

Results of the CONTROL Trial: Efficacy and Safety of Recombinant Activated Factor VII in the Management of Refractory Traumatic Hemorrhage

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Background: Traumatic coagulopathy contributes to early death by exsanguination and late death in multiple organ failure. Recombinant Factor VIIa

Submitted for publication December 1, 2009.

Accepted for publication June 21, 2010.

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Supported by Novo Nordisk A/S, Bagsvaerd, Denmark (sponsor).

Dr. Jeannett Dimsits and Dr. Bartholomew Tortella are employees of Novo Nordisk. Dr. Carl J. Hauser received consulting fees from Novo Nordisk and grant support from NIH/NIGMS. Dr. Kenneth Boffard received consulting fees from Novo Nordisk. Dr. Richard Dutton received consulting fees from Novo Nordisk and grant support from Octapharma and the Department of Defense. Dr. Gordon R. Bernard received consulting fees and grant support from Novo Nordisk. Dr. Martin A. Croce received consulting fees from Novo Nordisk and grant support from Wyeth and EISAI. Dr. John B. Holcomb received consulting fees from Novo Nordisk and HEMCON. Dr. Ari Leppaniemi received consulting fees from Novo Nordisk. Dr. Michael Parr received consulting fees, lecture fees from Novo Nordisk, and grant support from Novo Nordisk and PPD. Dr. Jean-Louis Vincent received consulting fees and grant support from Novo Nordisk. Dr. Bertil Bouillon received consulting fees and lecture fees from Novo Nordisk. Dr. G. Howard received compensation as an independent consultant.

The sponsor was responsible for providing clinical trial supplies, preparing the study protocol, data management, statistical analysis, and preparing the clinical trial report. Anders Rosholm, PhD, is an employee of Novo Nordisk and assisted with the statistical analyses. Jen Faleska, PhD, and Charlotte Yap, MSc, are employees of Novo Nordisk and provided editorial assistance.

A copy of the CONTROL database has been made available for academic study by special arrangement with the Trauma Audit Research Network (TARN) at the University of Manchester, UK (Maralyn Woodford, Executive Director, +44 (0) 161 206 5952).

Presented at the 40th Annual Meeting of the Western Trauma Association, February 28–March 6, 2010, Telluride, Colorado.

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DOI: 10.1097/TA.0b013e3181edf36e

(rFVIIa, NovoSeven) is a procoagulant that might limit bleeding and improve trauma outcomes.

Methods: We performed a phase 3 randomized clinical trial evaluating efficacy and safety of rFVIIa as an adjunct to direct hemostasis in major trauma. We studied 573 patients (481 blunt and 92 penetrating) who bled 4 to 8 red blood cell (RBC) units within 12 hours of injury and were still bleeding despite strict damage control resuscitation and operative management. Patients were assigned to rFVIIa (200 $\mu\text{g}/\text{kg}$ initially; 100 $\mu\text{g}/\text{kg}$ at 1 hour and 3 hours) or placebo. Intensive care unit management was standardized using evidence-based trauma “bundles” with formal oversight of compliance. Primary outcome was 30-day mortality. Predefined secondary outcomes included blood products used. Safety was assessed through 90 days. Study powering was based on prior randomized controlled trials and large trauma center databases.

Results: Enrollment was terminated at 573 of 1502 planned patients because of unexpected low mortality prompted by futility analysis (10.8% vs. 27.5% planned/predicted) and difficulties consenting and enrolling sicker patients. Mortality was 11.0% (rFVIIa) versus 10.7% (placebo) ($p = 0.93$, blunt) and 18.2% (rFVIIa) versus 13.2% (placebo) ($p = 0.40$, penetrating). Blunt trauma rFVIIa patients received (mean \pm SD) 7.8 \pm 10.6 RBC units and 19.0 \pm 27.1 total allogeneic units through 48 hours, and placebo patients received 9.1 \pm 11.3 RBC units ($p = 0.04$) and 23.5 \pm 28.0 total allogeneic units ($p = 0.04$). Thrombotic adverse events were similar across study cohorts.

Conclusions: rFVIIa reduced blood product use but did not affect mortality compared with placebo. Modern evidence-based trauma lowers mortality, paradoxically making outcomes studies increasingly difficult.

Key Words: Trauma, Hemorrhage, Outcome, Recombinant Factor VIIa, Randomized clinical trial.

(*J Trauma.* 2010;69: 489–500)

Trauma causes more than 5 million deaths per year.¹ Of the 174,000 trauma deaths in the United States each year,² about one-third die from hemorrhage.³ Bleeding can cause early death from shock or patients can die of organ failure triggered by hemorrhagic shock. Thus, rapid hemorrhage control is a primary aim of trauma care.⁴

Traumatic hemorrhage most commonly requires control by surgery or transvascular interventions. However, where blood loss and tissue injury are of sufficient magnitude, patients may develop an acute coagulopathy that markedly increases the risk of critical illness and death.^{4,5} Traumatic coagulopathy itself can cause massive bleeding and death from shock or it can obscure operative fields, impairing control of primary bleeding sites and delaying operative hemostasis. Thus, coagulopathic bleeding can contribute to the initiation of a

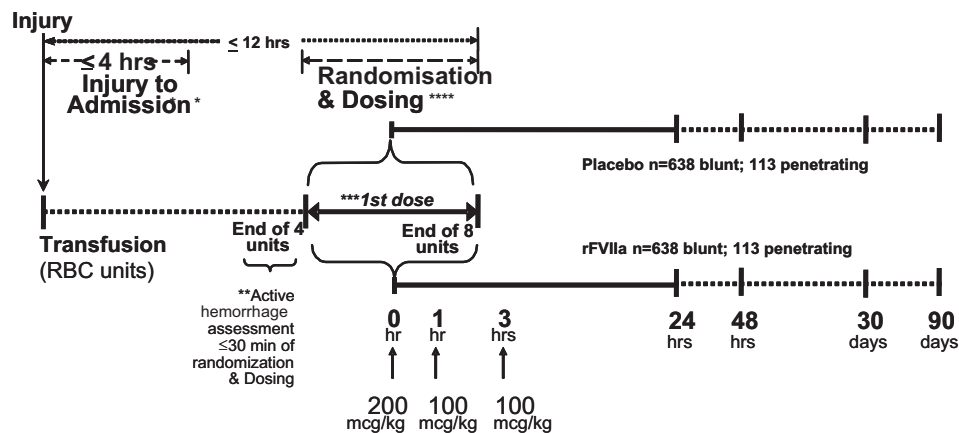
“vicious cycle”⁶ of acidosis, hypothermia, and further coagulopathy that often leads to death.⁷ In addition, coagulopathy may increase the risk of sepsis and organ failure via the prolongation of shock or the immune effects of excess transfusions.^{8–11}

Although traumatic coagulopathy is incompletely understood,⁴ its treatment usually begins with the administration of blood products aimed at restoring “normal” coagulation test results. However, in major injuries, this can be inadequate to reverse coagulopathy. Thus, agents that decrease coagulopathic bleeding after injury might be important adjuncts to direct hemorrhage control. Recombinant activated Factor VII (rFVIIa, NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark) acts physiologically by enhancing clot formation in the presence of tissue factor expressed on injured or ischemic vascular subendothelium. It also acts pharmacologically, binding directly to activated platelets, increasing thrombin burst, and promoting the formation of a stable hemostatic plug.¹² Recombinant FVIIa is approved for use in hemophilia with inhibitors but has been widely used anecdotally as an adjunct to the management of traumatic coagulopathy.^{13–16} In a large prospective phase 2 trauma trial, rFVIIa decreased blood loss in patients surviving the first 48 hours without significantly increasing thrombotic events.¹⁷ The CONTROL trial was therefore designed as a phase 3 trial of rFVIIa in severely injured trauma patients with life-threatening bleeding. It was designed to evaluate efficacy and safety in preventing death from hemorrhage, decreasing transfusions, and limiting organ failure complications.

METHODS

Trial Design

The CONTROL trial (registered at clinicaltrials.gov NCT00184548) was a prospective, randomized, double-blinded, multicenter (150 hospitals in 26 countries), placebo-controlled trial conducted from August 2005 to September 2008. An overview of the trial design is presented in Figure 1, but the trial design is described in detail elsewhere.¹⁸ It was designed to evaluate efficacy and safety of rFVIIa in patients with active hemorrhage caused by trauma who had already received 4 units of red blood cells (RBCs) but had not yet completed an eighth unit. Patients were randomized 1:1 to receive three i.v. doses of rFVIIa (200 $\mu\text{g}/\text{kg}$ at 0 hour, 100 $\mu\text{g}/\text{kg}$ at 1 hour and 3 hours) or placebo. The placebo contained the same formulation as the trial drug, except for the rFVIIa component. Both the placebo and rFVIIa were supplied as freeze-dried powder and were reconstituted with sterile water for injection. After reconstitution, the placebo contained calcium chloride, sodium chloride, glycyglycine, mannitol, and polysorbate 80. The trial drugs were provided by the Sponsor to the sites in patient-specific boxes that were provided with a unique identification box number. Randomization was conducted in random permuted blocks, with the allocation of every randomization block to a specific center. Eligible patients were randomized and assigned the lowest available randomization number. Randomization was confirmed through an interactive voice response system set up by the Sponsor who was accessible by telephone or the internet. The Sponsor was responsible for data management. Data were accrued on paper case report forms, source verified by



* Estimated time from injury to admission at investigative site was limited to a maximum of 4 hours

** Prior to Randomisation & Dosing, active hemorrhage was defined as either acidosis or hypotension or ongoing volume loading

*** First dose was to be administered as soon as possible upon the completion of 4 units of RBC and no later than at the completion of 8 units of RBC provided that all other entry criteria were met

**** Estimated time from injury to administration of first dose was limited to 12 hours

Figure 1. Trial schematic.

trial monitors, and site study personnel and entered into the Novo Nordisk clinical database by Novo Nordisk data management personnel. The authors designed the trial with assistance from the Novo Nordisk statistician and planned and wrote the article with full data access. Two of the authors (C.J.H. and B.B.) chaired the Steering Committee and assume responsibility for integrity and interpretation of the data.

Ethics and Safety Monitoring

The trial was conducted according to International Conference on Harmonization Good Clinical Practice standards.¹⁹ Protocols, amendments, and consents were approved by local Independent Ethics Committees/Institutional Review Boards. Written informed consent was obtained from patients or legally authorized representatives before enrollment. If authorized representatives were unavailable, patients could be enrolled according to the enrollment procedures as approved by the Independent Ethics Committees/Institutional Review Boards, which included reviews by independent physicians, judges, or ombudsmen. A Novo Nordisk safety committee periodically evaluated blinded safety data, and an Independent Data Monitoring Committee and an independent statistician (Novo Nordisk consultant but functioning independently and reporting data only to the Data Monitoring Committee) reviewed unblinded safety data at predefined intervals.

Trial Population

Blunt and/or penetrating trauma patients aged 18 years to 70 years were eligible if they had continuing torso and/or proximal lower extremity bleeding after receiving 4 units of RBCs despite standard hemostatic interventions. Acceptable markers for active bleeding were continuing hypotension (systolic blood pressure ≤ 90 mm Hg), acidosis (lactate > 6 mmol/L or base deficit ≥ 5 mEq/L), or intravenous fluid requirements of ≥ 1 L per hour to maintain vital signs before randomization. Patients who were moribund, had severe brain injury (Abbreviated Injury Scale score ≥ 4 or Glasgow Coma Scale [GCS] score always ≤ 5), or were injured > 12 hours before randomization or > 4 hours before hospital arrival were excluded.

Endpoints and Safety Assessments

The primary efficacy endpoint was tiered. The first-tier endpoint was superiority in all-cause 30-day mortality in blunt trauma; if the first-tier endpoint was not met, the second-tier primary conditional endpoint of noninferiority on mortality and superiority on durable morbidity was applied. Durable morbidity was defined as pulmonary and/or renal dysfunction at day 30. Predefined secondary endpoints included transfused units of RBC, fresh frozen plasma (FFP), platelets, cryoprecipitate, fibrinogen concentrate, and all allogeneic blood products at 24 hours and 48 hours after dosing and number of patients requiring massive RBC transfusions (defined as ≥ 10 units of RBC) at 24 hours. Other endpoints were number of patients with multiple organ failure (MOF)²⁰ or single organ failure (SOF)²¹ and days alive and free from MOF, SOF, intensive care unit (ICU), hospital or ventilator, and/or renal re-

placement therapy, through day 30. The GCS score was based on the highest score recorded for each subject. The Abbreviated Injury Scale score was based on a computed tomography scan. The attending trauma center surgeon or neurosurgeon evaluated and declared cases with severe brain surgery. Serious adverse events (SAEs) were assessed to day 90. Medical events of special interest were defined as thromboembolic events, disseminated intravascular coagulation, all fatalities, sepsis or septic shock, MOF, acute lung injury, and acute respiratory distress syndrome.

Patient Management and Oversight

To minimize the effects of local care variations on primary and secondary endpoints, we mandated the use of evidence-based guidelines and protocols (Appendix). Only operations controlling bleeding or tissue contamination were allowed in the first 24 hours. Operations reconstituting normal anatomy and/or mechanical function were deferred pending hemodynamic stability. This approach is referred to as “damage control” surgery.²² The use of blood products was restricted to evidence-based²³ indications in stable patients, but empiric blood product use was encouraged in unstable, bleeding patients. Evidence-based ICU ventilator management, including daily weaning trials, was used.²⁴ Independent physician specialists at the Vanderbilt Coordinating Center reviewed compliance and provided rapid feedback concerning adherence to enrollment and management guidelines to study sites. Site re-education was guided by the needs of the sites as identified by the Vanderbilt Coordinating Center review. Noncompliance resulted in re-education with possible center termination from the trial.

Statistical Analyses

Sample size calculations were based on comparisons of mortality for the intent-to-treat (ITT) population using the one-sided χ^2 test (significance level 2.5%). The aim was to detect a 16.7% mortality reduction with rFVIIa, assuming 30% mortality in placebo patients. Estimates were based on the outcomes of patients in the prior phase 2 trial¹⁷ as well as on outcomes of patients with similar entry criteria abstracted from three separate large trauma registries (M. Croce, University of Tennessee Health Science Center, Memphis, TN; R. Lefering, German Trauma Registry, University of Witten/Herdecke Cologne, Cologne, Germany; R. Lavery, UMDNJ-New Jersey Medical School, Newark, NJ, personal communications). The probability of demonstrating efficacy of the primary endpoint was estimated at 80.1% for a sample size of 1,276 blunt trauma patients.

The safety analysis set included all randomized patients receiving trial product. Demographic and baseline characteristics and transfusion requirements were presented for the ITT analysis set, and clinical outcomes were assessed for the subset of ITT patients who completed day 30. All analyses with the exception of 30-day mortality were assessed using two-sided superiority tests with a 5% significance level. Treatment differences in 30-day mortality were assessed

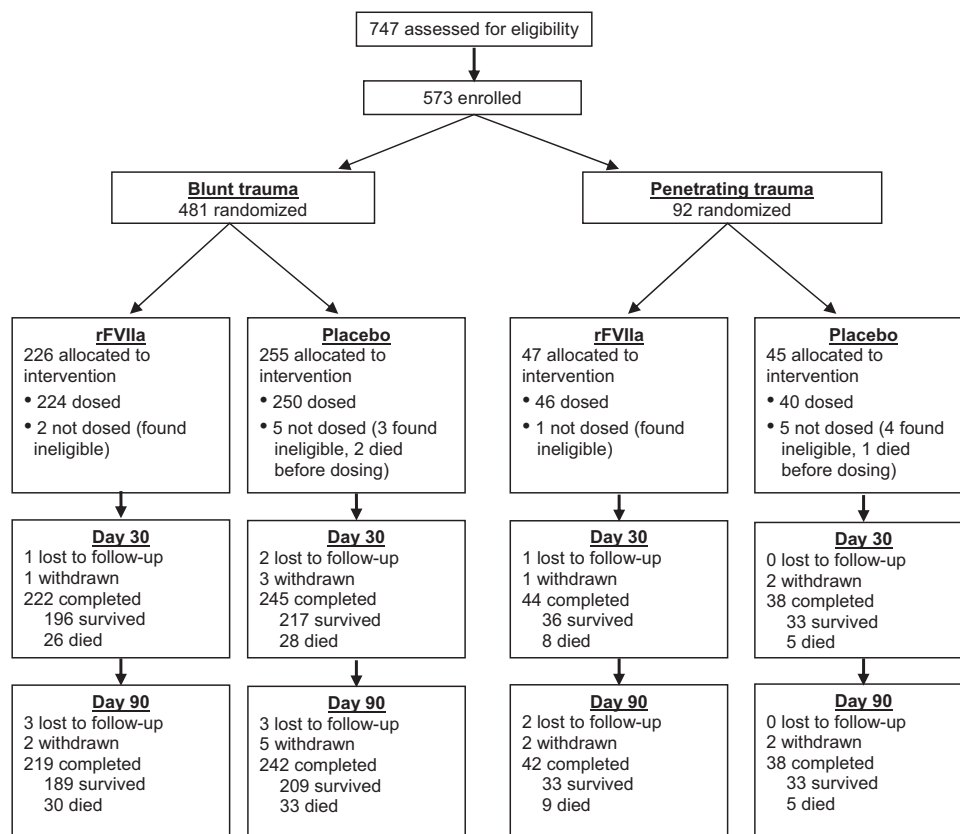


Figure 2. Subject disposition.

using both a two-sided superiority test and a noninferiority test, both with a 5% significance level. Mortality, MOF, and SOF rates through day 30 were compared using logistic regression with the following relevant baseline covariates: age, injury severity score (ISS),²⁵ GCS score, international normalized ratio, and acute lung injury (defined as $\text{PaO}_2/\text{FiO}_2$ ratio <300). Days alive and free of MOF, SOF, mechanical ventilation, renal replacement therapy, ICU, and hospitalization through day 30 were analyzed with the method of Schoenfeld and Bernard²⁶ using an analysis of covariance model with treatment as a factor and relevant baseline factors as potential covariates. Number of transfused units of RBC, FFP, platelets, cryoprecipitate/fibrinogen concentrates, and total allogeneic units transfused within 24 hours and 48 hours of trial drug were compared between treatment groups using the Wilcoxon-Mann-Whitney test (with an imputed value of 0 units for subjects who did not receive a transfusion of that particular blood product). No corrections were made for multiple comparisons, primarily because the transfusion parameters were highly correlated. Adverse events (AEs) were compared using the two-sided χ^2 test when expected cell counts were ≥ 5 and by a two-sided Fisher's test when expected cell counts were < 5 . A planned interim futility analysis of the blunt trauma mortality data was conducted. Initial statistical analyses were performed by the Sponsor and repeated by an independent statistician (George Howard, DrPH, Department

of Biostatistics, UAB School of Public Health, Birmingham, AL). The results of the analyses of the independent statistician are presented in this article.

RESULTS

The interim analysis of the mortality data from 447 blunt trauma patients showed lower than expected mortality rates. The power to demonstrate superiority of rFVIIa versus placebo was 11.2% (versus the predefined threshold of 50%). The trial was therefore stopped early (573 of 1502 patients) because of the high likelihood of futility in demonstrating the primary endpoint in the blunt trauma population.

Patient Enrollment and Characteristics

A total of 573 patients (481 blunt and 92 penetrating trauma) were enrolled and randomized, and 560 (474 blunt and 86 penetrating) were dosed (Fig. 2). Ten patients (5 blunt and 5 penetrating injury patients) were randomized but withdrawn from the study before trial product was administered because they were found to be ineligible. Three patients (2 blunt and 1 penetrating injury patients) died before trial product could be administered. Six rFVIIa-dosed patients with blunt injury were randomized but excluded from the ITT set because of inadequate informed consent. The ITT analysis set consisted of 221 rFVIIa and 247 placebo patients (blunt) and 46 rFVIIa and 40 placebo patients (penetrating). Of the blunt injury patients, 461 of

TABLE 1. Demographics and Baseline Characteristics (ITT Population)

Variable	Blunt Trauma		Penetrating Trauma	
	rFVIIa (n = 221)	Placebo (n = 247)	rFVIIa (n = 46)	Placebo (n = 40)
Male sex, n (%)	162 (73.3)	182 (73.7)	43 (93.5)	37 (92.5)
Age, yr	39.2 ± 14.3	39.9 ± 14.2	33.8 ± 11.9	29.4 ± 10.3
Race				
Caucasian	182 (82.4)	211 (85.4)	29 (63.0)	15 (37.5)
Black or African American	9 (4.1)	5 (2.0)	13 (28.3)	17 (42.5)
Asian	21 (9.5)	24 (9.7)	2 (4.3)	5 (12.5)
Other	9 (4.1)	7 (2.8)	2 (4.3)	3 (7.5)
ISS	32.8 ± 11.3	32.8 ± 11.5	20.5 ± 10.1	22.0 ± 8.9
GCS (admission)	13.0 ± 3.0	13.2 ± 2.9	13.6 ± 2.8	14.5 ± 1.0
Time from injury to first dose (h)	5.1 ± 2.6	5.4 ± 3.1	4.2 ± 2.5	5.2 ± 3.1
Vital signs (admission)				
SBP, mm Hg	100.9 ± 27.17	96.6 ± 26.29	105.6 ± 26.95	107.1 ± 24.13
Body temperature, °C	35.7 ± 1.2	35.6 ± 1.2	35.6 ± 1.4	35.8 ± 0.8
pH (30 min before randomization)	7.26 ± 0.09	7.25 ± 0.09	7.26 ± 0.11	7.28 ± 0.09
Hemoglobin, g/dL (admission)	9.7 ± 2.8	10.2 ± 2.9	10.3 ± 2.7	10.3 ± 2.8
INR (admission)	1.61 ± 0.77	1.49 ± 0.52	1.60 ± 0.97	1.60 ± 0.68
Lactate (30 min before randomization), mmol/L	3.64 ± 2.21	3.67 ± 2.18	5.43 ± 3.22	4.48 ± 2.18
Base deficit (30 min before randomization)	6.10 ± 3.04	8.66 ± 4.13	7.21 ± 4.10	6.51 ± 4.01
Total RBC before dose (units)	5.61 ± 1.46	5.59 ± 2.49	5.50 ± 1.62	5.35 ± 1.46

SBP, systolic blood pressure.

Values are mean ± SD unless otherwise specified.

474 dosed patients completed the trial to day 90 (including patients who survived or died but excluding patients who were withdrawn or lost to follow-up) (219 rFVIIa and 242 placebo). Of the penetrating injury patients, 80 of 86 completed to day 90 (42 rFVIIa and 38 placebo). The safety analysis set included 224 rFVIIa and 250 placebo blunt trauma patients and 46 rFVIIa and 40 placebo penetrating trauma patients. No subjects were de-enrolled because of noncompliance with the care guidelines. The subject distribution among study sites and countries followed one that was commonly seen in clinical trials.

As expected, the populations were young and predominantly male. Baseline characteristics of the treatment groups were similar for blunt and penetrating traumas (Table 1). There were no relevant differences in baseline ISS, GCS, blood pressure, hemoglobin, or markers of acidosis and coagulopathy between groups. Mean RBC transfusions before entry were 5.6 units in both blunt trauma groups and 5.5 versus 5.4 units in penetrating trauma patients receiving rFVIIa versus placebo.

Although consent from independent physicians or legal or judicial bodies accounted for 56% of all consents obtained in this trial, exception from consent procedures (21 CFR 50.24) was not used in the United States.

Blunt Trauma Population

There was no significant difference between 30-day mortality rates for blunt trauma patients receiving rFVIIa or placebo (11.0% vs. 10.7%; odds ratio: 0.97; 95% CI 0.53–1.80, $p = 0.93$) or durable morbidity rates at day 30 (8.7% vs. 9.5%, $p = 0.75$) (Table 2). Ventilator-free days and renal replacement therapy-free days through day 30 were similar in

both groups (rFVIIa: 17.2 days and placebo: 16.4 days) (Table 2). There was a trend toward decreased MOF rates in patients treated with rFVIIa (45%), compared with placebo (53%) ($p = 0.06$).

The major secondary endpoints were related to blood product use. The rFVIIa-treated blunt trauma group showed significant reductions in RBC, FFP, and total allogeneic transfusions (Table 3). Units transfused from dosing to 24 hours were 6.9 versus 8.1 for RBC ($p = 0.04$), 4.7 versus 6.9 for FFP ($p < 0.001$), and 17.1 versus 20.7 for total allogeneic products ($p = 0.03$) in the rFVIIa group, compared with placebo group, respectively. Similar results were seen from dosing to 48 hours, where rFVIIa-treated patients had fewer units of total transfused allogeneic blood products than placebo-treated patients (19.0 units vs. 23.5 units, respectively, $p = 0.04$). No significant differences were observed between groups for the use of platelets, fibrinogen concentrate, or cryoprecipitate.

No significant difference was seen in the safety profile of rFVIIa compared with placebo after blunt trauma. Physician-reported SAEs and prespecified medical events of special interest, including thrombotic events, were similar between treatments (Table 4). As expected, the total number of SAEs was high after blunt injury, and many patients had several SAEs: 348 SAEs were reported in 147 (65.6%) rFVIIa-treated patients versus 390 SAEs in 177 (70.8%) placebo-treated patients through day 90 ($p = 0.23$). Thrombotic AEs through day 90 were 45 events in 36 (16.1%) rFVIIa-treated patients and 35 events in 33 (13.2%) placebo-treated patients ($p = 0.38$). There were 16 arterial and 29 venous thrombotic events in the rFVIIa group versus 11 arterial and 24 venous

TABLE 2. Clinical Outcomes (30-d ITT Analysis)

	Blunt Trauma			Penetrating Trauma		
	rFVIIa (n = 218)	Placebo (n = 242)	p	rFVIIa (n = 44)	Placebo (n = 38)	p
30-d mortality, n (%)	24 (11.0)	26 (10.7)	0.93 [†] 0.37 [‡]	8 (18.2)	5 (13.2)	0.40 [†]
Durable morbidity*, n (%)	19 (8.7)	23 (9.5)	0.75	1 (2.3)	0	1.00
Days alive and free from ventilator/RRT through day 30, mean ± SD	17.2 ± 10.3	16.4 ± 10.3	0.31	21.2 ± 11.1	21.9 ± 10.0	0.73
Days alive and free of ICU through day 30	13.7 ± 10.4	12.9 ± 9.9	0.32	18.7 ± 11.2	19.5 ± 10.6	0.65
MOF through day 30§, n (%)	98 (45.0)	129 (53.3)	0.06	10 (22.7)	9 (23.7)	0.90
Days alive and free from MOF through day 30§, mean ± SD	24.6 ± 9.7	24.4 ± 9.4	0.66	24.1 ± 11.6	25.4 ± 10.2	0.45
SOF through day 30, n (%)	214 (98.2)	235 (97.1)	0.49	40 (90.9)	35 (92.1)	0.91
Days alive and free from SOF through day 30, mean ± SD	19.9 ± 8.9	19.5 ± 8.6	0.53	21.9 ± 11.1	23.1 ± 9.8	0.50
Days alive and free of hospital through day 30	4.0 ± 6.9	3.5 ± 6.4	0.39	13.2 ± 10.4	11.3 ± 9.1	0.71

MOF, multiple organ failure; SOF, single organ failure; RRT, renal replacement therapy.

Patients in the ITT analysis set were excluded from the 30-d ITT analysis set for the following reasons: blunt rFVIIa group: 2 withdrawn, 1 lost to follow-up; blunt placebo group: 3 withdrawn, 2 lost to follow-up; penetrating rFVIIa group: 1 withdrawn, 1 lost to follow-up; penetrating placebo group: 2 withdrawn.

*On mechanical ventilator and/or renal replacement therapy (RRT) at day 30. All analyses with the exception of 30-d mortality were assessed using two-sided superiority tests with a 5% significance level. Only 30-d mortality is tested for noninferiority.

†Treatment differences in 30-d mortality were assessed using both a two-sided superiority test (†) and a noninferiority test (‡), both with a 5% significance level.

§Denver organ failure score >3.

TABLE 3. Transfusion Requirements (ITT Population)

	Blunt Trauma					Penetrating Trauma				
	rFVIIa (n = 221)		Placebo (n = 247)		p [†]	rFVIIa (n = 46)		Placebo (n = 40)		p [†]
	N*	Mean ± SD	N*	Mean ± SD		N*	Mean ± SD	N*	Mean ± SD	
Units administered from dosing to 24 h										
Allogeneic transfusions	198	17.1 ± 26.8	228	20.7 ± 25.7	0.03	39	11.2 ± 15.0	35	16.8 ± 19.3	0.09
RBC	184	6.9 ± 10.4	222	8.1 ± 10.9	0.04	37	4.5 ± 7.3	33	6.2 ± 6.5	0.11
FFP	160	4.7 ± 6.4	188	6.9 ± 8.6	<0.001	29	3.8 ± 6.0	33	5.7 ± 6.4	0.04
Platelets	112	3.3 ± 8.4	117	3.4 ± 7.0	0.84	15	1.6 ± 3.7	21	2.5 ± 4.1	0.08
Fibrinogen concentrate	28	1.5 ± 6.7	28	1.3 ± 4.7	0.68	1	0.1 ± 0.4	1	0.4 ± 2.7	0.92
Cryoprecipitate	34	0.9 ± 3.3	41	1.3 ± 4.3	0.66	8	1.6 ± 4.1	11	2.0 ± 4.8	0.33
Units administered from dosing to 48 h										
Allogeneic transfusions	201	19.0 ± 27.1	231	23.5 ± 28.0	0.04	39	12.2 ± 15.7	37	18.4 ± 20.7	0.06
RBC	191	7.8 ± 10.6	228	9.1 ± 11.3	0.04	39	5.0 ± 7.4	35	6.8 ± 6.9	0.11
FFP	166	5.3 ± 6.7	195	8.0 ± 10.1	0.001	29	4.0 ± 6.2	33	6.5 ± 7.6	0.02
Platelets	117	3.7 ± 8.6	124	3.9 ± 7.8	0.95	16	1.9 ± 3.9	21	2.7 ± 4.1	0.12
Fibrinogen concentrate	29	1.5 ± 6.7	28	1.3 ± 4.8	0.59	1	0.1	1	0.4	0.92
Cryoprecipitate	34	0.9 ± 3.3	41	1.4 ± 4.5	0.64	8	1.6 ± 4.1	11	2.0 ± 4.8	0.33
Patients requiring massive RBC transfusion (≥10 units of RBC) from injury to 24-h postdose, n (%) [‡]	111 (50.2)		134 (54.3)		0.38	14 (30.4)		21 (52.5)		0.04

*N = numbers of patients receiving a transfusion of each agent (all allogeneic, RBC, FFP, platelets, fibrinogen concentrate, and cryoprecipitate). A value of 0 units was imputed for subjects who did not receive a transfusion of that particular blood product. The means are calculated for the entire n (blunt trauma: 221 rFVIIa patients, 247 placebo patients; penetrating trauma: 46 rFVIIa patients, 40 placebo patients).

†P value was calculated using Wilcoxon test, as the data were non-normally distributed.

‡An equal proportion of blunt trauma patients in the rFVIIa group (50.2%) and placebo group (54.3%) received massive transfusion. Statistically fewer penetrating trauma patients in the rFVIIa group (30.4%) than in the placebo group (52.5%) received massive transfusion, although the actual number of patients was small.

thrombotic events in the placebo group (Table 4). Post hoc analysis combining blunt and penetrating trauma patients showed a significantly greater number of acute respiratory distress syndrome events in the placebo group ($p = 0.022$) than in the rFVIIa group.

Penetrating Trauma Population

Patients with penetrating trauma were younger, predominantly male, and had lower ISS than patients with blunt trauma. The rFVIIa group was slightly older (34 years vs. 29 years) than the placebo group, but the penetrating trauma

TABLE 4. Adverse Events Through Day 90 (Safety Population)

	Blunt Trauma			Penetrating Trauma		
	rFVIIa (n = 224)	Placebo (n = 250)	<i>p</i>	rFVIIa (n = 46)	Placebo (n = 40)	<i>p</i>
Serious adverse events						
Patients with events, n (%)	147 (65.6)	177 (70.8)	0.23	18 (39.1)	20 (50.0)	0.31
Number of events	348	390		35	44	
Average number of events per patient	2.4	2.2		1.9	2.2	
MESIs*						
Patients with events, n (%)	89 (39.7)	100 (40.0)	0.95	13 (28.3)	10 (25.0)	0.73
Number of events	133	160		17	17	
Sepsis*						
Patients with events	33 (14.7)	45 (18.0)	0.34	4 (8.7)	2 (5.0)	0.69 [†]
Number of events	34	45		4	2	
All fatalities*						
Patients with events	30 (13.4)	33 (13.2)	0.95	9 (19.6)	5 (12.5)	0.38
Number of events	30	33		9	5	
MOF*						
Patients with events	10 (4.5)	17 (6.8)	0.27	1 (2.2)	1 (2.5)	1.00 [†]
Number of events	10	18		1	1	
ARDS*						
Patients with events	8 (3.6)	18 (7.2)	0.08	0	3 (7.5)	0.10 [†]
Number of events	8	19			3	
DIC*						
Patients with events	6 (2.7)	10 (4.0)	0.43	1 (2.2)	1 (2.5)	1.00 [†]
Number of events	6	10		1	1	
Thrombotic AEs*						
Patients with events, n (%)	36 (16.1)	33 (13.2)	0.38	2 (4.3)	4 (10.0)	0.41 [†]
Number of events	45	35		2	5	
Arterial thrombotic AEs, no. events	16	11	0.20	2	1	1.00 [†]
Venous TEs, no. events	29	24	0.25	0	4	0.04 [†]

*Based on local principal investigator reporting.

[†]*p* values are based on a two-sided χ^2 test when expected cell counts were 5 or more and by a two-sided Fisher exact test when expected cell counts were less than 5.

groups were otherwise very comparable, especially in terms of blood loss and shock (Table 1). The observed mortality rate in the ITT penetrating rFVIIa group was 18.2%, compared with 13.2% in the placebo group. This difference was not significant (*p* = 0.40) (Table 2). Durable morbidity was low in both rFVIIa and placebo groups (2.3% vs. 0.0%, *p* = 1.00).

In penetrating as in blunt trauma group, rFVIIa reduced transfusion requirements. The rFVIIa group showed consistent trends toward reduction in allogeneic blood product use from dosing to 24 hours and 48 hours, although many results did not achieve significance in these small sample groups (Table 3). The decreased FFP use in the rFVIIa group was significant; 3.8 units were administered versus 5.7 units in the placebo group (*p* = 0.04) from dosing to 24 hours and 4.0 units versus 6.5 units (*p* = 0.02) from dosing to 48 hours.

No differences were seen in the overall safety profile of rFVIIa compared with placebo after penetrating trauma. Physician-reported SAEs and thrombotic events showed no difference between groups, with the exception of venous thrombotic events, which occurred in significantly higher numbers in placebo-treated patients (*p* = 0.04) (Table 4).

Total reported SAEs were 35 in 18 (39.1%) patients (rFVIIa) versus 44 in 20 (50.0%) patients (placebo). Only 2 (4.3%) rFVIIa-treated patients reported thrombotic AEs through day 90 versus 4 (10.0%) placebo patients (*p* = 0.41).

DISCUSSION

The CONTROL trial was terminated early. Thus, it was underpowered for its primary endpoints, and the results should be interpreted in that context. Nonetheless, there are very few large, randomized trauma trials. So, there is much to be learned here. As with any new therapy, the evaluation of rFVIIa centers on three critical issues: First, does it demonstrate the expected effects? Second, is it safe? And third, in the aggregate, does it help patients?

An effective procoagulant is first and foremost expected to reduce blood loss and the need for blood products. We found that rFVIIa did reduce the need for blood products in bleeding trauma patients. The previous prospective rFVIIa trauma study¹⁷ used the per-protocol population to suggest similar conclusions; but the current study uses uncensored, ITT data to unequivocally demonstrate the hemostatic effect of rFVIIa in injured patients. It

can be argued that the sparing of blood products was modest, but multiple studies confirm that any decreased blood use is important in critical illness.^{10,11}

Our second critical evaluation was drug safety, and because the benefits of sparing blood use were expected to be incremental, it was especially important to identify any potential drug risks. Thrombotic complications are always frequent after major trauma,^{27–29} and any procoagulant therapy is expected to increase such thrombotic risk. Moreover, uncontrolled reports have suggested that excess thrombotic events are observed with rFVIIa use.^{30,31} Thus, it is very important that, although not powered for safety, two large, randomized, controlled trauma trials (the current trial and the trial by Boffard et al.¹⁷; a total of 837 subjects) have demonstrated no increases in thrombotic events where patients received rFVIIa rather than placebo. Because rFVIIa decreased blood product requirements without an observable increase in complications in this study, further studies seeking specific trauma populations in which to optimize the therapeutic profile of rFVIIa may be justifiable.

The third critical assessment was whether in the aggregate, rFVIIa could be shown to improve outcomes. No prevention of death and only a trend toward less-frequent MOF ($p = 0.06$) could be identified in the population studied at the current trial size. Survival benefits are intrinsically difficult to demonstrate in trauma because of the heterogeneity of trauma populations, but in this case, the study was also underpowered because patients did much better than expected. Nonetheless, because CONTROL was one of the largest prospective trauma trials ever performed, this unexpectedly low mortality rate is itself important. Placebo mortality rate had been predicted to be approximately 30% based on prior prospective study¹⁷ and registry data. Therefore, it was quite unexpected that the mortality was less than half that predicted (Table 2). Two possible explanations exist. First, suboptimal inclusion and/or exclusion criteria may have led to enrollment of a patient population at lower than expected risk. Although patients were enrolled after the receipt of 4 units to 8 units of RBC, only 30% of rFVIIa-treated patients with penetrating trauma and 50% with blunt trauma went on to require massive transfusion (Table 2). Also unfortunately, this is the population most likely to benefit from a hemostatic resuscitation intervention.^{16,32}

Second, better patient care due to application and oversight of “best-practice” protocols may have lowered mortality. The primary intent of our practice protocols had been to minimize variability in clinical outcomes due to variability in care within and among trial sites. However, the protocols also stressed aggressive, multidisciplinary “damage control” hemostasis, evidence-based ventilator management, and evidence-based blood product use (Appendix). Each of these was expected to have incremental effects on the outcomes studied. Moreover, center performance was tracked with rapid response oversight to ensure compliance. Thus, our evidence-based protocolized approach is likely to have had a major beneficial effect on the survival of bleeding patients even as it led to underpowering and early termination of the CONTROL trial.

We therefore now believe with current best practices, improved trauma survival due to the administration of any

one single agent is unlikely. Progress is likely to be incremental, with multiple small improvements in intermediate outcomes leading to improved global outcomes. Because its hemostatic effect is clear, the search for trauma patient subsets where rFVIIa may have more significant benefits should continue; recognizing that the risks of prothrombotic therapies must always be weighed carefully, and that where large vessel injuries are suspected, direct attack on bleeding sources should always be the first step in hemorrhage control.

APPENDIX: PATIENT MANAGEMENT PROTOCOLS

Guidelines for Management (Adapted from Rotondo et al. 1993)²²

- Attempted definitive management (Operative and/or Interventional Radiology) for bleeding injuries should begin within 2 hours 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., I&D 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 $35^{\circ}\text{C}/95^{\circ}\text{F}$.

Use of Aprotinin, activated Prothrombin Complex Concentrate, or Prothrombin Complex Concentrate is not allowed in this trial.

Transfusion Guidelines (Adapted from Hebert 1998)²³

Overall Transfusion Goals

Fluid resuscitation (administration of fluids and serial laboratory assay) must continue until the following goals are reached:

Lactate <2.5 mmol/L or
 Base deficit <2 mEq/L
 Within 24 hours of admission

The type of fluid administered should be adjusted to maintain the following standards:

Hemoglobin >8 g/dL and <10 g/dL for the first 24 hours or not yet euvolemic
INR <1.5 and/or PT <16 seconds and/or APTT <30 seconds and/or fibrinogen >100 mg/dL
Platelets >50,000/mm³

It is understood that the choice and timing of fluids administered and laboratory measurements must be adjusted to match the clinical situation, and that greater latitude in meeting these targets is appropriate early in resuscitation when clinical information may be limited or lacking.

Allogeneic and autologous transfusions of blood products comprises RBC, whole blood, cell saver chest tube drainage, FFP, platelets, or cryoprecipitates.

Transfusion Guidelines for RBC

The following transfusion guideline covers all RBC transfusions (autologous and allogenic) and whole blood and must be adhered to unless the clinical situation justifies deviations:

In patients hemodynamically unstable as defined by:

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”

In patients hemodynamically stable as defined by:

No SBP ≤90 mm Hg for 1 hour 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 investigator's 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

Site-specific definitions of hypoperfusion may be allowed in case of high altitude.

Transfusion Guidelines for Other Blood Products

The following transfusion guideline covers all FFP, cryoprecipitate, and platelet transfusion and must be adhered to unless the clinical situation justifies deviations:

In patients hemodynamically unstable as defined by:

SBP ≤90 mm Hg or
SBP is only maintained >90 mm Hg with massive fluids or vasopressor support
Blood products should be administered as determined by “clinical necessity”

In patients hemodynamically stable as defined by:

No SBP ≤90 mm Hg for 1 hour and
No resuscitation (or use of vasopressor support) (exception: use of low-dose vasopressor support for neurogenic shock)

With bleeding:

- INR >1.5 or PT >16 seconds: FFP at the discretion of the investigator
- Fibrinogen <100 mg/dL: Cryoprecipitate/fibrinogen concentrate at the discretion of the investigator
- Platelets <50,000/mm³: Platelets at the discretion of the investigator

Without bleeding, but still in the perioperative period:

- INR >2: FFP at the discretion of the investigator
- Platelets <50,000/mm³: Platelets at the discretion of the investigator

Without bleeding in the ICU:

- No blood product transfusion unless the clinical situation justifies deviations

Guideline for the Use of High Molecular Weight Colloids

The following guideline covers the use of Colloids/Plasma expanders and Dextran (or equivalent) and must be adhered to unless the clinical situation justifies deviations.

- Use of Colloids/Plasma expanders must be limited to no more than 2,000 mL within 24 hours
- Use of Dextran (and equivalent) is not recommended in the first 48 hours

Evaluation of Adherence to the Transfusion Guidelines

Compliance with transfusion guideline for the first 24 hours after randomization based on a standardized form listing.

The following data as part of the clinical surveillance will be forwarded to Novo Nordisk or designee no later than day 10 after the initial dose of trial drug for evaluation of adherence to transfusion guidelines (see section 21):

1. For unstable patients, the following information will need to be determined:

- SBP is ≤90 mmHg
- BP is only maintained with massive fluids or by using pressors
- Clinically determined massive bleeding

Approximate time period of instability is to be documented.

All blood products given during this inclusive time period are to be administered at the discretion of the treating Investigator as guided by clinical necessity. No further documentation is needed.

2. For stable patients, the following information will need to be determined.

2A. RBC transfusions in stable patients

- Hemoglobin <7g/dL (RBC to be given at Investigator's discretion)
- Hemoglobin 7–9g/dL (RBC to be given for evidence of hypoperfusion)

- Continued slow bleeding with downward trend in hemoglobin
 - Decreased urine output (U/O)
 - Heart rate >120 beats/min with adequate analgesia
 - Cardiac Index (CI) <3 L/m² with low wedge pressure (PCWP) or central venous pressure (CVP)
 - Low SaO₂ due to altitude, Acute Lung Injury (ALI)
 - Coronary or other organ ischemia syndromes
 - Other special circumstance—provide reason
- Hemoglobin >9g/dL reason to be documented
- 2B. FFP transfusions in stable patients:
- Patient still bleeding with INR >1.5 and PT >16 seconds (FFP given at Investigator's discretion)
 - Patient clinically not bleeding but continued perioperative risk
 - INR >2.0 per the discretion of the treating physician
 - Other special circumstances provide a reason
- 2C. Platelet transfusions in stable patients
- Any time perioperative: platelets <50,000/mm³
 - Other special circumstance—provide a reason
- 2D. Cryoprecipitate transfusions in stable patients
- Fibrinogen <100 mg/dL at the Investigator's discretion
 - Other special circumstance provide a reason

Ventilator Treatment and Weaning Guidelines (Adapted from NHLBI ARDS Network Ventilator Protocol)²⁴

Patients randomized in this trial requiring mechanical ventilation (by any mode) will be ventilated to achieve the following parameters:

1. Decreasing PEEP and FIO₂ as early as possible given oxygenation guidelines below
2. Limiting ventilation volumes to no greater than 6 ± 2 mL/kg predicted body weight as much as possible
3. Limiting plateau pressures to ≤30 cm H₂O whenever possible
4. Avoiding the use of muscle relaxants, except when specifically indicated
5. Attempting to wean on an ongoing basis, at least once daily when weaning criteria are met

Ventilator protocols at individual centers will be reviewed by the Steering Committee as part of the center selection criteria, for compliance with these broad guidelines.

Mechanical ventilation protocol

Requirement for ventilation treatment will be assessed each day between 06:00 and 10:00. If any procedure/test, or other extenuating circumstance, prevents assessment for these criteria between 06:00 and 10:00, then the assessment may be delayed for up to 6 hours.

Patients randomized in this trial requiring mechanical ventilation will be ventilated according to the following within 24 hours after meeting trial inclusion:

- a. Vt set at 6 ± 2 mL /kg predicted body weight (PBW) calculated as follows:
 For males: PBW (kg) = 50 + 2.3 [height (in.) - 60] = 50 + 0.91 (height (cm) - 152.4)
 For females: PBW (kg) = 45.5 + 2.3 [height (in.) - 60] = 45.5 + 0.91 (height (cm) - 152.4)
- b. Pao₂ 55–80 mm Hg or Spo₂ 88%–95%. Percent O₂/PEEP ratio to be = 5 ± 1. (i.e., patient with FIO₂ 50% and PEEP 12 cm H₂O and PEEP must be <35 cm H₂O if using a ventilator mode with PEEP).
- c. Keep pH 7.25–7.45 using respiratory rate (RR) ≤35 and PaCO₂ ≥25. HCO₃⁻ infusion may be given at the discretion of the bedside physician. If pH less than or equal to 7.15 then Vt may be increased by 1 mL/kg to achieve pH >7.15 and target plateau pressures (see below) may be exceeded.
- d. Keep plateau pressures (PP) less than or equal to 30 cm H₂O if necessary by reducing Vt to no less than 4 mL/kg. If Vt <6 mL/kg and PP <25 then increase Vt until PP = 25–30 or Vt = 6 mL/kg

Commencement of Weaning

Weaning readiness will be assessed each day between 06:00 and 10:00. If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 06:00 and 10:00, then the assessment and initiation of subsequent weaning procedures may be delayed for up to 6 hours. The patient is ready for a spontaneous breathing trial if all the following apply:

- FIO₂ ≤0.40.
- Ventilator support at minimal levels (PEEP or CPAP <10 cm H₂O, if using a ventilator mode with PEEP).
- Not receiving neuromuscular blocking agents and without neuromuscular blockade.
- Without anatomical lesions that preclude the ability to ventilate (e.g., spinal cord lesions, flail chest, abdominal hypertension).
- Patient exhibiting inspiratory efforts. If no efforts are evident at baseline, ventilator mandatory rate will be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory efforts.
- Systolic arterial pressure ≥90 mm Hg without vasopressor support (≤5 μg/kg/min dopamine or dobutamine will not be considered a vasopressor).

Spontaneous Breathing Trial

Initiate a trial of 30–120 minutes of spontaneous breathing with FIO₂ >0.5 using any of the following approaches:

- T-piece or tracheostomy mask
- Pressure support <10 cm H₂O without mandatory ventilation
- CPAP <10 cm H₂O without mandatory ventilation

Monitor for intolerance using the following. If the patient meets any of the three criteria, they are considered intolerant of weaning and must be placed back on ventilatory

support to be re-evaluated the next morning at the latest. Repeated earlier trials are acceptable at the discretion of the investigator.

1. SpO₂ ≤90% or PaO₂ ≤60 mm Hg.
2. Respiratory rate >35/min.
3. Respiratory distress (defined as marked use of accessory muscles or paradoxical breathing).

Decision to Remove Ventilatory Support

For intubated patients, if no intolerance criteria for spontaneous breathing are met for at least 30 minutes, the clinical team should discontinue assisted breathing. However, the spontaneous breathing trial can continue for up to 120 minutes if tolerance remains in question. If any of the criteria 1–3 above are met during unassisted breathing, then the ventilator settings that were in use before the attempt to wean will be restored and adjusted for comfort and the patient will be reassessed for weaning the following day.

Unassisted breathing is defined as tracheostomy tent, t-piece, extubated on room air or oxygen. Any amount of pressure support or tidal volume support regardless of method of delivery (e.g., noninvasive mask ventilation or endotracheal intubation) will be considered to be assisted ventilation.

Readiness for Extubation

The following criteria should be assessed to determine readiness for extubation:

- Does not require suctioning more than every 4 hours.
- Good spontaneous cough.
- Lack of upper airway obstruction, as evidenced by a leak around the endotracheal tube with the cuff deflated.

Completion of Ventilation

Patients will be considered to have completed the trial ventilator protocol if any of the following conditions occur:

- Death.
- Hospital discharge.
- Alive at day 30 after enrollment.

If, within 30 days of enrollment, a patient again requires positive pressure ventilation after a period of unassisted breathing, the trial ventilator protocol will be resumed.

ACKNOWLEDGMENTS

We thank all the investigators, patients, and study coordinators at each center for their contributions to this study.

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G. WHITAKER INTERNATIONAL BURNS PRIZE-PALERMO (Italy)

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By law n.57 of June 14th 1983 the Sicilian Regional Assembly authorized the President of the Region to grant the “Giuseppe Whitaker Foundation”, a non profit-making organisation under the patronage of the Accademia dei Lincei with seat in Palermo. The next G. Whitaker International Burns Prize aimed at recognising the activity of the most qualified experts from all countries in the field of burns pathology and treatment will be awarded in 2011 in Palermo at the seat of the G. Whitaker Foundation.

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