Original Article

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Protocolized ventilator weaning verses usual care: A randomized controlled trial

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ABSTRACT

Background: Protocolized ventilator weaning (PW) strategies utilizing spontaneous breathing trials (SBTs) result in shorter intubation duration and intensive care unit (ICU) length of stay (LOS). We compared respiratory therapy (RT)-driven PW versus usual care (UC) as it pertains to physiologic respiratory parameters, intubation duration, extubation success/reintubation rates, and ICU LOS.

Methods: A prospective, multicentric, randomized controlled trial was performed in closed medical and surgical ICUs with 24/7 in-house intensivist coverage at six academic medical centers in a resource-limited setting from October 18, 2007, to May 03, 2014. Extubation readiness was determined by the attending physician (UC) or the respiratory therapist (PW) using predefined criteria and SBT. Physiologic variables, serial blood gas measurements, and weaning indices were assessed including the Rapid Shallow Breathing Index (RSBI), negative inspiratory force (NIF), occlusion pressure (P0.1), and dynamic and static compliance (C_{dyn} and C_s).

Results: A total of 5502 patients were randomized (PW 2787; UC 2715), of which 167 patients died without ventilator weaning (PW 90; UC 77) and 645 patients were excluded (PW 365; UC 280). Finally, a total of 4200 patients were analyzed (PW 2075; UC 2125). The PW group displayed improvements in minute ventilation ($P < 0.001$), C_s and C_{dyn} (both $P < 0.05$), P0.1 ($P < 0.001$), NIF ($P < 0.001$), and RSBI ($P < 0.001$). Early re-intubation (≤48 h) rates were lower in the PW group (16.7% vs. 24.8%; $P < 0.0001$), as were late re-intubation rates (5.2% vs. 25.8%; $P < 0.0001$). Intubation duration was longer in the PW group ($P < 0.001$), however, hospital LOS was shorter ($P < 0.001$). Mortality was unchanged ($P = 0.19$).

Conclusion: PW with RT-driven extubation decisions is safe, effective, and associated with decreased re-intubation (early and late), shorter hospital stays, increased intubation duration (statistically but not clinically significant), and unchanged in-patient mortality.

Key Words: Airway extubation, critical care, respiration artificial, respiratory insufficiency, ventilator weaning

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INTRODUCTION

Mechanical ventilation (MV) is a life-saving and supportive measure highly utilized in critical care medicine. Despite its advantages, complications may include barotrauma, volutrauma, and infections. Although expeditious ventilator weaning is necessary to limit complications, the optimal timing and technique remains debated. Successful weaning and ventilator liberation remains a

critical component of intensive care unit (ICU) patient care, as up to 42% of time on the ventilator is spent amid the discontinuation process.[1] Failed extubation is associated with increased mortality, prolonged MV, longer ICU and hospital length-of-stay (LOS), and higher transfer rates to long-term-care facilities.[2]

Spontaneous breathing trials (SBTs) have been demonstrated as a successful means to predict weaning success.[3] Ideal SBT settings vary, with little difference seen between common settings including low levels of continuous positive airway pressure (CPAP), pressure support, or "T-piece" breathing.[4-6] Studies suggest that SBT duration of 30–120 min results in a 77% rate of successful ventilator liberation.[3,7-9] Protocolized ventilator weaning (PW) strategies utilizing SBTs have been reported to decrease the MV duration and ICU LOS.[2,10,11] The objective of this trial was to determine if in patients on MV for ≥24 h (population), does a respiratory therapy (RT)-driven PW strategy perform as well as usual care (UC) as it pertains to duration-of-intubation (DoI; primary outcome) or reintubation rates (early and late) or ICU LOS (secondary outcomes). In addition, we aimed to assess the performance of physiologic respiratory parameters and indices to predict extubation success.

METHODS

Study design and settings

This was a prospective, multicentric, randomized controlled trial in the closed medical and surgical ICUs at six academic medical centers in a resource-limited setting from October 18, 2007, to May 3, 2014. Each ICU had 24-h in-house intensivist coverage. All parts of the study were reviewed according to the Consolidated Standards for Reporting Trials statement [Figure 1].[12] The trial was registered with Clinicaltrials.gov (identifier NCT03724643). Crossover was not allowed. Patients were blinded to randomization group, as were the health-care providers and statistician. Block randomization (groups of 4) was performed with a computer-generated list prepared by a statistician using Random Allocation Software© (RAS; Informer Technologies Inc., Los Angeles, USA). Randomly allocated numbers were placed into sequential containers that were kept in a secure location until allocation consignment. Allocation consignment occurred through confidential communication between the patient's nurse and a third party not involved in recruitment. The data analyzer was blinded to group randomization and was not present during ventilator weaning. There were no important changes to methods after trial commencement. The study ended because it achieved the necessary sample size.

Patient population

Patients were eligible for study participation if: (1) age ≥18 years; (2) admitted to the ICU; (3) endotracheally intubated on MV ≥24 h; (4) full-code status; and if (5) informed consent was provided by the patient, legal guardian, or health-care surrogate prior to ventilator weaning. Patients were excluded for: (1) declining consent, (2) death without ventilator weaning, (3) cardiopulmonary arrest on the ventilator, (4) permanent ventilator dependence, (5) tracheostomy placement for long-term weaning, (6) self-extubation, (7) pulmonary edema, (8) aspiration during the wean, (9) copious secretions and mucus plugging precluding wean, (10) severe obstructive lung disease, (11) chronic obstructive pulmonary disease (COPD, determined by medical records, history, and examination) with hypercapneic respiratory failure, (12) cardiopulmonary arrest during weaning process, (13) concurrent neurologic or neuromuscular comorbidity, (14) drug or alcohol intoxication, and (15) incomplete data.

Intervention

All patients were ventilated using Dräger Evita® XL or Evita® 4 ventilators (Dräeger Medical, Inc., Lubeck,

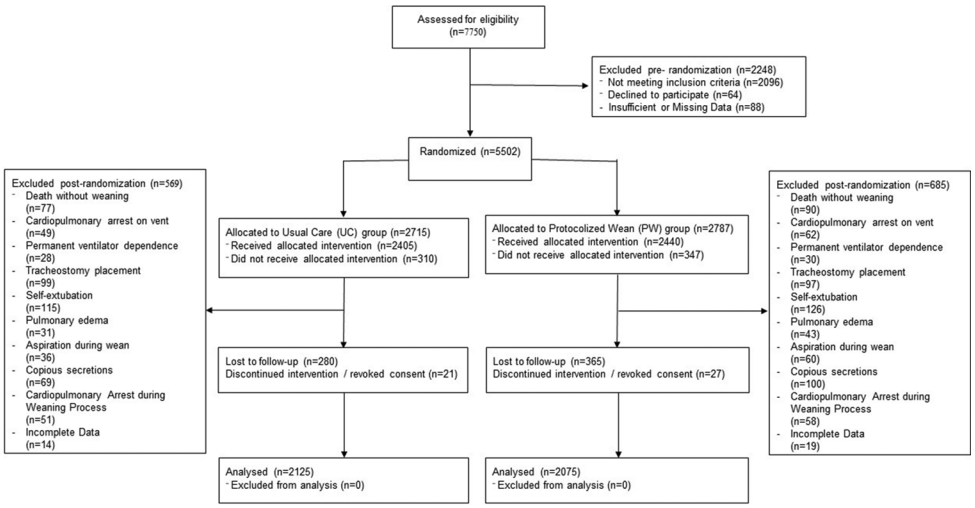

Figure 1: CONSORT 2010 flow diagram

Germany). Prior to the SBT, management of each group was the same. In the PW group, weaning and extubation readiness was determined by the RT using predefined criteria and the SBT result. Predefined weaning criteria included: (1) patent upper airway; (2) ability to protect airway (defined by mental status and adequate gag and cough reflexes); (3) ability to clear secretions; (4) decreasing secretion burden (not more frequently than every 2 h); (5) ventilator support level (fraction of inspired oxygen [F_iO_2] <50%, positive end-expiratory pressure of 5 cmH_2O); and (6) hemodynamic stability not requiring chemical (vasopressors, inotropes) or mechanical (e.g., intra-aortic balloon pump and extracorporeal life support) circulatory support. The SBT in the PW group consisted of CPAP of 5 cmH_2O with an $F_iO_2 \leq 0.4$. After 3 min, patients were assessed for appropriateness to continue according to arterial oxygen saturation (S_aO_2) ≥92% without arrhythmias, and a Rapid Shallow Breathing Index (RSBI = respiratory rate (RR)/tidal volume [V_T]) <105 breaths/min/L. Specified signs of respiratory distress included RR >30 breaths/min; S_aO_2 <90%; heart rate (HR) >140 beats/min, or a sustained increase or decrease of HR >20%; systolic blood pressure (BP) >200 mmHg or <80 mmHg; or agitation, anxiety, or diaphoresis without other identified cause. The SBT was performed for 120 min in accordance with prior studies.[9,13] At the end of the SBT, the RSBI was re-measured, and an arterial blood gas was obtained.

In the UC group, the SBT type and extubation decision were determined by the attending intensivist on service based on neurologic status, airway competence (gag, cough, and suction requirements), and respiratory indices including RSBI or negative inspiratory force (NIF). Extubation success was defined as remaining extubated for ≥48 h without need for further invasive or noninvasive MV.

Data collection

Baseline demographics; initial diagnosis; and preextubation clinical, ventilator, laboratory, and radiographic data were collected. DoI, re-intubation rates, and hospital LOS were recorded, as were the physiologic variables and respiratory indices [Table 1] including peak inspiratory pressure (PIP), minute ventilation (V_E), V_T, partial pressure of O_2 in alveoli (P_AO_2) or arterial blood (P_aO_2), S_aO_2, partial pressure of CO_2 in arterial blood (P_aCO_2) and F_iO_2, dynamic and static compliance (C_{dyn} and C_S), occlusion pressure (P0.1), NIF, and RSBI.

Sample size and data analysis

Quantitative variables were presented as mean with standard deviation (SD). Qualitative variables were presented as frequency (percentage). The normality of quantitative variables was assessed and confirmed using one-sample Kolmogorov–Smirnov test. The homogeneity of background variables was assessed via the independent *t*-test and Chi-square test for quantitative and qualitative variables, respectively.

Table 1: Comparison of physiologic and respiratory parameters

Parameters*	PW (n = 2075)	UC (n = 2125)	P**
RSBI	68.48 ± 5.43	86.18 ± 5.92	<0.001
NIF	-23.19 ± 2.79	-22.53 ± 3.54	<0.001
P0.1	4.15 ± 1.08	4.46 ± 1.63	<0.001
C_{dyn} (ml/cmH_2O)	61.14 ± 9.07	60.36 ± 9.59	0.007
C_S (ml/cmH_2O)	74.31 ± 8.90	73.34 ± 9.16	0.001
PIP (cmH_2O)	58.58 ± 3.50	58.52 ± 3.43	0.580
V_E (L/min)	9.82 ± 2.13	10.04 ± 2.00	<0.001
V_T (ml)	484.45 ± 85.76	491.70 ± 83.12	0.005
Respiratory rate (#/min)	17.67 ± 3.23	17.78 ± 3.14	0.270
P_AO_2 mmHg	237.51 ± 20.37	231.66 ± 24.44	<0.001
P_aO_2 mmHg	96.37 ± 7.98	95.58 ± 5.98	<0.001
S_aO_2 (%)	94.37 ± 2.73	95.84 ± 2.91	<0.001
PH	7.40 ± 0.05	7.40 ± 0.06	0.078
P_aCO_2 mmHg	45.81 ± 3.98	45.79 ± 3.86	0.860
F_iO_2	25.03 ± 2.87	24.93 ± 2.71	0.240
Hgb (g/dl)	10.92 ± 1.62	11.38 ± 1.42	<0.001
DOI (hours)	53.11 ± 33.29	47.33 ± 23.73	<0.001
Re-intubation within 48 h of extubation (n, %)	347, 16.7	527, 24.8	<0.0001
Reintubation beyond 48 h of extubation (n, %)	107, 5.2	548, 25.8	<0.0001
Hospital LOS-PTE (days)	15.20 ± 7.99	17.35 ± 13.70	<0.001

*Mean ± SD was presented, **P value based on independent t-test. PW: Protocolized wean, UC: Usual care, ICU: Intensive care unit, RSBI: Rapid Shallow Breathing Index, NIF: Negative inspiratory force, P0.1: Occlusion pressure, C_S: Static compliance, C_{dyn}: Dynamic compliance, PIP: Peak inspiratory pressure, V_E: Minute ventilation, V_T: Tidal volume, P_AO_2: Partial pressure of O_2 in alveoli, P_aO_2: Partial pressure of O_2 in arterial blood, S_aO_2: Mean arterial oxygen saturation, PaCO2: Partial pressure of CO_2 in arterial blood, F_iO_2: Fraction of inspired oxygen, Hgb: Hemoglobin, DOI: Duration of intubation, LOS-PTE: Length of stay prior to extubation, SD: Standard deviation

Univariate and multivariate Cox models were used to assess the time to successful weaning considering DoI and hospital LOS as the time variables. In the multivariate analyses, the significant variables were reported in a step-wise selection modeling (considering the P for enter = 0.05 and P for remove = 0.10). All analyses were conducted using IBM® SPSS 15 (IBM Corp, Armonk, NY, USA) at α =0.05 significance level.

RESULTS

A total of 7750 eligible patients were screened, and 2248 were excluded prerandomization [Figure 1], resulting in 5502 patients randomized (PW 2787; UC 2715), of which 657 patients did not receive the allocated intervention [PW 347; UC 310; Figure 1] and 645 patients were lost to follow-up (PW 365; UC 280). Consent was revoked in 48 cases (PW 27; UC 21). The remaining 4200 patients (PW 2075; UC 2125) were included in the final analysis.

Patient demographics were similar between groups [Table 2]. The mean age was 69.42 ± 12.08 years, with a slight female predominance (58.1%). Significant differences in respiratory parameters were noted

between the groups [Table 1]. Statistically significant improvements were noted in the P_aO_2 ($P < 0.001$) and S_aO_2 ($P < 0.001$), without difference in the F_iO_2 ($P = 0.24$) or P_aCO_2 ($P = 0.86$). A lower hemoglobin level was observed in the PW group (10.9 vs. 11.4, $P < 0.001$). Patients in the PW group displayed statistically significant improvements in V_E ($P < 0.001$), C_S and C_{dyn} (both $P < 0.05$), P0.1 ($P < 0.001$), NIF ($P < 0.001$), and RSBI ($P < 0.001$). DoI was longer in the PW group ($P < 0.001$), however hospital LOS was shorter [$P < 0.001$; Table 1].

Table 2: Baseline demographics at the time of extubation

Parameters	PW ($n = 2075$)	UC ($n = 2125$)	*P*
Age (years), mean ± SD	64.26 ± 16.89	64.59 ± 16.53	0.456[a]
Heart rate (bpm), mean ± SD	79.27 ± 10.79	80.49 ± 11.08	0.210[a]
Systolic BP (mmHg), mean ± SD	127.35 ± 13.05	127.78 ± 12.60	0.312[a]
Diastolic BP (mmHg), mean ± SD	73.88 ± 9.42	74.24 ± 10.52	0.607[a]
Temperature (°C), mean ± SD	36.77 ± 0.40	36.79 ± 0.40	0.400[a]
Respiratory rate (bpm), mean ± SD	17.68 ± 3.23	17.78 ± 3.15	0.132[a]
Hgb (g/dl), mean ± SD	10.92 ± 1.62	11.38 ± 1.42	0.326[a]
Gender - female, *n* (%)	1178 (56.8)	1261 (59.3)	0.804[b]
Marital - married, *n* (%)	1649 (79.5)	1711 (80.5)	0. 234[b]
Smoking - current and past (%)	1449 (69.8)	1285 (60.5)	0. 345[b]
Multiple diagnoses, *n* (%)	1694 (81.6)	1595 (75.1)	0.123[b]
Normal CXR - yes, *n* (%)	1206 (58.1)	1280 (60.2)	0. 308[b]

[a]*P* value based on independent t-test, [b]*P* value based on Chi-squared test. SD: Standard deviation, CXR: Chest X-ray, Hgb: Hemoglobin, PW: Protocolized wean, UC: Usual care, BP: Blood pressure

Duration of intubation

Univariate analysis

Factors associated with extubation success in the PW group on univariate Cox analysis included a normal chest X-ray (CXR), multiple organ dysfunction (MOD) status, diastolic BP, temperature, V_E, V_T, P_AO_2, P_aO_2, S_aO_2, pH, P_aCO_2, F_iO_2, C_S and C_{dyn}, RSBI, NIF, P0.1, and Hgb [all $P < 0.05$; Table 3]. Variables associated with extubation success in the UC group included age, normal CXR, MOD status, HR, systolic BP, temperature, P_AO_2, P_aO_2, S_aO_2, P_aCO_2, F_iO_2, V_E, V_T, C_S, RSBI, NIF, and P0.1, which were significant [all $P < 0.05$; Table 3].

Multivariate analysis

Factors independently associated with extubation success in the PW group on multivariate Cox analysis included age, MOD status, normal CXR, systolic BP, T, V_T, P_aO_2, S_aO_2, pH, P_aCO_2, F_iO_2, C_S, C_{dyn}, RSBI, and Hgb [all $P < 0.05$; Table 4]. NIF did not correlate ($P = 0.07$). Variables associated with extubation success in the UC group included age, MOD status, systolic BP, RR, P_AO_2, V_T, PIP, C_S, RSBI, NIF, and P0.1 [all $P < 0.05$; Table 4].

Table 3: Univariate Cox model analysis for variables associated with duration of intubation and intensive care unit length of stay before extubation

Parameters	Duration of intubation						Hospital length of stay					
	PW			UC			PW			UC		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	1.002	1.000-1.005	0.11	0.997	0.994-1.000	0.031	1.01	0.998-1.003	0.55	0.999	0.997-1.001	0.72
Sex (male)	1.031	0.945-1.125	0.49	1.009	0.915-1.113	0.86	1.049	0.961-1.144	0.29	0.855	0.775-0.943	0.002
Smoking (yes)	1.035	0.942-1.137	0.48	1.058	0.959-1.168	0.26	0.929	0.846-1.022	0.13	0.896	0.811-0.990	0.031
MOD (yes)	0.594	0.528-0.668	<0.0001	0.669	0.594-0.753	<0.0001	0.275	0.245-0.310	<0.0001	0.148	0.128-0.171	<0.0001
Normal CXR (yes)	1.189	1.089-1.298	<0.0001	1.210	1.095-1.337	<0.0001	1.177	1.078-1.285	<0.0001	1.825	1.649-2.019	<0.0001
Heart rate	0.999	0.995-1.003	0.728	1.008	1.003-1.012	0.001	1.007	1.002-1.011	0.002	1.000	0.996-1.005	0.889
Systolic BP	0.999	0.996-1.003	0.755	1.010	1.006-1.014	<0.0001	0.994	0.991-0.998	0.001	1.004	1.001-1.008	0.020
Diastolic BP	1.004	1.000-1.009	0.045	1.002	0.997-1.007	0.40	0.989	0.984-0.993	<0.0001	0.996	0.991-1.001	0.106
Temperature	0.727	0.649-0.814	<0.0001	0.701	0.616-0.798	<0.0001	1.203	1.078-1.342	0.001	1.413	1.252-1.594	<0.0001
RSBI	0.963	0.955-0.971	<0.0001	0.946	0.937-0.954	<0.0001	1.001	0.992-1.010	0.799	0.861	0.852-0.871	<0.0001
NIF	1.028	1.013-1.043	<0.0001	1.017	1.002-1.032	0.025	0.970	0.956-0.985	<0.0001	0.987	0.973-1.000	0.054
P0.1	1.098	1.053-1.144	<0.0001	1.044	1.010-1.078	0.010	0.956	0.914-0.999	0.044	0.909	0.878-0.940	<0.0001
C_{dyn}	0.987	0.983-0.992	<0.0001	0.995	0.990-1.001	0.091	0.980	0.975-0.985	<0.0001	0.994	0.989-0.999	0.020
C_S	0.986	0.981-0.991	<0.0001	0.994	0.989-1.000	0.046	0.980	0.975-0.984	<0.0001	0.992	0.987-0.997	0.001
PIP	0.998	0.986-1.010	0.733	1.024	1.010-1.039	0.001	0.991	0.980-1.004	0.17	1.001	0.987-1.015	0.913
V_E	0.973	0.954-0.993	0.008	1.044	1.020-1.070	<0.0001	0.918	0.899-0.937	<0.0001	0.886	0.865-0.907	<0.0001
V_T	0.998	0.997-0.998	<0.0001	0.997	0.996-0.997	<0.0001	0.998	0.998-0.999	<0.0001	0.997	0.997-0.998	<0.0001
Respiratory rate	0.987	0.974-1.000	0.054	1.006	0.991-1.021	0.48	1.002	0.989-1.015	0.776	1.018	1.003-1.034	0.022
P_AO_2	0.996	0.994-0.999	0.001	0.995	0.993-0.997	<0.0001	0.998	0.996-1.000	0.054	0.991	0.989-0.993	<0.0001
P_aO_2	0.969	0.963-0.975	<0.0001	0.970	0.962-0.978	<0.0001	1.014	1.008-1.019	<0.0001	1.022	1.014-1.030	<0.0001
S_aO_2	0.984	0.969-0.999	0.041	0.904	0.888-0.920	<0.0001	1.016	1.000-1.032	0.043	1.005	0.989-1.022	0.53
pH	0.087	0.037-0.204	<0.0001	0.829	0.419-1.638	0.59	2.529	1.003-6.380	0.049	0.322	0.157-0.661	0.002
P_aCO_2	0.945	0.934-0.956	<0.0001	0.953	0.942-0.965	<0.0001	0.929	0.968-0.991	<0.0001	0.941	0.929-0.954	<0.0001
F_iO_2	0.970	0.957-0.985	<0.0001	1.029	1.009-1.049	0.004	1.020	1.003-1.036	0.019	1.015	0.998-1.033	0.084
Hgb	0.894	0.869-0.919	<0.0001	0.999	0.967-1.032	0.96	0.995	0.968-1.023	0.71	0.816	0.788-0.844	<0.0001

PW: Protocolized wean, UC: Usual care, ICU: Intensive care unit, MOD: Multiple organ dysfunction, CXR: Chest X-ray, BP: Blood pressure, C_{dyn}: Dynamic compliance, CS: Static compliance, RSBI: Rapid Shallow Breathing Index, NIF: Negative inspiratory force, PIP: Peak inspiratory pressure, V_E: Minute ventilation, V_T: Tidal volume, P_AO_2: Partial pressure of O_2 in alveoli, P_aO_2: Partial pressure of O_2 in arterial blood, S_aO_2: Arterial oxygen saturation, P_aCO_2: Partial pressure of CO_2 in arterial blood, F_iO_2: Fraction of inspired oxygen, Hgb: Hemoglobin, PW: Protocolized wean, UC: Usual care, CI: Confidence interval, HR: Heart rate

Table 4: Multivariate Cox model analysis for variables associated with duration of intubation and intensive care unit length of stay before extubation

Parameters	Duration of intubation						Hospital length of stay					
	PW			UC			PW			UC		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.004	1.001-1.007	0.006	0.996	0.993-0.999	0.014	0.998	0.995-1.001	0.179	1.003	1.000-1.007	0.046
Sex (male)	-	-	-	1.033	0.931-1.146	0.55	-	-	-	-	-	-
Smoking history - yes	-	-	-	1.104	0.993-1.229	0.065	0.844	0.763-0.933	0.001	0.862	0.774 - -.961	0.007
MOD - yes	0.636	0.559-0.724	<0.0001	0.724	0.632-0.829	<0.0001	0.205	0.180-0.235	<0.0001	0.137	0.114-0.163	<0.0001
Normal CXR - yes	1.192	1.083-1.312	<0.0001	-	-	-	0.735	0.666-0.812	<0.0001	0.775	0.785-0.878	<0.0001
Heart rate	-	-	-	1.003	0.999-1.008	0.168	1.003	0.998-1.008	0.191	1.009	1.004-1.014	<0.0001
Systolic BP	0.992	0.988-0.995	<0.0001	1.004	1.000-1.008	0.046	0.996	0.992-1.000	0.036	1.002	0.998-1.007	0.339
Diastolic BP	-	-	-	0.999	0.994-1.004	0.737	0.985	0.980-0.990	<0.0001	0.981	0.975-0.986	<0.0001
Temperature	0.667	0.584-0.761	<0.0001	1.047	0.897-1.223	0.558	0.912	0.784-1.061	0.232	1.566	1.345-1.824	<0.0001
RSBI	0.973	0.965-0.981	<0.0001	0.939	0.929-0.950	<0.0001	1.015	1.005-1.025	0.003	0.862	0.851-0.873	<0.0001
NIF	0.984	0.967-1.001	0.073	0.963	0.943-0.983	<0.0001	0.987	0.968-1.007	0.217	1.024	1.000-1.049	0.50
P0.1	-	-	-	1.061	1.010-1.114	0.018	1.062	1.011-1.117	0.018	0.923	0.878-0.970	0.002
C_{dyn}	1.030	1.094-1.046	<0.0001	-	-	-	1.005	0.989-1.021	0.543	-	-	-
C_S	0.957	0.943-0.974	<0.0001	0.988	0.983-0.994	<0.0001	0.975	0.959-0.991	0.002	0.990	0.985-0.996	0.001
PIP	-	-	-	1.251	1.165-1.344	<0.0001	0.899	0.815-0.990	0.031	1.084	1.011-1.162	0.023
V_E	-	-	-	-	-	-	0.943	0.909-0.976	0.001	0.986	0.946-1.028	0.50
V_T	0.999	0.998-0.999	<0.0001	0.997	0.996-0.998	<0.0001	0.999	0.998-0.999	<0.0001	0.996	0.995-0.997	<0.0001
Respiratory rate	-	-	-	0.790	0.734-0.850	<0.0001	1.132	1.026-1.248	0.013	0.934	0.871-1.002	0.057
P_AO_2	-	-	-	0.996	0.993-0.998	<0.0001	1.002	1.000-1.005	0.088	-	-	-
P_aO_2	0.969	0.961-0.997	<0.0001	-	-	-	1.025	1.016-1.035	<0.0001	-	-	-
S_aO_2	0.984	0.965-1.003	0.092	-	-	-	0.964	0.943-0.986	0.001	-	-	-
pH	0.225	0.088-0.572	0.002	-	-	-	-	-	-	-	-	-
P_aCO_2	0.995	0.981-0.968	0.006	-	-	-	0.978	0.964-0.992	0.002	-	-	-
F_iO_2	1.020	1.001-1.040	0.044	-	-	-	-	-	-	-	-	-
Hgb	0.960	0.929-0.992	0.014	-	-	-	-	-	-	-	-	-

PW: Protocolized wean, UC: Usual care, ICU: Intensive care unit, MOD: Multiple organ dysfunction, CXR: Chest X-ray, BP: Blood pressure, RSBI: Rapid Shallow Breathing Index, NIF: Negative inspiratory force, P0.1: Occlusion pressure, C_{dyn}: Dynamic compliance, C_S: Static compliance, V_E: Minute ventilation, V_T: Tidal volume, P_AO_2: Partial pressure of O_2 in alveoli, P_aO_2: Partial pressure of O_2 in arterial blood, S_aO_2: Arterial oxygen saturation, P_aCO_2: Partial pressure of CO_2 in arterial blood, F_iO_2: Fraction of inspired oxygen, Hgb: Hemoglobin, CI: Confidence interval, HR: Heart rate

Hospital length-of-stay

Univariate analysis

Factors associated with hospital LOS in the PW group on univariate Cox analysis included normal CXR, MOD status, HR, systolic and diastolic BP, T, P_aO_2, S_aO_2, pH, P_aCO_2, F_iO_2, V_T, V_E, C_S, C_{dyn}, NIF, and P0.1 [all $P < 0.05$; Table 3]. RSBI did not correlate with preextubation ICU LOS ($P = 0.79$). Variables associated with hospital LOS in the UC group included male sex, smoking history, normal CXR, MOD status, systolic BP, T, RR, P_aO_2, P_AO_2, pH, P_aCO_2, V_T, V_E, C_S, C_{dyn}, RSBI, NIF, and P0.1 [all $P < 0.05$; Table 3].

Multivariate Cox model analysis

Factors independently associated with hospital LOS in the PW group on multivariate Cox analysis included smoking history, MOD status, normal CXR, systolic and diastolic BP, P_aO_2, S_aO_2, P_aCO_2, RR, V_T, V_E, C_S, RSBI, and P0.1 [all $P < 0.05$; Table 4]. NIF did not correlate with hospital LOS ($P = 0.21$). Variables associated with hospital LOS in the UC group included age, smoking history, MOD status, normal CXR, T, HR, diastolic BP, V_T, C_S, C_{dyn}, RSBI, and P0.1 [all $P < 0.05$; Table 4].

Reintubation

Forty-eight-hour re-intubation rates were lower in the PW versus UC groups (347 [16.7%] vs. 527 [24.8%]; $P < 0.0001$). Re-intubation rates ≥48-h postextubation were lower in the PW group (107 [5.2%] vs. 548 [25.8%]; $P < 0.0001$).

Survival

No significant difference in mortality was observed between the groups [$P = 0.19$; Figure 2].

DISCUSSION

Interventions leading to earlier and safer MV liberation may improve patient outcomes.[13] Multiple randomized trials have demonstrated that daily SBT is a safe means to help identify patients ready for MV liberation, and that SBTs reduce time to extubation when compared with gradually weaning ventilator support.[13] Ventilator liberation protocols are designed to reduce assessment variability for liberation readiness.[13] PW provides a standardized, and possibly more efficient, approach to MV weaning and extubation. MV liberation strategies vary significantly by practice, location, and culture. Some employ personnel-driven protocols that may be SBT based,[14-20] step-wise reduction,[11,21-23] SBT with step-wise reduction,[24] or even computer- driven protocols. Similarly, a recent randomized controlled trial ($n = 65$) reported the feasibility and safety of a nurse-led

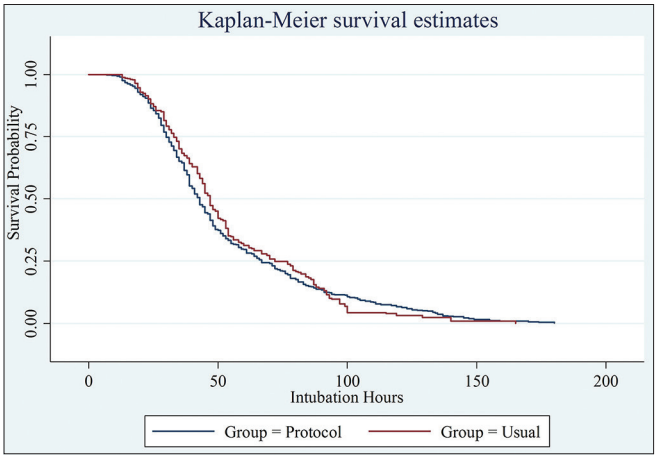

Figure 2: Patient survival according to intubation duration

tracheostomy weaning protocol.[25] Despite these findings, very little data is available from resource-limited settings.

Based largely on the results of a meta-analysis,[2] a joint statement from the American Thoracic Society and the American College of Chest Physicians conditionally recommended (low certainty in evidence) that ventilator liberation protocols be used for patients on MV >4 h.[13] Among the personnel studies employing SBTs, results for DoI either favored a PW strategy[15,18,20] or reported no difference.[14] Although this study observed a slight prolongation of DoI in the PW group, the difference was not clinically significant. In addition, hospital LOS was lower in the PW group in contrast to some prior studies that have not observed a difference.[14,15] Despite this, total hospital LOS was fairly long in both groups. This likely reflects a difference in aftercare between Iran and Western countries. In Iran, homecare, rehab, and hospice services are in the early stages of development. Therefore, patients generally must be hospitalized until their physical and psychological situations are acceptable for hospital discharge without significant homecare needs.

Furthermore, a decrease in re-intubation rates improved with PW similar to prior studies.[16,20,26] Lastly, no mortality difference was observed. Whereas one Brazilian study reported decreased in-patient mortality (0% vs. 20%) with PW;[16] data is limited as mortality is not commonly reported in such studies [Figure 2].

As regards physiologic parameters and breathing indices, the mean RSBI was significantly lower in the PW (68) compared to the UC group (86), however both groups were well below the threshold of 105. It is unclear whether the greater rate of extubation success in the PW group may in part be explained by the lower RSBI. Of the remaining respiratory parameters that were studied, differences in NIF, P0.1, C_S, and V_E were statistically but likely not clinically significant given the minimal difference in mean values and relatively large SDs.

Regarding the evaluated physiologic indices, statistically significant differences were noted in P_AO_2, P_aO_2, S_aO_2, and Hgb levels. The P_AO_2 and P_aO_2 levels were slightly better in the PW group, and Hgb and S_aO_2 were slightly worse. Although statistically significant, differences were not clinically significant and unlikely to have significantly impacted patient outcomes.

Limitations

As one might expect, the PIP was high in both groups, but these numbers do not necessarily correlate to the pressure seen by the alveoli. For this purpose, measurements of plateau pressure or mean airway pressure are needed. One limitation of this study was the failure to record corresponding plateau pressure measurements. In future studies, we intend to report this metric.

CONCLUSION

Protocolized ventilator weaning with extubation decisions driven by respiratory therapists is a safe and efficacious technique for extubation in resource-limited settings and is associated with decreased need for early or late re-intubation, shorter hospital stays, and a statistically (not clinically) significant increase in duration of intubation, without increasing in-patient mortality.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Research quality and ethics statement

This study was approved by the Institutional Review Board / Ethics Committee at Baqiyatallah Medical Sciences University (IRB # BUMS-PWvUC-RCT), and was registered with Clinicaltrials.gov (identifier NCT03724643).

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