

Rate of reintubation in mechanically ventilated neurosurgical and neurologic patients: Evaluation of a systematic approach to weaning and extubation

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain the protocol used in the intervention group.
2. Explain the pros and cons identified related to protocol use.
3. Demonstrate this information in a clinical setting.

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Objective: To assess whether a systematic approach to weaning and extubation (intervention) is superior to the sole physician's judgment (control) in preventing reintubation secondary to extubation failure in patients with neurologic disorders.

Design: Randomized controlled trial.

Setting: Intensive care unit of a large teaching hospital.

Patients: Three hundred eighteen intubated patients who had been receiving mechanical ventilation for at least 12 hrs and were able to trigger the ventilator.

Interventions: Patients were randomized to the intervention (n = 165) or control group (n = 153).

Measurements: Rate of reintubation after extubation failure occurring within 48 hrs (primary end point). Duration of mechanical ventilation, length of intensive care unit stay, mortality, rate of tracheotomy (secondary end points). The perception of the research protocol by the intensive care unit staff was also assessed.

Main Results: The rate of reintubation was lower in the intervention (5%) than in the control (12.5%) group ($p = 0.047$). There

was no difference in any of the other outcome variables (secondary end points). Simplified Acute Physiologic Score II (adjusted odds ratio 1.042 per unit; 95% confidence interval 1.006–1.080; $p = 0.022$) and inclusion in the control group (adjusted odds ratio 2.393; 95% confidence interval 1.000–5.726; $p = 0.05$) were the only two independent predictive factors for the risk of extubation failure. The protocol was felt by the staff to determine an improvement in patients' clinical outcome, but to increase intensive care unit workload; nurses and physiotherapists considered its impact on their professional role more positively than physicians.

Conclusions: In patients with neurologic diseases, a systematic approach to weaning and extubation reduces the rate of reintubation secondary to extubation failure without affecting the duration of mechanical ventilation, and is overall positively perceived by intensive care unit professionals. (*Crit Care Med* 2008; 36:2986–2992)

KEY WORDS: weaning; extubation failure; mechanical ventilation; neurosurgery; neurologic disorders; randomized clinical trial

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Supported in part by Azienda Ospedaliera "Niguarda Ca' Granda" (Milano, Italy) that provided salary support for Pamela Frigerio, Maurizio Sommariva, Maria Pia Moretti, Sergio Vesconi, and Anna Levati, who were full-time institutional employees at the time this study was conducted.

The authors have not disclosed any potential conflicts of interest.

The trial allocated the Australian Clinical Trial Registration (www.actr.org.au) (ACTRN012607000115437).

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DOI: 10.1097/CCM.0b013e31818b35f2

Although a life-saving intervention, mechanical ventilation is apt to unwanted side-effects and life-threatening complications (1). Unnecessarily delaying withdrawal of mechanical ventilation increases the rate of complications (2), the length of stay in intensive care unit (ICU) (2, 3) and the costs (3–5). In patients with acute brain injury, delaying weaning and extubation increases the rate of death and prolongs the length of ICU stay (6).

With respect to the physician's clinical judgment, a systematic assessment of the patient's potential to be weaned off the ventilator combining daily screening of physiologic and clinical data with a trial of spontaneous breathing, may help to reduce the risk of unduly postponing withdrawal of ventilator support and extubation (2–5, 7). In neurosurgical mechanically ventilated patients, however, compared with the conventional weaning based on the physician's clinical judgment, a ventilator-management protocol, not including neurologic function assessment, failed to produce any beneficial effect (8), compared with the sole physician's judgment.

Premature attempts of withdrawing mechanical ventilation are complicated by postextubation respiratory failure and reintubation, which is associated with higher mortality (9–14), increased rate of tracheotomy (10, 11), and longer duration of mechanical ventilation, and ICU stay (10, 11). A rate of extubation failure and reintubation exceeding 35% has been reported when the indexes commonly adopted to assess readiness for weaning and extubation are used in patients with neurologic disorders (13).

We undertook this randomized controlled trial to evaluate whether a systematic approach to weaning and extubation based on daily screening of meaningful physiologic and clinical variables (including indexes of neurologic function) followed by spontaneous breathing trial, is superior in patients with neurologic disorders, compared with the physician's judgment only, in preventing the rate of reintubation secondary to extubation failure occurring within 48 hours (primary end point). Secondary end points were mortality, rate of tracheotomy, duration of mechanical ventilation, and length of ICU stay. In addition, we appraised the factors associated with unsuccessful extubation and reintubation. Finally, we evaluated how the research protocol was perceived by the ICU staff.

METHODS

Patients and Setting. The study was conducted in the neuro-ICU of the Emergency Department, Azienda Ospedaliera Ospedale Niguarda Ca' Granda, a 1200 bed hospital in Milan (Italy). The ICU is a closed nine-beds unit, attended around the clock by physicians all certified and trained in anesthesiology and critical care. The nurse to patient ratio is 1:2 for the entire day; in addition, two senior nurses, and one respiratory physiotherapist are present during day time.

From October 2002 to June 2004, all patients who met the following inclusion criteria were considered eligible: 1) age between 18 and 80 years, 2) not being admitted already intubated from other institutions, 3) mechanical ventilation for >12 hrs, 4) no need for continuous intravenous sedative infusion and/or controlled mechanical ventilation, 5) ability to trigger the ventilator, 6) absence of tracheotomy, and 7) no scheduled surgery in the following 72 hours. Exclusion criteria were: 1) lesion affecting the upper airway, and 2) pre-existing decision to limit life support. After enrolment, patients were assigned to the intervention or control group through a previously generated random sequence. The trial was unblinded. The ethics committee of the hospital approved the protocol and waived the need for informed consent. The study was conducted following the principles outlined in the Declaration of Helsinki.

Study Protocol. The protocol design for the intervention group is summarized in Figure 1. The ICU staff were trained and piloted in the protocol during a 3-month run-in period. All patients randomized to the treatment group were screened every morning to assess readiness for the spontaneous breathing trial. The criteria for readiness, which had been concurred and agreed upon by physicians, nurses, and respiratory physiotherapists in staff based on their usual practice were: 1) Glasgow Coma Scale ≥ 8 , 2) presence of clearly audible cough during suctioning (15), 3) tracheal suctioning ≤ 2 /hr, 4) normal sodium blood values, 5) core temperature $< 38.5^\circ$ during the previous 8 hours, 6) pH ≥ 7.35 , and arterial carbon dioxide tension (P_{aCO_2}) ≤ 50 mm Hg [6.7 kPa], 7) arterial oxygen tension (P_{aO_2}) to fraction of inspired oxygen (F_{IO_2}) ratio (P_{aO_2}/F_{IO_2}) ≥ 200 with positive end-expiratory pressure ≤ 5 cm H_2O , 8) $F_{IO_2} \leq 0.4$, 9) heart rate ≤ 125 beat/min, and 10) systolic blood pressure ≥ 90 without epinephrine or norepinephrine infusion and with dopamine infusion ≤ 5 $\mu g/Kg/hr$.

The patients who passed the screening underwent a 1-hr spontaneous breathing trial, breathing through the circuit of a flow triggered ventilator, set to deliver 2–3 cm H_2O of continuous positive airway pressure, with a F_{IO_2} 0.4. Heart rate, arterial blood pressure, tidal volume, respiratory rate, and saturation by pulse-oxymetry (SpO_2) were continuously monitored. The trial was interrupted and mechanical ventilation resumed whenever one of

the following occurred: 1) respiratory rate > 35 /min, 2) evident respiratory distress (diaphoresis, accessory muscle recruitment, thoraco-abdominal paradox), 3) $SpO_2 < 90\%$, 4) systolic arterial pressure < 90 mm Hg or > 180 mm Hg, 5) heart rate > 140 /min, and 6) coma or agitation. At the end of the trial, patients who had a respiratory rate/tidal volume ratio ≤ 105 and $P_{aO_2}/F_{IO_2} \geq 200$, pH ≥ 7.35 , and $P_{aCO_2} \leq 50$ mm Hg [6.7 kPa] were immediately extubated. Conversely, if the respiratory rate/tidal volume exceeded 105 or the arterial blood gas analysis criteria were not met, mechanical ventilation was resumed.

Patients randomized to the control group, as routinely done in the ICU before the study, were evaluated every day by the attending physicians who were allowed to discontinue mechanical ventilation and extubate the patient following their own clinical judgment; although the decision was left entirely to the discretion of the physicians, all the information collected and recorded for the intervention group were also available.

Routine care, sedation protocols, i.e., propofol 1–5 mg/kg/hr alone or in combination with opiates (remifentanyl 0.05–0.15 $\mu g/Kg/min$ or fentanyl 0.5–1 $\mu g/Kg/hr$) and/or midazolam 0.03–3 mg/Kg/hr, mechanical ventilators (Servo 300 and Servo I, Maquet-Critical Care, Sweden), and modes of ventilation (i.e., Pressure Support Ventilation alone or combined with 1–6 volume targeted mandatory breaths) were the same for the two groups. Irrespective of the group of randomization, patients were considered successfully extubated if they did not meet criteria for reintubation within the following 48 hours. Criteria for reintubation were: 1) emergency, such as respiratory or cardiac arrest, and gasping for air, 2) neurologic deterioration (coma or agitation requiring continuous intravenous sedation), 3) hemodynamic instability (i.e., need for continuous infusion of epinephrine, norepinephrine or vasopressin, or dopamine > 5 $\mu g/Kg/min$ to maintain systolic arterial pressure > 90 mm Hg), despite adequate filling, 4) upper airway obstruction with stridor and/or tirage, 5) unmanageable tracheo-bronchial secretions, and 6) respiratory distress, as assessed by the combination of $SpO_2 < 90\%$, respiratory rate > 35 /min, and visible accessory muscle recruitment or thoraco-abdominal paradox, despite administration of oxygen and noninvasive ventilation (NIV). As previously reported (16), and following the protocol in use in the ICU, NIV was administered through an oro-nasal mask when a F_{IO_2} of 0.4 failed to maintain $SpO_2 \geq 90\%$ and the patient showed evidence of respiratory distress, as assessed by the combination of tachypnea (> 30 /min) and visible accessory muscle recruitment. Positive end-expiratory pressure and inspiratory pressure support were initially set at 5 and 10 cm H_2O and then increased up to a maximum of 10 and 15 cm H_2O , respectively, to achieve a respiratory rate ≤ 25 breaths/min and a $SaO_2 \geq 94\%$ with an $F_{IO_2} \leq 0.5$. In the

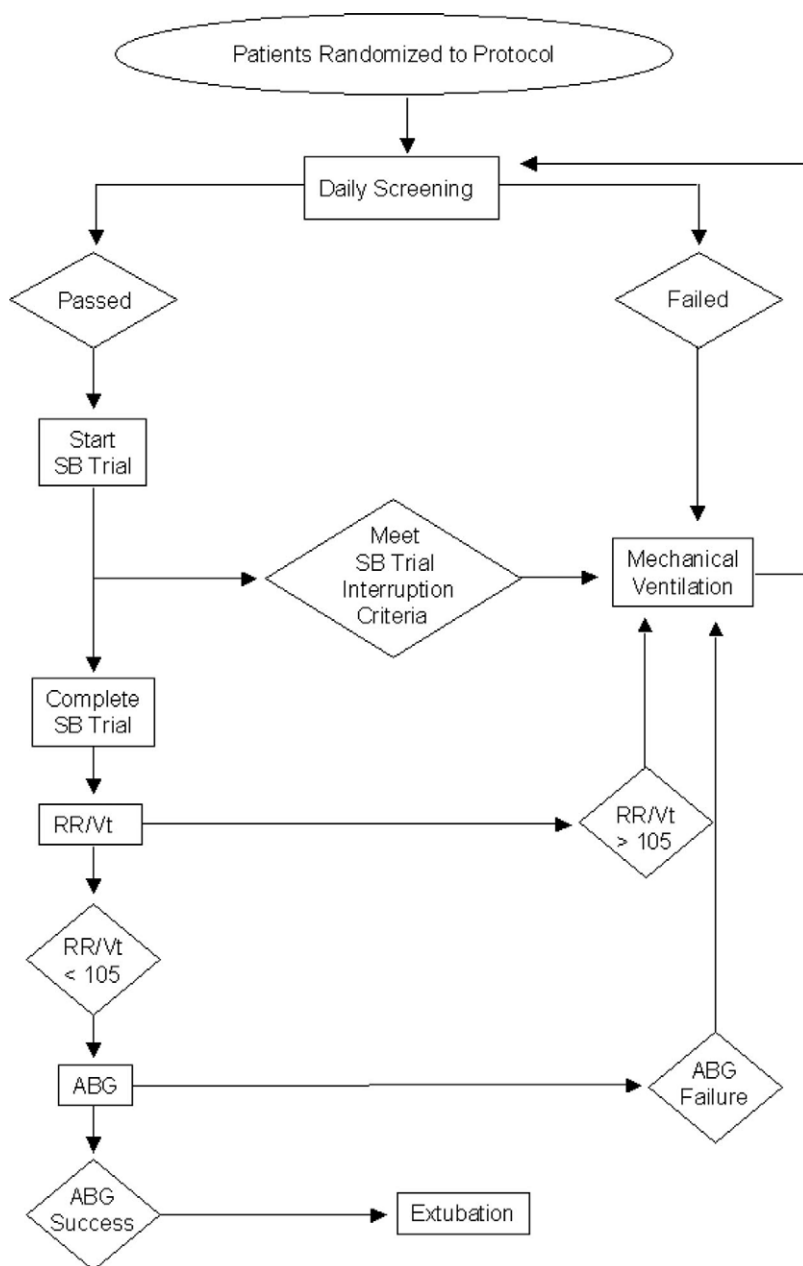


Figure 1. Protocol description. SB, spontaneous breathing; ABG, arterial blood gas; RR/Vt, respiratory rate/tidal volume ratio.

case of leaks interfering with ventilator cycling, the overall applied pressure was decreased of 2 cm H₂O and the ventilator was set for cycling from inspiration to expiration according to a preset inspiratory time.

To evaluate the ICU staff perception of the protocol, we constructed a questionnaire where the respondents were asked to give a written answer using a five-point Likert-like scale (1, absolutely worsened; 2, quite worsened; 3, unchanged; 4, quite improved; and 5, absolutely improved). The question "How was the following aspect affected by the implementation of the research protocol in the ICU daily practice?" was asked with respect to: 1) overall patients outcome, 2) duration of mechanical

ventilation, 3) rate of extubation failure, 4) overall ICU workload, and 5) own professional role. In addition, the ICU staff were asked to answer the following question: "How your consideration of the protocol changed from beginning to end of the study period?" The questionnaire was administered immediately after study completion, before the final data analysis.

Outcomes and Statistical Analysis. We hypothesized that, as opposed to the sole physician's clinical judgment, a systematic approach for assessing readiness for discontinuation of mechanical ventilation and extubation would reduce the rate of reintubation secondary to extubation failure occurring within 48

hours (primary end point). *A priori* power analysis showed that recruitment of 280 patients (140 patients per group) over a 21-month period would have allowed detecting a decrease in reintubation rate from 15% (6, 8) to 5%, with 80% power at the 5% two-sided level of significance. Regardless of the group of randomization, the patients who had been recruited before June 30, 2004 completed the observation and were analyzed. We also compared the two groups with respect to duration of mechanical ventilation, length of ICU and hospital stay, mortality, rate of tracheotomy (secondary end points). An intention-to-treat analysis was performed; normally distributed variables were compared by two-tailed Student's *t*-test, whereas proportions and rates by chi-square or Fisher's exact test, as indicated. Forward stepwise logistic regression was used for risk factor assessment. First, univariate analysis was performed to assess the association between reintubation and each of the following variables: age, body mass index, GCS on ICU admission and on study entry, Simplified Acute Physiologic Score II on ICU admission, and group of randomization (included as a binary variable). Second, variables found to be associated with reintubation ($p \leq 0.05$ in the univariate analysis) were entered into a logistic regression model and adjusted odds ratio and 95% confidence interval (CI) were calculated for independent predictors of reintubation.

Longitudinal analysis was applied to determine the probability of successful weaning over time and the differences between curves were assessed using the log-rank test.

To compare differences in the perception of the protocol between physicians and other ICU professionals, as assessed by the questionnaire, we used the Mann-Whitney U test, as indicated (17). The *p* values of 0.05 or less were considered statistically significant.

RESULTS

As depicted in Figure 2, 318 of 956 patients admitted to the ICU during the 21-month study period were randomized to either the intervention (165 patients) or control group (153 patients). As shown in Table 1, patient characteristics at ICU admission and reasons for ICU admission did not significantly differ between the two groups. Not shown in the table, the GCS at the time of extubation averaged 10.6 ± 0.7 in the intervention group and 10.5 ± 0.9 in the control group ($p = 0.232$).

Unplanned extubation occurred in five patients, four in the intervention group and one in the control group ($p = 0.373$); four of these patients underwent NIV and one, included in the intervention group, required reintubation because of unmanageable secretions. There were five protocol violations in the intervention group.

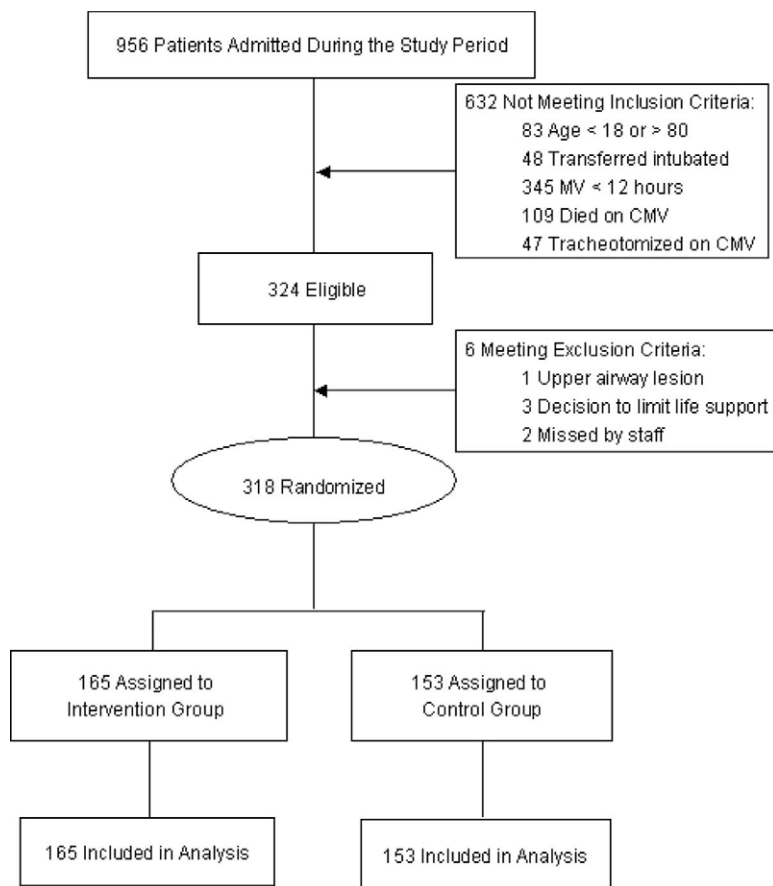


Figure 2. Flow of patients through the trial. *MV*, mechanical ventilation; *CMV*, controlled mechanical ventilation.

Table 1. Patients' characteristics at enrollment and reasons for ICU admission

	Intervention Group (n = 165)	Control Group (n = 153)	<i>p</i>
Patients' characteristics			
Age, yr, mean (sd)	50 (16)	50 (18)	0.692
Male/Female, n	94/72	92/61	0.570
Body mass index, mean (sd)	24.6 (3.9)	24.6 (4.1)	0.916
SAPS II, score, mean (sd)	27.5 (11.1)	28.5 (11.4)	0.430
Glasgow Coma Scale, mean (sd)	9.4 (1.9)	9.3 (1.9)	0.662
Reasons for ICU admission			
Subarachnoid or intracerebral hemorrhage, n (%)	75 (45.4)	53 (34.6)	0.064
Head trauma, n (%)	25 (15.1)	34 (22.2)	0.140
Cerebral tumor, n (%)	43 (26.1)	35 (22.9)	0.597
Spinal trauma, n (%)	10 (6.1)	14 (9.2)	0.407
Other, n (%)	12 (7.3)	17 (11.1)	0.321

ICU, intensive care unit; SAPS, Simplified Acute Physiologic Score.

Two patients were not extubated, as indicated by the protocol, based on medical decision; both patients were successfully extubated the following day. Three patients were extubated based on medical decision, although they did not meet criteria for extubation; all these three patients underwent NIV and none of them required reintubation in the following 48 hrs.

NIV was used after extubation in 36 (22%) and 37 (24%) patients in the intervention and control group, respectively ($p = 0.689$). Sixteen (9.7%) patients in the intervention group and 17 (11.1%) patients in the control group received NIV for >48 hrs ($p = 0.714$); none of these patients ever required reintubation irrespective of the randomization group.

The inspiratory support ranged between 10 and 15 cm H₂O and positive end-expiratory pressure between 5 and 8 cm H₂O. NIV was applied 8–22 hrs/day for 3.0 (± 1.8) and 3.0 (± 2.1) days, in the intervention and control group, respectively ($p = 0.898$).

As shown in Table 2, nine patients (5%) in the intervention group and 18 (12%) in the control group failed extubation and were reintubated ($p = 0.047$). As also shown in Table 2, ICU mortality, rate of tracheotomy, duration of mechanical ventilation, and ICU length of stay were not significantly different between the two groups. The causes of reintubation for both groups are listed in Table 3. The rate of reintubation over time for the two groups, as indicated by 7-month period, is also shown in Table 3: extubation failure and reintubation were more frequent in the control group, as opposed to the intervention group, in each of the three periods. As depicted in Figure 3, the percentage of patients remaining on mechanical ventilation over time was not different between the two groups ($p = 0.838$); only 1.8% and 1.3% of patients in the intervention and control group, respectively, were still on mechanical ventilation after 3 wks.

At the univariate analysis, Simplified Acute Physiologic Score II (odds ratio 1.04 per unit; 95% CI 1.01–1.08; $p = 0.016$), GCS on study entry (odds ratio 0.66 per unit; 95% CI 0.44–0.99; $p = 0.044$), and inclusion in the control group (odds ratio 2.48; 95% CI 1.05–5.90; $p = 0.039$) were the only variables significantly correlated with the risk of failing extubation and being reintubated. Logistic regression analysis, including the factors used in the univariate analysis, found that Simplified Acute Physiologic Score II score (adjusted odds ratio 1.042 per unit; 95% CI 1.006–1.080; $p = 0.022$) and inclusion in the control group (adjusted odds ratio 2.393; 95% CI 1.000–5.726; $p = 0.05$) were the only two independent predictive factors for the risk of reintubation secondary to extubation failure.

Table 4 depicts how the ICU staff perceived the protocol. The overall clinical outcome was believed to be quite improved; in particular, the rate of extubation failure was considered to be improved following the implementation of the protocol, whereas the duration of mechanical ventilation was perceived not to be modified. The overall ICU workload was felt to be quite worsened after implementation of the new protocol. The opin-

Table 2. Comparison of outcomes between study groups

	Intervention Group (n = 165)	Control Group (n = 153)	<i>p</i>
Primary end point			
Rate of reintubation, n (%)	9 (5)	18 (12)	0.047
Secondary end points			
Days of mechanical ventilation, mean (SD)	5.0 (5.6)	5.0 (5.0)	0.942
ICU stay, days, mean (SD)	8.1 (7.2)	8.8 (7.3)	0.379
Tracheotomy, n (%)	5 (3)	11 (7)	0.122
ICU mortality, n (%)	2 (1)	6 (4)	0.160

ICU, intensive care unit.

Table 3. Causes of reintubation and rate of reintubation over time

	Intervention Group (n = 9)	Control Group (n = 18)
Cause of reintubation		
Emergency, n (%)	0 (0)	1 (6)
Neurological deterioration, n (%)	1 (12)	4 (22)
Hemodynamic instability, n (%)	0 (0)	0 (0)
Upper airway obstruction, n (%)	3 (38)	4 (22)
Excess of tracheobronchial secretion, n (%)	2 (22)	1 (6)
Respiratory failure, n (%)	3 (38)	8 (44)
Rate of reintubation over time		
1st 7-month period, n (%)	2 (22)	4 (22)
2nd 7-month period, n (%)	3 (33)	9 (50)
3rd 7-month period, n (%)	4 (44)	5 (28)

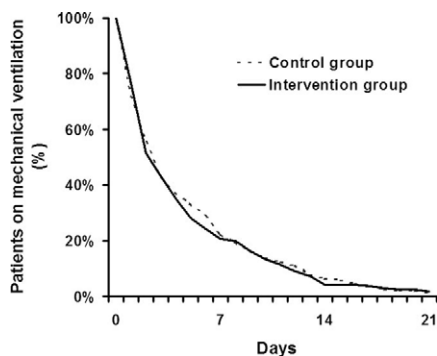


Figure 3. Kaplan-Meier analysis of the duration of mechanical ventilation. The proportion of patients who could not be successfully weaned off the ventilator after 21 days was not different (*p* = 0.838) between the two groups.

ions of the physicians regarding the impact of the protocol on patients' clinical outcome and professional role were less positive than those of nurses and physiotherapists; also, the opinion of the protocol improved over time for nurses and physiotherapists, but not for physicians.

DISCUSSION

A systematic approach based on daily assessment of meaningful physiologic and clinical variables followed by a trial of spontaneous unassisted breathing reduced the rate of reintubation, as opposed to the sole physician's clinical judgment. Furthermore, the inclusion in the control group and the severity score,

as assessed by the Simplified Acute Physiologic Score II, at ICU admission were the only two independent predictive factors for the risk of extubation failure and reintubation.

Determining readiness for extubation is of considerable clinical relevance. Unsuccessful extubation, which occurs in up to 35% of neurologic patients following a planned extubation (13), and reintubation are associated with increased mortality (9–14) and prolonged duration of ICU and hospital stay (10, 11). Consistent with previously published data (9–14), in our study the 27 patients who failed extubation had a higher rate of death than those who were successfully extubated (18.5% vs. 1%, *p* = 0.046); also, the length of ICU stay was significantly longer in the group of patients who were reintubated, as opposed to those who were successfully extubated (15.7 vs. 7.8 days, *p* < 0.001). A recent retrospective study reported a significant reduction in extubation failure (from 13.7% to 7.4%) after introduction of a weaning and extubation protocol in a surgical ICU with mixed trauma and surgical population (18). Another nonrandomized study with prospective design compared the rate of extubation failure before and after implementation of protocol-directed weaning and found a significant reduction in the rate of extubation from 12.7% to 3.0% in an ICU with heterogeneous patient population (19). To date, our study is the first randomized controlled trial, specifically designed and powered to assess a difference in the rate of reintubation following extubation failure, showing a significant reduction in the rate of reintubation. Noteworthy, the rate of reintubation in our control group was in line with those previously reported by other investigators in patients with neurologic disorders (6, 8).

In a prior study aimed to determine whether a ventilator management proto-

Table 4. Perception of the protocol by the ICU staff, as scored by a Likert-like five-point scale

Question	Overall ICU Staff (n = 45)		Physicians (n = 16)		Nurses and Therapists (n = 29)		<i>p</i> ^a
	Mean (95% CI)	Median (min–max)	Mean (95% CI)	Median (min–max)	Mean (95% CI)	Median (min–max)	
Overall clinical outcome	3.5 (3.2–3.7)	4.0 (1–5)	3.0 (2.5–3.5)	3.0 (1–4)	3.8 (3.5–4.0)	4.0 (3–5)	0.01
Length of mechanical ventilation	3.1 (2.7–3.4)	3.0 (1–5)	2.8 (2.2–3.5)	3.0 (1–5)	3.2 (2.8–3.6)	3.0 (2–5)	0.33
Rate of extubation failure	3.6 (3.3–3.8)	3.0 (1–5)	3.4 (2.9–4.0)	3.5 (1–5)	3.6 (3.3–3.9)	3.0 (2–5)	0.75
Overall ICU workload	2.0 (1.8–2.2)	2.0 (1–4)	1.9 (1.5–2.3)	2.0 (1–4)	2.1 (1.9–2.3)	2.0 (1–3)	0.32
Professional role	3.5 (3.2–3.8)	3.0 (1–5)	3.0 (2.3–3.7)	3.0 (1–5)	3.7 (3.5–4.0)	4.0 (3–5)	0.05
Opinion over time	3.3 (3.0–3.6)	3.0 (1–5)	2.8 (2.3–3.3)	3.0 (1–4)	3.4 (3.0–3.8)	3.0 (1–5)	0.05

ICU, intensive care unit; CI, confidence interval.

^aPhysicians vs. nurses and respiratory physiotherapists.

col, previously validated in a general patient population, could be useful for neurosurgical patients, Namen et al. (8) randomized 100 patients either to intervention or control group and found that duration of mechanical ventilation, length of ICU stay, mortality, and rate of reintubation were not different between the two groups. Several differences may contribute to explain these different results. First of all, Namen et al. chose not to incorporate in their protocol the assessment of the level of consciousness. At a multivariate analysis, however, these authors found the level of consciousness, as assessed by the GCS, to be one of the strongest independent predictors of successful extubation, which reached 75% for scores ≥ 8 and only 36% for scores ≤ 7 (8). In view of that, we incorporated the GCS into the daily screening and considered eligible for extubation the patients with a score ≥ 8 . At the time of extubation, nevertheless, the GCS was on average not different between the two groups; moreover, in no patient in the control group the GCS at the time of extubation was lower than 8, suggesting that the mental status was considered by the clinicians an essential prerequisite for weaning and extubation. We also evaluated the ability to cough and clear secretions, as suggested by Vallverdu et al. (13) who reported, in patients with central nervous system disease, a rate of reintubation as high as 35% when adopting the usual respiratory parameters to assess readiness for weaning and extubation. Second, while in the study by Namen et al. the primary end points were duration of mechanical ventilation, length of ICU stay (8), and time to successful extubation, we powered our study on the rate of reintubation secondary to extubation failure. Third, in contrast to the study by Namen et al. (8) that was characterized by limited adherence to the protocol by the attending physicians, we limited protocol violations to only five cases and achieved a protocol adherence as high as 97%.

We did not find significant differences between the two groups in any of the secondary end points. In particular, the days spent on mechanical ventilation and in ICU were not different. The probability of remaining on mechanical ventilation over time was also not different between the two groups. On the one hand, these findings confirm those obtained in a recent study by Krishnan et al. (20); in keeping with this latter study, the amount of physician time per bed per day

was considerably higher in our study than in other randomized controlled trials reporting significant reductions of the time spent on mechanical ventilation and in ICU with weaning protocols. On the other hand, the finding that duration of mechanical ventilation and ICU length of stay were definitely not different between the two groups is not necessarily a negative result; in fact, although effective in reducing the risk of premature extubation, an excessively protective protocol might cause a delay in weaning and extubation and, accordingly, prolong the time spent on mechanical ventilation and in the ICU. Even though the rates of tracheotomy and ICU mortality were not significantly different between the two groups, both rates showed a trend toward a reduction in the intervention group, compared with the control group. It should be kept in mind, however, that our study was not powered to ascertain differences in the rate of tracheotomy and death in ICU between the two groups. Moreover, regardless of the group of randomization, the patients who were tracheotomized and died after enrollment in the study protocol were quite few, in contrast to the overall ICU population (Fig. 2).

The design of this study shares a few limitations with several previous randomized controlled trials (2–4, 20, 21). First, it was impossible to blind the ICU professionals to treatment; in an attempt to limit the impact of this bias, however, the analysis of data were performed by two investigators not involved either in the clinical management of patients and in data acquisition and report. Second, it was not possible to avoid that the same ICU professionals treated at the same time different patients included in the two groups. Third, as the study lasted 21 months, we cannot exclude that the use of the protocol might have influenced the treatment of the control group over time; as reported in Table 3, however, we calculated the rate of reintubation over time (Table 3) and could not ascertain any significant difference between the three 7-month periods.

As this study was conducted in a specific ICU setting of a single center, our findings might not be fitting to other situations. While ICU patients are in general mechanically ventilated because of acute respiratory failure, unconsciousness and/or need for heavy sedation are the main reasons for instituting mechanical ventilation in neurologic and neurosurgical patients (1). On the one hand,

however, in the course of the ICU stay impairment in gas exchange may occur also in patients who are primarily affected by neurologic disorders; on the other hand, peripheral or central nervous system alterations may intervene in ICU patients, regardless of the cause of admission, because of sepsis, use of sedatives, hepatic and renal failure. When applied to complex phenomena involving medical judgment, randomized controlled trials may have limitations. Randomization improves the validity of a trial by avoiding bias from differences between intervention and control populations; however, it may also homogenize relevant clinical factors that are variable within populations, a risk that is increased in composite populations of patients with poorly quantifiable differences between individuals (22). Also, assessing procedures involving human skills and careful clinical judgment with a multicenter trial may be extremely cumbersome (22).

The possibility to transfer in the clinical practice a study protocol also varies between studies (8, 23, 24). When seen as a limitation or a complete removal of clinical judgment, protocols may generate frustration and resentment among healthcare professionals (19). Improving staff's perceptions of a proposed procedural protocol may reduce errors and conflicts (19, 25). In our study, the protocol was not conducted by a single type of ICU professional, but planned and shared by physicians, nurses, and physiotherapists. This true multidisciplinary approach was, in our opinion, the most likely explanation for the high protocol adherence obtained. Although it was felt to increase the ICU workload, the implementation of the protocol was considered to improve the clinical outcome in general and the rate of extubation failure in particular, and had a positive effect on the perception that nurses and physiotherapists had of their professional role, which improved their job satisfaction and potentially reduced the risk of burn-out.

CONCLUSIONS

In patients receiving mechanical ventilation for neurologic disorders, arranging physiologic and clinical data in a systematic fashion by means of a written flow chart improves the outcome of extubation without affecting the time spent on mechanical ventilation and in the ICU, and is well accepted by the ICU staff. Further studies are necessary to assess

whether and to what extent these results are applicable to other situations.

ACKNOWLEDGMENTS

Chiara Orsini, Enrica Pugnetti, and Bruna Benini assisted with data management and analysis. We are indebted to nurses, physiotherapists, and physicians of the neuro-ICU of Azienda Ospedaliera Ospedale Niguarda Ca' Granda for their dedication in applying the study protocol. We also thank Jennifer Beck who revised the manuscript.

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