration of MV by a median of 1 day in children receiving protocolized weaning compared to conventional weaning.

On average, the weaning phase constitutes 40% of the total MV duration.[6,27,28] In our study, it was 25.4% in SBT and 23.3% in control group ($p = 0.33$). This shorter weaning time could be because weaning was decided by a pediatric intensivist in our study instead of a respiratory therapist. We also did not find any difference in the weaning time in two groups like Randolph et al.[12] However, Restrepo et al., Schulze et al., and a Cochrane review by Blackwood et al. found reduction in weaning time by protocolized weaning.[30–33]

The extubation failure rates were also similar between the intervention and control groups, i.e., 13% and 10.5%, respectively. Randolph et al. and Foronda et al. found no difference in the extubation failure rate between the protocol and no protocol groups.[12,13] The extubation failure rate reported in pediatric patients is quite heterogeneous and lies anywhere between 2.7% and 22% in various pediatric studies.[1,3,19] Important to note is that the reintubated group had significantly higher mortality compared to the successfully extubated group, which had also been seen in previous adult and pediatric studies.[15,19] According to a study by Kurachek et al., extubation failure leads to a fivefold increased risk of death in pediatric patients.[1] He reported that nearly 83% of reintubation occurred within the first 12 hours. Average time for reintubation in our study was 5.6 hours in the control group and 17.5 hours in the intervention group.

We also had two patients who failed multiple PS SBTs but were still successfully extubated. Chavez et al. also found that while using CPAP of 5 cm H_2O as SBT, 9% of patients failed the trial of which half were still successfully extubated.[33] Ferguson et al. reported that 2.7% (15/538) patients who underwent a PS SBT got extubated without passing it with only three extubation failures in them (20%).[24] Thus SBT is a reliable bedside test for assessing extubation readiness, but SBT failure does not always predict extubation failure.

The strengths of the study are that it was a prospective RCT and that the same pediatric intensivist assessed weaning and extubation readiness in all patients. Also, all patients were ventilated on the same mode of ventilation, i.e., pressure control SIMV. This study also had few limitations. This was a single-center study and the number of patients was small. The pediatric intensivist cannot be blinded in such studies to the type of weaning method being used. A larger sample size would give more conclusive results.

Conclusion

A significant number of patients could be extubated after passing PS SBT. Most of the patients who failed the SBT did so early (average being 23 minutes). However, the benefit of PS SBT in shortening the duration of ventilation was not seen in our study. Some patients failing the trial can still get successfully extubated with careful assessment and at the discretion of the intensivist. We did not find any serious events or adverse effects associated with PS SBT, e.g., accidental extubation, hemodynamic instability, or death. The extubation failure rate was similar in both groups. Mortality was seen to be higher in patients requiring reintubation compared to those successfully extubated.

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