

Deviations from evidence-based clinical management guidelines increase mortality in critically injured trauma patients*

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Objectives: The effect of treatment guidelines on clinical outcomes in general and specifically for trauma patients has not been well-studied. We hypothesized that better compliance with guidelines would be associated with improved clinical outcomes.

Design: Prospective, randomized, double-blinded, multicentered, placebo-controlled study of recombinant factor VII in severe trauma that utilized guidelines for damage control, transfusions, and mechanical ventilation. Vanderbilt Coordinating Center reviewed compliance in near real-time and reported deviations classified as minor, moderate, or major to investigators. Multivariate regression analysis measured the association between outcomes (30-day and 90-day mortality, development of multiple organ failure, ventilator-free days, renal failure-free days, and blood products transfused) and compliance with each guideline, as well as a composite assessment of overall compliance.

Setting: One hundred hospitals in 26 countries.

Patients: Blunt and/or penetrating trauma patients aged 18–70 yrs who had received 4–8 units of red blood cells for active torso and/or proximal lower extremity bleeding despite standard interventions.

Measurements and Main Results: When assessed as composite end point, major deviations from guidelines were associated with significantly higher mortality at 30 and 90 days after injury and fewer renal failure-free days. Moderate deviations were associated with a significantly higher risk of multiple organ failure and fewer ventilator-free days. Moderate and major deviations from damage control and ventilation guidelines were also significantly associated with higher risk of death at days 30 and 90. Within the ventilation protocol, noncompliance with tidal volume and plateau pressure targets was associated with significantly higher mortality at days 30 and 90 and fewer ventilator-free days, whereas noncompliance with weaning guideline was only associated with significantly fewer ventilator-free days.

Conclusions: In a clinical trial of trauma patients, higher compliance with guidelines for damage control, transfusion, and ventilation management is associated with lower mortality and improved outcomes. (Crit Care Med 2012; 40:778–786)

KEY WORDS: blood transfusion; clinical guidelines; damage control; hemorrhage; mechanical ventilation; mortality; trauma

A treatment guideline is a detailed plan to direct care in a consistent way based on individual patient circumstances (1). The emergent care of traumatic hemorrhagic shock is highly standardized (primary and secondary surveys). Damage control measures are undertaken emergently to control massive hemorrhage while procedures for nonbleeding injuries are deferred (2). Randomized clinical trials also use protocols to assure

the intervention being tested is consistently and safely administered to a well-defined patient cohort who potentially stand to benefit. When successful, many such protocols, including guidelines for blood glucose control (3, 4), transfusion (5, 6), fluid management (7, 8), sedation (9–11), ventilation, and weaning (10–12), have been adapted for clinical use. Because of concerns that poor routine care or nonrandomly applied usual care practices could influence important clin-

ical outcomes (e.g., survival, organ failures) and in an attempt to better describe the care provided, critical care trials have used guidelines or protocols to standardize aspects of routine care with increasing frequency (8, 13, 14).

The effect of guidelines for routine care practices in clinical trials in general and in the care of trauma patients specifically (15) is not well-studied. Therefore, we utilized near real-time assessments of compliance with damage control, transfusion, and ventilation protocols in a large multicenter study conducted in 26 countries (16) to test the hypothesis that protocol compliance was associated with lower mortality and other improved clinical outcomes.

MATERIALS AND METHODS

Study Population. The CONTROL trial (clinicaltrials.gov NCT00184548) was a prospective, randomized, double-blinded comparison of recombinant activated factor VII vs. placebo in severe trauma patients with refractory bleeding conducted from August 2005 to

*See also p. 990.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (<http://journals.lww.com/ccmjournal>).

Supported, in part, by Novo Nordisk A/S.

Dr. Rice has received consulting fees from Novo

Nordisk regarding the conduct of the recombinant activated factor VII trauma trial. Dr. Christensen is employed by and holds stock ownership with Novo Nordisk, Inc. Dr. Morris received consultancy fees from Novo Nordisk, Inc. Dr. Tortella was formally employed by Novo Nordisk, Inc. The remaining authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e318236f168

September 2008 in 100 recruiting hospitals in 26 countries (16). Informed consent was obtained from the patient or a legally acceptable surrogate in all cases. The trial was approved by local Institutional Review Boards, Ethics Committees, and national regulatory authorities as applicable.

Inclusion and Exclusion Criteria. The study population consisted of blunt and/or penetrating trauma patients aged 18–70 yrs who had received between 4 and 8 units of red blood cells for active torso and/or proximal lower extremity bleeding despite standard interventions. Active bleeding was defined by ongoing hypotension (systolic blood pressure ≤ 90 mm Hg), acidosis (lactate > 6 mmol/L or base deficit ≥ 5 mEq/L), or the need for ongoing intravenous fluid (≥ 1 L/hr) to maintain vital signs. Patients who were moribund, had severe brain injuries, or were injured > 12 hrs before randomization or > 4 hrs before hospital arrival were excluded.

Measuring Compliance With Clinical Management Guidelines. To reduce practice variation, the trial utilized guidelines for damage control, transfusions, and mechanical ventilation (Table 1). Patients were to be managed using generally accepted medical standards for traumatic injury, including surgical interventions and damage control maneuvers (17). Transfusion guidelines were utilized to standardize the administration of colloid, starch, and blood products (5, 6). Ventilation guidelines were used to provide a lung-protective strategy, guide the use of positive end-expiratory pressure, and ensure discontinuation of ventilation at the earliest possible time (9–12). Critical care and trauma physicians at the Vanderbilt Coordinating Center (Nashville, TN) evaluated clinical data from the first 5 study days in near real-time to score three levels of adherence with each guideline: no or only minor deviations (category 1); moderate deviations (category 2); and major deviations (category 3) (Table 2). Vanderbilt Coordinating Center physicians also scored noncompliance with ventilator management and transfusion guidelines by type of violation (ventilator: tidal volume, plateau pressure, weaning; transfusion: platelet, fresh-frozen plasma, red blood cell, starch/colloid, prohibited clotting factor violations). Overall or composite compliance with all of the guidelines was also assessed in three categories (Table 2). Vanderbilt Coordinating Center physicians were blinded to treatment allocation (recombinant activated factor VII/placebo) and outcomes but not to clinical site to enable feedback to investigators. Ventilator and damage control compliance were scored exclusively by the critical care and trauma physician, respectively. Transfusion and overall compliance were scored by both the critical care and trauma physician. When disagreements occurred, the worst score from either physician was utilized.

Outcome Variables. The effect of compliance with all three guidelines and overall com-

pliance on mortality at 30 and 90 days after injury was evaluated. The effects of damage control guideline compliance on the number of units of fresh-frozen plasma, platelets, and red blood cells administered in the first 24 hrs after randomization were measured. The effect of compliance with ventilation guidelines was measured using the number of ventilator-free days (VFD) (18). The effect of transfusion guideline compliance was measured on renal failure-free days, both through 30 days (renal failure was defined as a renal Sequential Organ Failure Assessment score of ≥ 3 (creatinine ≥ 3.5 mg/dL) (19), use of renal replacement therapy and the number blood products transfused. The effect of overall compliance on VFD, renal failure-free days, and development of multiple organ failure was also measured.

Covariates. Age, gender, region of the world, type of injury (blunt/penetrating), time from injury to hospitalization, red blood cell units transfused before hospitalization, Injury Severity Score, Glasgow Coma Scale score, shock at baseline, baseline hemoglobin, creatinine, and activated partial thromboplastin time were covariates in the multivariate analysis. These covariates were chosen before any analyses based on previously published associations with mortality in trauma patients and the authors' clinical judgment (20, 21).

Statistical Analysis. Descriptive statistics were calculated for each guideline compliance measure and also for the covariates by categories of overall compliance with management guidelines, testing for significant differences between categories using one-way analysis of variance models for continuous variables, and chi-squared tests for categorical and ordinal variables. Each outcome variable was regressed against the compliance categories using either logistic or least-squares regression, for binary or continuous variables, respectively. Unadjusted and adjusted models were estimated; the latter included all the covariates. Category 1 (no or only minor deviations) was the reference category in all models. For ventilator management, transfusion, and damage control compliance, but not overall compliance, categories 2 and 3 (moderate deviations and major deviations) were combined because of small number of observations in category 3. For ventilation management and transfusion compliance, the effect of type of guideline violation was investigated when patients with more than one type of noncompliance were included in all areas in which they had moderate or major deviations. Patients who did not require damage control or mechanical ventilation or who died before documentation of ventilator parameters were included in the analysis and assigned to a "not applicable" category. The management of such patients still received an overall compliance score for adherence to the other clinical guidelines. Standard errors were adjusted for hospital level clustering in all models to account for the possibility that patients were not independent within hospitals. All models were

estimated using Stata version 11 (StataCorp LP, College Station, TX). Two-sided $p < .05$ was considered statistically significant.

RESULTS

Compliance data were available for 556 of the 573 (97%) enrolled patients (Table 3). In terms of overall compliance, 53% of patients had no or only minor deviations, 37% had moderate deviations, and 10% had major deviations. Transfusion guidelines had the highest compliance rate (81% of patients had no or minor protocol deviations), followed by the damage control guidelines (80%), and then ventilation management guidelines (46%). The most common deviations from ventilation management guideline were tidal volume violations (36% patients); the most common transfusion guideline violations were for starch/colloid administration (10%).

Mortality at 30 days after injury was 10% among those with no or minor deviations, 9% for moderate deviations, and 29% among those with major deviations ($p < .001$; Table 4, Fig. 1). Similarly, mortalities at 90 days were 11%, 12%, and 31%, respectively ($p < .001$). Significant differences were observed for all outcomes by overall compliance category (all $p \leq .001$) except for units of platelets transfused in the first 24 hrs ($p = .229$). None of the covariates varied significantly by overall compliance category (all $p > .10$) except for baseline activated partial thromboplastin time ($p = .007$).

Compared to patients with no or minor guideline deviations overall, those with major deviations had more than a three-fold risk of death at 30 and 90 days after injury, even after adjusting for the covariates (all odds ratios > 3 , all $p \leq .002$; Table 5). Patients with moderate deviations were more likely to have multiple organ failure and at least three fewer VFDs compared to those with no or minor deviations. Patients with major deviations had at least four fewer renal failure-free days compared to those with no or minor deviations but were not more likely to have multiple organ failure develop, probably because of the higher rate of mortality in this group.

Patients with moderate or major deviations from damage control guidelines had significantly higher mortality at 30 days and 90 days after injury compared to those with no or minor deviations in both adjusted and unadjusted models (all odds ratios > 1.8 , all $p \leq .026$; Table 6).

Table 1 Clinical management guidelines

Damage control	- Attempted definitive management (operative and/or interventional radiology) for bleeding injuries should begin within 2 hrs of arrival to hospital. - All operations and procedures within the first 24 hours shall conform to a “damage control” approach, and be aimed at controlling of hemorrhage and contamination. No orthopedic, maxillofacial, vertebral, or complex gastrointestinal reconstructive surgery shall be performed until after the subject is outside this ‘window’. Limited procedures with specific emergent aims (e.g. irrigation and debridement and external fixation of open fractures, fasciotomies, decompressive laparotomy) can be performed at the primary investigator’s discretion. - A “damage control” approach (i.e. no definitive surgical care for other than bleeding injuries) will be initiated when any of the below is present: - Temperature $<35^{\circ}\text{C}/95^{\circ}\text{F}$ or - Lactate >4 mmol/L (or more than twice the local upper limit of normal) or - Corrected pH <7.3. - Active warming devices (forced hot air blankets, heated humidification of the ventilator circuit, fluid warmers) should be used to maintain a minimum core temperature of $35^{\circ}\text{C}/95^{\circ}\text{F}$.
Transfusion	Transfusion guideline for RBCs <i>In patients hemodynamically unstable as defined by:</i> - SBP ≤ 90 mm Hg or SBP is only maintained >90 mm Hg with massive fluids or vasopressor support. - RBC should be administered as determined by “clinical necessity”. <i>In patients hemodynamically stable as defined by:</i> - No SBP ≤ 90 mm Hg for 1 hr and no resuscitation (or use of vasopressor support) (exception: use of low dose vasopressor support for neurogenic shock). - Hemoglobin <7 g/dL: RBC administered at the investigators discretion. - Hemoglobin 7–9 g/dL: RBC should only be administered at the discretion of the investigator, if evidence of hypoperfusion is present. - Hemoglobin >9 g/dL: No RBC transfusions. Transfusion guideline for other blood products <i>In patients hemodynamically unstable as defined by:</i> - SBP ≤ 90 mmHg or SBP is only maintained >90 mm Hg with massive fluids or vasopressor support. - Other blood products should be administered as determined by “clinical necessity”. <i>In patients hemodynamically stable as defined by:</i> - No SBP ≤ 90 mm Hg for 1 hr and no resuscitation (or use of vasopressor support) (exception: use of low dose vasopressor support for neurogenic shock). - With bleeding: - International normalized ratio >1.5 or prothrombin time >16 secs: Fresh frozen plasma administered at the investigator’s discretion. - Fibrinogen <100 mg/dL: Cryoprecipitate/fibrinogen concentrate at the investigator’s discretion. - Platelets $<50,000/\text{mm}^3$: Platelets at the investigator’s discretion. - Without bleeding, but still in the peri-operative period: - International normalized ratio >2.0: Fresh frozen plasma administered at the investigator’s discretion. - Platelets $<50,000/\text{mm}^3$: Platelets at the investigator’s discretion. - Without bleeding in the intensive care unit - No blood product transfusion. Guideline for use of high molecular weight colloids - Use of starch or colloids should be limited to ≤ 2.0 L total within 24 hrs from time of injury. - Use of dextran (and equivalent) is not allowed in the first 48 hrs from time of injury. Guideline for use of aprotinin, activated prothrombin complex concentrate, or prothrombin complex concentrate - Use of aprotinin, activated prothrombin complex concentrate or prothrombin complex concentrate is not allowed at any time during the study.
Ventilator management	Patients requiring mechanical ventilation (by any mode) will be ventilated to achieve the following parameters: - Decreasing PEEP and FiO_2 as early as possible given oxygenation guidelines below. - Limiting ventilation volumes to no greater than 6 ± 2 mL/kg predicted body weight as much as possible. - Limiting plateau pressures to ≤ 30 cm H_2O whenever possible. - Avoiding the use of muscle relaxants, except when specifically indicated. - Attempting to wean on an ongoing basis, at least once daily when weaning criteria are met. Patients requiring mechanical ventilation will be ventilated according to the following within 24 hours of meeting trial inclusion: V_t set at 6 mL/kg ± 2 mL/kg predicted body weight calculated as follows: For males: Predicted body weight (kg) = $50 + 2.3 [\text{height (inches)} - 60] = 50 + .91 (\text{height (cm)} - 152.4)$. For females: Predicted body weight (kg) = $45.5 + 2.3 [\text{height (inches)} - 60] = 45.5 + 0.91 (\text{height (cm)} - 152.4)$. PaO_2 55–80 mm Hg or SpO_2 88%–95%. Percent O_2/PEEP ratio to be $= 5 \pm 1$. (i.e. patient with FiO_2 50% and PEEP 12 cm H_2O and PEEP must be <35 cm H_2O if using a ventilator mode with PEEP). - Keep pH 7.25–7.45 using respiratory rate ≤ 35 and $\text{PaCO}_2 \geq 25$. HCO_3^- infusion may be given at the discretion of the bedside physician. If pH ≤ 7.15 then tidal volume may be increased by 1 mL/kg to achieve pH >7.15 and target plateau pressures (see below) may be exceeded. - Keep plateau pressures ≤ 30 cm H_2O if necessary by reducing V_T to no less than 4 mL/kg. If $V_T < 6$ mL/kg and PP < 25 then increase V_T until plateau pressures = 25–30 or $V_T = 6$ mL/kg.

(continued)

Table 1 (Continued)

Weaning readiness will be assessed between the same four hour period each day. The patient is considered ready for a spontaneous breathing trial if all the following apply:
• $\text{FiO}_2 \leq 0.40$. • PEEP (or continuous positive airway pressure) < 10 cm H_2O. • Not receiving neuromuscular blockade agents and without neuromuscular blockade. • Without anatomical lesions that preclude the ability to ventilate (e.g. spinal cord lesions, abdominal hypertension, neck injuries). • Patient exhibiting inspiratory efforts. If no efforts apparent at baseline, ventilator mandatory rate will be decreased by 50% for up to 5 mins to detect efforts. • SBP ≥ 90 mm Hg without vasopressor support.
If all of the above weaning readiness criteria apply, initiate a trial of 30–120 mins of spontaneous breathing with $\text{FiO}_2 < 0.50$ using any of the following approaches:
• T-piece or tracheostomy mask. • Pressure support < 10 cm H_2O without mandatory ventilation. • Continuous positive airway pressure < 10 cm H_2O without mandatory ventilation.
While on the spontaneous breathing trial, ANY of the following 3 criteria represent intolerance of weaning and the patient should be placed back on ventilatory support and be re-evaluated the next morning at the latest:
• $\text{SpO}_2 < 90\%$ or $\text{PaO}_2 < 60$ mm Hg. • Respiratory rate $> 35/\text{min}$. • Respiratory distress (marked use of accessory muscles or paradoxical breathing).

PEEP, positive end-expiratory pressure; RBC, red blood cell; V_T , tidal volume.

Table 2. Measuring compliance with clinical management guidelines

Damage control compliance
No or minor deviations: Meets trauma care standards as outlined in the clinical management guidelines (minor departures may be present but are not clinically significant)
Moderate deviations: Meets trauma care standards as outlined in the clinical management guidelines (although departures are present, the majority of care rendered follows protocol and treatment guidelines)
Major deviations: Does not meet trauma care standards as outlined in the clinical management guidelines
Transfusion compliance
No or minor deviations: Follows transfusions standards as outlined in the clinical management guidelines
Moderate deviations: Minor departures from transfusion standards outlined in the clinical management guidelines
Major deviations: Repeated departure from transfusion standards outlined in the clinical management guidelines without justification despite training by the Vanderbilt Coordinating Center
Ventilator management compliance
No or minor deviations: Follows standards as outlined in clinical management guidelines $\geq 75\%$ of the time or provides acceptable rationale as to why deviated from guidelines
Moderate deviations: Standards as outlined in clinical management guidelines followed $< 75\%$ of the time in any area of the ventilator protocol without justification from the site
Major deviations: Systematic nonadherence to standards outlined in clinical management guidelines despite training by the Vanderbilt Coordinating Center
Overall compliance
No or minor deviations: Meets inclusion/exclusion criteria with no or only minor departures from damage control, transfusion, and ventilator guideline standards as outlined in the clinical management guidelines (minor departures may be present but are not clinically significant)
Moderate deviations: Meets inclusion/exclusion with more than minor departures in damage control, transfusion, or ventilator guideline standards as outlined in the clinical management guidelines but majority of care rendered follows protocol and treatment guidelines
Major deviations: Does not meet inclusion/exclusion criteria or damage control standards as outlined in the clinical management guidelines, or repeated nonadherence to transfusion or ventilator management guidelines

guideline violation had an impact on outcomes (results not shown).

Patients with moderate or major deviations from ventilation guidelines had more than twice the mortality at 30 days and 90 days compared to those with no or minor deviations in both adjusted and unadjusted models (all ORs > 2 , all $p \leq .05$; Table 7), as well as significantly fewer VFDs. Tidal volume and plateau pressure deviations were associated with significantly higher mortality at 30 days and 90 days and also fewer VFDs. Failure to wean violations were only associated with significantly fewer VFDs.

DISCUSSION

This study is the first to our knowledge to investigate the effect of protocol compliance with routine care measures on clinical outcomes of a clinical trial. We found that major deviations in overall composite compliance from damage control, transfusion, and/or ventilation guidelines were associated with significantly higher 30-day and 90-day mortality and fewer VFDs. These associations remained robust even after adjustment for confounders such as age, gender, time from injury to hospitalization type and severity of injury, and markers of disease severity.

Worse compliance with damage control guidelines was associated with more transfusions and higher mortality. By contrast, worse compliance with transfusion guidelines was associated with more blood product administration, which was

Compliance with transfusion guidelines was not associated with higher mortality or higher rate of renal dysfunction (Supplemental Table 1 [Supplemental Digital Content 1, <http://links.lww.com/CCM/A358>]),

but moderate or major deviations were associated with administration of more units of fresh-frozen plasma and red blood cell during the first 24 hrs. There was no systematic evidence that the type of transfusion

Table 3. Compliance with clinical management guidelines

	Observations (%)
Overall compliance (n = 556)	
No or minor deviations	295 (53%)
Moderate deviations	203 (37%)
Major deviations	58 (10%)
Damage control compliance (n = 450) ^a	
No or minor deviation	358 (80%)
Moderate deviation	58 (13%)
Major deviation	34 (8%)
Transfusion compliance (n = 552)	
No or minor deviation	448 (81%)
Moderate deviation	94 (17%)
Major deviation	10 (2%)
Type of moderate or major transfusion violation ^b	
Platelet	5 (1%)
Fresh-frozen plasma	6 (1%)
Red blood cells	37 (7%)
Starch/colloid	55 (10%)
Prohibited clotting factor	8 (2%)
Ventilator management compliance (n = 480) ^c	
No or minor deviations	221 (46%)
Moderate deviations	256 (53%)
Major deviations	3 (1%)
Type of moderate or major ventilator deviation ^b	
Tidal volume	165 (36%)
Plateau pressure	46 (10%)
Weaning	115 (25%)

^aOne hundred four patients did not require damage control; ^bpatient may have had more than one type of deviation; ^cseventy-six patients did not receive mechanical ventilation or died before ventilator parameters were recorded.

expected given that this was the main marker of compliance, but was not associated with higher mortality or fewer organ failure-free days. Noncompliance with the tidal volume or plateau pressure components of the ventilation protocol was associated with both higher mortality and fewer VFDs, whereas noncompliance with the weaning portion of the protocol was only associated with fewer VFDs.

Previous studies have shown that violations of inclusion or exclusion criteria or study drug administration instructions in clinical trials were associated with worse clinical outcomes (22). Other studies have demonstrated that protocols, especially those for sedation, ventilator management, and weaning, improve clinical outcomes (10, 23–25). Our findings, which represent the largest global study on compliance and outcomes, add to these previous studies in two ways. First, we demonstrate that outcomes com-

Table 4. Descriptive statistics for outcome measures and covariates by overall compliance with clinical management guidelines

	No or Minor Deviations (n = 295)	Moderate Deviations (n = 203)	Major Deviations (n = 58)	p
Outcome measures				
Mortality				
30-day (%)	10	9	29	<.001
90-day (%)	11	12	31	<.001
Ventilator-free days through 30 days (mean)	20	16	15	<.001
Blood products in first 24 hrs				
Fresh-frozen plasma, units (mean)	7	8	11	.001
Platelets, units (mean)	4	3	5	.229
Red blood cells, units (mean)	12	12	17	.001
Multiple organ failure (% of patients)	45	65	59	<.001
Renal failure-free days through 30 days				
Renal Sequential Organ Failure Assessment score 3+, days (mean)	27	27	21	<.001
Renal replacement therapy duration, days (mean)	26	27	21	<.001
Covariates				
Age, yr (mean)	37	39	41	.101
Female (%)	26	20	22	.215
Type of injury: penetrating (%)	17	13	14	.449
Type of injury: blunt (%)	83	87	86	
Time from injury to hospitalization, hrs (mean)	1.2	1.1	1.6	.101
Red blood cell units before arrival at hospital (mean)	6	5	9	.668
Injury Severity Score (median)	29	30	29	.797
Glasgow Coma Scale score (median)	15	15	13	.344
Shock population (%)	68	69	79	.217
Baseline hemoglobin, g/dL (mean)	9.9	10.1	10.2	.587
Baseline creatinine, mg/dL (mean)	1.2	1.2	1.2	.994
Baseline activated partial thromboplastin time, sec (mean)	39.6	38.8	50.5	.007
Country				.229

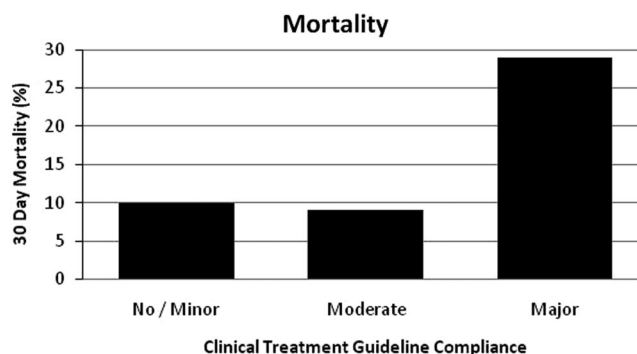


Figure 1. Effect of overall compliance with clinical management guidelines on mortality.

monly measured in clinical trials can be significantly influenced by usual care practices. Second, the mere inclusion of protocols or guidelines in clinical trials seems to be insufficient; better protocol compliance is associated with improved clinical outcomes.

The association of overall compliance with mortality and VFDs is not surprising. Improved overall compliance with a group of protocols shown individually to be beneficial resulted in better outcomes (1). Improved compliance with guidelines may also reflect better overall care at the individual site or by the primary medical

team. In addition, patients enrolled in the study, despite not meeting the eligibility criteria, also represented a major deviation in overall compliance. Application of the inclusion and exclusion criteria sought to select patients with major torso trauma at high risk for complications who could benefit from recombinant activated factor VII. Because pre-enrollment approval of patients meeting the inclusion and exclusion criteria was impractical, some patients who were at unacceptably high risk for complications or moribund may have been enrolled. Data from previous critical care trials suggest

Table 5. Effect of overall compliance with clinical management guidelines

Category ^a	Unadjusted (95% Confidence Interval)				Adjusted ^d (95% Confidence Interval)			
	Odds Ratio ^a		<i>p</i>		Odds Ratio ^a		<i>p</i>	
30-day mortality ^b								
Moderate deviation	0.91 (0.53–1.57)		.739		1.11 (0.60–2.06)		.744	
Major deviation	3.66 (1.88–7.15)		<.001		3.60 (1.62–7.98)		.002	
90-day mortality ^b								
Moderate deviation	1.12 (0.68–1.83)		.668		1.28 (0.69–2.37)		.441	
Major deviation	3.57 (1.91–6.70)		<.001		3.28 (1.53–7.03)		.002	
Multiple organ failure ^b								
Moderate deviation	2.23 (1.45–3.44)		<.001		2.22 (1.34–3.70)		.002	
Major deviation	1.70 (0.98–2.97)		.061		1.41 (0.70–2.83)		.331	
	Coefficient ^a	(SE)	[t]	<i>p</i>	Coefficient ^a	(SE)	[t]	<i>p</i>
Ventilation-free days (number) ^c								
Moderate deviation	–3.82	(0.85)	[–4.51]	<.001	–3.03	(0.79)	[–3.83]	<.001
Major deviation	–5.05	(1.92)	[–2.64]	.010	–1.80	(1.88)	[–0.95]	.342
Renal failure-free days, Sequential Organ Failure Assessment score 3+ (n) ^c								
Moderate deviation	–0.21	(0.73)	[–0.28]	.776	–0.82	(0.62)	[–1.33]	.188
Major deviation	–5.87	(1.89)	[–3.11]	.002	–4.63	(1.51)	[–3.07]	.003
Renal failure-free days, renal replacement therapy (n) ^c								
Moderate deviation	0.21	(0.67)	[0.31]	.760	–0.05	(0.64)	[–0.08]	.934
Major deviation	–5.43	(1.86)	[–2.92]	.004	–4.07	(1.46)	[–2.79]	.006

^aReference category is no or minor deviations (category 1); ^bestimated using logistic regression; odds ratio >1 indicates the likelihood of the unfavorable outcome is higher in that compliance category compared with the reference category; ^cestimated using ordinary least squares regression; coefficients <0 indicate lower values of the dependent variable in that compliance category compared with the reference category; ^dcontrols are included for age, gender, type of injury, time from injury to hospitalization, red blood cell units transfused before hospitalization, Injury Severity Score, Glasgow Come Scale score, whether the patient was in shock, baseline hemoglobin, creatinine and activated partial thromboplastin time, and country.

Table 6. Effect of moderate or major deviations from damage control management guidelines

Outcome Measure	Unadjusted (95% Confidence Interval)				Adjusted ^d (95% Confidence Interval)			
	Odds Ratio ^a		<i>p</i>		Odds Ratio ^a		<i>p</i>	
30-day mortality ^b	1.96 (1.12–3.42)		.018		2.32 (1.17–4.62)		.016	
90-day mortality ^b	1.82 (1.11–3.00)		.018		2.02 (1.09–3.75)		.026	
	Coefficient ^a	(SE)	[t]	<i>p</i>	Coefficient ^a	(SE)	[t]	<i>p</i>
Fresh-frozen plasma units in first 24 hrs (n) ^c	2.29	(1.16)	[1.97]	.052	2.21	(1.19)	[1.85]	.067
Platelets units in first 24 hrs (n) ^c	0.68	(1.00)	[0.68]	.498	0.90	(0.85)	[1.06]	.293
Red blood cell units in first 24 hrs (n) ^c	2.58	(1.48)	[1.75]	.083	2.49	(1.46)	[1.71]	.091

^aReference category is no or minor deviations (category 1). Categories 2 and 3 (moderate and major deviations) were combined because of the small number of observations in category 3; ^bestimated using logistic regression; odds ratios >1 indicate the likelihood of the unfavorable outcome is higher in that compliance category compared with the reference category; ^cestimated using ordinary least squares regression; coefficients <0 indicate lower values of the dependent variable in that compliance category compared with the reference category; ^dcontrols are included for age, gender, type of injury, time from injury to hospitalization, red blood cell units transfused before hospitalization, Injury Severity Score, Glasgow Come Scale score, whether the patient was in shock, baseline hemoglobin, creatinine and activated partial thromboplastin time, country, and patients who did not require damage control.

such patients are likely to experience worse outcomes (22).

Deviations from the lung-protective ventilator protocol represented the most common violation in our study. The worse outcomes associated with these deviations indirectly serve to support previous studies showing better results when lung-protective ventilation strategies are utilized in nontrauma patients with or at risk for acute lung injury (12, 26–28).

Specifically, these strategies have resulted in decreased mortality and more VFDs in patients with lung injury and decreased the incidence of lung injury in patients at risk (12, 27).

In addition to providing standardization, protocols may improve efficiency by facilitating the progression of care rather than having such progress rely on a particular health care provider recognizing readiness or initiating the next step.

Weaning from mechanical ventilation represents a classic example in which, using standardized “readiness” criteria, patients undergo a spontaneous breathing trial earlier than when a physician subjectively determines (or fails to determine) readiness (10, 25). Data suggest that many patients classified as “weaning failures” can be successfully removed from the ventilator, and that only approximately half the patients who extubate

Table 7. Effect of compliance with ventilator management guidelines

Category/Type	Unadjusted (95% Confidence Interval)				Adjusted ^d (95% Confidence Interval)			
	Odds Ratio ^a		<i>p</i>		Odds Ratio ^a		<i>p</i>	
30-day mortality ^b								
Moderate or major deviations ^a	2.97 (1.48–5.96)		.002		2.74 (1.15–6.53)		.023	
Type of violation								
Tidal volume violation	2.41 (1.02–5.70)		.045		3.07 (1.25–7.55)		.015	
Plateau pressure violation	2.73 (1.11–6.70)		.029		2.31 (0.88–6.08)		.091	
Failure to wean violation	0.81 (0.36–1.85)		.619		0.80 (0.32–2.02)		.632	
90-day mortality ^b								
Moderate or major deviations ^a	2.81 (1.45–5.45)		.002		2.37 (1.00–5.62)		.050	
Type of violation								
Tidal volume violation	1.90 (0.85–4.24)		.118		2.04 (0.91–4.58)		.085	
Plateau pressure violation	3.15 (1.28–7.78)		.013		3.26 (1.32–8.04)		.010	
Failure to wean violation	0.98 (0.44–2.16)		.955		0.75 (0.32–1.77)		.515	
	Coefficient ^a	(SE)	[t]	<i>p</i>	Coefficient ^a	(SE)	[t]	<i>p</i>
Ventilator-free days (n) ^c								
Moderate or major deviations ^a	–6.53	(0.72)	[–9.11]	<.001	–4.67	(0.73)	[–6.43]	<.001
Type of violation								
Tidal volume violation	–3.60	(1.06)	[–3.40]	.001	–2.91	(0.93)	[–3.14]	.002
Plateau pressure violation	–4.04	(1.55)	[–2.61]	.011	–4.17	(1.38)	[–3.04]	.003
Failure to wean violation	–4.43	(0.95)	[–4.65]	<.001	–2.36	(1.03)	[–2.29]	.024

^aReference category is no or minor deviations (category 1). Categories 2 and 3 (moderate and major deviations) were combined because of the small number of observations in category 3; ^bestimated using logistic regression; odds ratios >1 indicate the likelihood of the unfavorable outcome is higher in that compliance category compared with the reference category; ^cestimated using ordinary least squares regression; coefficients <0 indicate lower values of the dependent variable in that compliance category compared with the reference category; ^dcontrols are included for age, gender, type of injury, time from injury to hospitalization, red blood cell units transfused before hospitalization, Injury Severity Score, Glasgow Coma Scale score, whether the patient was in shock, baseline hemoglobin, creatinine and activated partial thromboplastin time, country, and patients who did not require ventilator management or who died before ventilator parameters being recorded.

themselves before being “medically cleared” for extubation do not have successful outcomes and require re-intubation (29). Our finding that noncompliance with the weaning portion of the ventilation protocol was associated with fewer ventilator-free days but not improved survival reinforces several studies showing a weaning protocol and, specifically, spontaneous breathing trials expedited liberation from ventilation but did not significantly alter mortality (10, 23, 24). A recent study (11) reported a mortality benefit by coupling daily awakening trials with spontaneous breathing trials. Unfortunately, our weaning protocol only evaluated the performance of the spontaneous breathing trial; therefore, we do not know if the addition of, and compliance with, a spontaneous awakening trial might have influenced mortality.

This study has several strengths, among them the large, well-defined, and reasonably homogeneous international study population and its extensive prospectively collected database. The near real-time classification of protocol compliance by experienced trauma and critical care physicians who were unaware of randomization groups or patient out-

comes also add credence to the findings. Clear, clinically important end points adjusted for important confounders are also study strengths.

The intent in establishing guidelines in this study was that they are to be followed; however, no written guideline can be practicably applied to every patient at all times. To account for this clinical reality, investigators were given the opportunity to explain to the coordinating center how apparent deviations followed the essence of the guideline. In cases in which the investigator’s explanation comported with the essence of the guideline, the deviation was considered justifiable. This process strengthens the results, making them more applicable to the real practice of critical care in this polytrauma population, acknowledging guideline adherence must encompass the totality of the patient’s condition.

The explanation for the finding that moderate deviations overall are significantly associated with organ failure while major deviations overall have a nonsignificant effect is unclear. This may be attributable to small numbers of patients with major deviations resulting in lack of statistical power or potentially an effect

seen because those with major deviations had higher mortality and therefore were more likely to have died before they had organ failure. However, these remain speculations and the study design does not allow determination of which of these or even if other possibilities or combinations are the explanation.

A limitation of our study is that only the first 5 days of care were evaluated for compliance. However, the areas of care that were evaluated, especially damage control and transfusion practices, are delivered almost exclusively during that time. Although ventilator management may have extended beyond 5 days, we have no reason to believe that compliance would have worsened over time, especially because lung function generally improves over time (8, 12). Although 54% of patients continued to be mechanically ventilated beyond day 5, with each passing day fewer and fewer patients were ventilated, providing less opportunity for guideline violations. Another potential limitation is the inability to control or adjust for the effect of other nonprotocolized practices like infection control, glucose control, or sedation.

Although the determination of minor, moderate, and major determinations is somewhat subjective, the guidelines relied on objective criteria, such as ventilator parameters (tidal volume, positive end-expiratory pressure, respiratory rate), oxygen saturation, and laboratory values (international normalized rate, platelet count, hematocrit) logged in case report forms for assessment. Judgment was required in assessing compliance with the damage control guideline, but specific Injury Severity Score data were used to reduce subjectivity in forming the compliance assessment and Abbreviated Injury Scale values for all injuries were reported to the coordinating center to facilitate assessment of the totality of injuries. Furthermore, guideline compliance was graded by a limited number of evaluators to decrease interevaluator subjectivity. Last, the evaluations were based on near real-time data used to assess compliance to objective criteria without knowledge of treatment arm or clinical outcomes (i.e., mortality, ventilator-free days, organ failures, and others).

It is also important to bear in mind that our study design only permits determination of associations, not definitive conclusions that better compliance causes improved outcomes. Better compliance at some sites may be a marker of higher quality of care overall. Compliance may simply represent a proxy for quality differences, or other covariates, among the different hospitals, or even doctors, in the study. Given the small number of patients enrolled at each hospital (or by each doctor), individual hospital or doctor factors could not be assessed. However, the multivariable analysis adjusted for hospital clustering in regions of the world, with the thought that hospitals within a region would have similar practice patterns because they could interact with each other (meetings, conferences, and others) and be exposed to similar literature (books, journals, and others).

Obviously, even perfect compliance with guidelines does not preclude death, because patients in the study who had no deviations in every compliance measure (overall, damage control, transfusion, and ventilator) still had 5% 30-day mortality and 6% 90-day mortality. Numerous effects drive mortality separately from protocol compliance itself.

There are many potential reasons for guideline noncompliance, including patient characteristics, physician workload

and hospital resources, and lack of detailed information about the guidelines (30). Educational efforts were used to establish the guidelines and to promote adherence (investigator meetings, regular newsletters, timely written feedback from the coordinating center), but other domains noted by Gurses et al (30) to be associated with guideline compliance, such as clinician or system characteristics, were beyond the ability of the clinical trial to address. With regard to patient characteristics, a patient with uncontrollable hemorrhage might be in violation of both transfusion and ventilation protocols because physicians transfuse quantities of blood products and (prohibited) clotting factors and use tidal volumes above those recommended to compensate for refractory metabolic acidosis in a last ditch effort to save the exsanguinating patient. Sicker patients may be unable to be adequately managed with the protocols, rendering severity of illness a potential confounder in the relationship between protocol compliance and outcomes. Although we attempted to account for this with baseline severity of illness measures, these would not account for patients who decompensate during the course of their illness. Physician workload and hospital resources may also affect compliance. The surgical literature notes an association between emergency, night-time, and weekend cases and noncompliance with antibiotic guidelines (31). The problem of staff training or shortages is especially relevant to ventilation and weaning protocol compliance. We attempted to minimize this problem by selecting sites that met specific criteria for trial participation and by providing extensive training and near real-time feedback with regard to protocol compliance. Lack of detailed information about the guidelines could lead to noncompliance if the requirements for adherence are unclear or lacking face validity. We attempted to minimize this problem by using evidence-based practices coupled with investigator training.

CONCLUSIONS

Major deviations from overall clinical management and damage control guidelines were associated with markedly higher 30-day and 90-day mortality and fewer VFDs and renal failure-free days. Compliance with lung-protective ventilation guidelines was associated with lower mortality and more VFDs, whereas compliance with ventilator weaning guidelines

was associated with more VFDs. Our study shows that adherence to clinical management guidelines for damage control, transfusion, and ventilator management may confer substantial clinical benefits.

ACKNOWLEDGMENTS

We thank all members of the Steering Committee for the CONTROL trial (Carl Hauser, Bertil Bouillon, John Holcomb, Michael Parr, Richard Dutton, Gordon Bernard, Jean-Louis Vincent, Ken Bofard, Martin Croce, Ari Leppäniemi, and Jeannett Dimsits) for their diligent efforts in designing and managing the conduct of the trial and for making this study possible.

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