Five percent albumin for adult burn shock resuscitation: lack of effect on daily multiple organ dysfunction score

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BACKGROUND: The effect of 5 percent human albumin on multiple organ dysfunction was investigated during the first 14 days of treatment to determine whether albumin resuscitation might benefit adult burn patients.

STUDY DESIGN AND METHODS: Multicenter unblinded controlled trial with stratified block (two patients per block) randomization by center and mortality prediction at enrollment (high-risk stratum [predicted mortality, 50%-90%] and low-risk stratum [predicted mortality, <50%]). The primary outcome was the worst multiple organ dysfunction score (MODS), excluding the cardiovascular component, to Day 14. Eligible adults (>15 years) suffering from thermal injury not more than 12 hours before enrollment received fluid resuscitation with Ringer's lactate (n = 23) or 5 percent human albumin plus Ringer's lactate (n = 19) by protocol to achieve recommended (American Burn Association) resuscitation endpoints.

RESULTS: Forty-two patients were randomly assigned. There were no significant differences (median [95% confidence intervals]) in age (36 [24-45] vs. 31 [25-39] years), burn size (39 [32-53] vs. 32 [26-34] total body surface area percentage), inhalation injury (n = 12/19 vs. n = 11/23), or baseline MODS (3 [1-5] vs. 1.5 [0-2]) between the treatment and control groups. In an intention-to-treat analysis, there was no significant difference between the treatment and control group in the lowest MODS from Day 0 to Day 14 (analysis of covariance, p = 0.73).

CONCLUSION: Treatment with 5 percent albumin from Day 0 to Day 14 does not decrease the burden of MODS in adult burn patients.

The use of albumin for fluid resuscitation in critically ill patients continues to be controversial.¹ Meta-analyses in critically ill and other patient groups have yielded inconsistent results, suggesting that the treatment has either adverse effects² or no effect on mortality.³ Expert consensus statements continue to recommend the use of albumin in subgroups of critically ill patients such as patients with trauma or sepsis.⁴ They make appeals for improved clinical evidence to guide practice because the results of modern, large randomized controlled trials are often discordant with the results of meta-analyses of older, smaller clinical trials.⁵ A recent well-designed clinical trial of 4 percent albumin versus saline for fluid resuscitation in a large sample of critically ill patients showed equivalency for all important clinical outcomes, including death. Burn patients, however, were excluded.⁶ The only trial in an adult burn population to compare the use of albumin to crystalloid for fluid resuscitation was conducted more than 20 years ago.⁷ Another study compared three different resuscita-

ABBREVIATIONS: ANCOVA = analysis of covariance; AFR = additional fluid rate; BR = basal rate; ICU = intensive care unit; MODS = multiple organ dysfunction score; TBSA = total body surface area; TFV = transport fluid volume.

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tion formulas including albumin with hypertonic saline, nearly 30 years ago.⁸ Finally, the most recent study was conducted in pediatric patients, using albumin therapy solely to maintain serum levels.⁹ Because it is characterized by marked temporal and interventional heterogeneity, the existing evidence does not support confident recommendations for the use of albumin in burn patients.

We undertook the present investigation of the effect of albumin versus crystalloid-based resuscitation on clinical outcome in adult, critically ill burn patients to determine the feasibility of a randomized controlled clinical trial in this setting and to assess the safety and efficacy of albumin for this indication in the context of modern clinical practice. Acknowledging the difficulty of conducting a definitive efficacy study (with mortality as an endpoint) we chose to use the multiple organ dysfunction score (MODS)¹⁰ as our primary outcome. Other investigators have described the development of organ dysfunction in the natural history of burns and its association with mortality and morbidity.¹¹⁻¹³ These data and the relationship between adequacy of fluid resuscitation and organ dysfunction in burns led us to believe that MODS would be a clinically relevant surrogate efficacy outcome for our investigation.¹⁴

MATERIALS AND METHODS

Approval of study design

This prospective randomized controlled trial was reviewed and approved by all five institutional review boards for human research at each of the participating sites. Safety surveillance during the study was performed by the Bayer Biologics Division safety, efficacy, and data monitoring committee.

Selection criteria

From June 1999 to June 2001, patients who presented to the participating institutions with cutaneous thermal burns were assessed for possible enrollment. Our inclusion criteria were a thermal burn of at least 20 percent total body surface area (TBSA), assessed according to the Lund and Browder diagram; time elapsed since injury not more than 12 hours; written informed consent from the patient or a suitable substitute decision maker; and availability of data regarding fluids administered before arrival at the study center. Exclusion criteria were:

- Unlikely survival, defined by one or more of clinical judgment of the admitting physician, APACHE II score of greater than 30,¹⁵ or predicted mortality of at least 90 percent according to the method of Smith and colleagues.¹⁶
- Ventricular fibrillation, ventricular tachycardia, unstable angina, known congestive heart failure, or

myocardial infarction within the month before the thermal injury.

- Clinically significant ventricular dysfunction evidenced by history (decreased exercise tolerance, edema, orthopnea, paroxysmal nocturnal dyspnea), physical examination (increased jugular venous pressure, hepatojugular reflux, cardiomegaly, rales, S3 or S4 gallop), or laboratory testing (radionuclide ejection fraction); angiographic or echocardiographic left ventricular grade of at least II to IV; or ejection fraction of less than 0.35, angiographic (left ventricular end diastolic pressure >18, regional wall motion abnormalities, valvular stenosis or insufficiency).
- Severe underlying diseases or medical conditions, that is, trauma necessitating operation or transfusion, marrow transplantation, immunosuppression, or chemotherapy.
- Treatment with another investigational drug within 30 days.
- Electrical or chemical burn injury.
- Pregnancy.
- Infusion of synthetic starches or other colloids during preenrollment assessment.
- Documented allergic reaction to blood products or components.

Treatment assignments

Patients were allocated to study groups with stratified randomization with a computer-generated randomization list and sequentially numbered sealed, opaque envelopes. Randomization was stratified by center and mortality prediction in low- and high-risk strata: less than 50 percent predicted mortality and 50 to less than 90 percent, respectively.¹⁶

Study protocol

All patients received two fluids (Ringer's lactate and albumin, treatment; or Ringer's lactate and Ringer's lactate, control) through two independently controlled infusions (basal rate [BR] and additional fluid rate [AFR]) over two periods: not more than 24 hours after injury (resuscitation phase) and more than 24 hours after injury (stabilization phase; Fig. 1).

BR Ringer's lactate infusion: resuscitation and stabilization phases. The volume of all fluids given during $t = 0$ up to enrollment was totaled as "transport fluid volume" (TFV). By use of the surgeon's assessment of TBSA injured (TBSA% partial and full-thickness thermal wound) the BR infusion for the resuscitation period was calculated as

$$BR = [(2 \text{ mL} \times \text{body weight} \times \text{TBSA}\%) - \text{TFV}] / 24 \text{ mL/hour.}$$

Fig. 1. Overview of study design and plan. After randomization (R), the temporal relation to injury determined treatment fluid protocols until wound closure when treatment with the allocated resuscitation fluid stopped. Solid line = change in fluid administration rates after resuscitation; interrupted line = end of randomized treatment fluid administration.

If TFV exceeded $2 \text{ mL} \times \text{body weight} \times \text{TBSA}\%$, BR was set at a minimum rate to maintain infusion line patency until the beginning of the stabilization phase. When the stabilization phase was entered, the BR infusion was adjusted so that the total of BR Ringer's lactate and enteral feeding equaled 125 mL per hour.

AFR treatment fluid infusion: resuscitation and stabilization phases. Treatment fluid was given in an open label fashion owing to differences in the physical properties (color, tendency to bubble) and medium of delivery (glass vials vs. polymer bags) between Plasbumin-5 and Ringer's lactate, which we did not conceal from treating physicians and nurses. Ringer's lactate or Plasbumin-5 was given through the second, independently controlled infusion at an initial AFR rate of

$$[(2 \text{ mL} \times \text{body weight} \times \text{TBSA}\%)/24] \text{ mL per hour,}$$

so that the initial prescribed fluid volume for the first 24 hours, for both independent infusions totaled 4 mL per kg per TBSA%, the initial estimate recommended by the Parkland formula and American Burn Association (ABA).¹⁷ AFR was titrated to achieve American Burn Association–recommended resuscitation endpoints, which were a minimum mean arterial pressure of 70 mmHg and a minimum urine output of 0.5 mL per kg per hour. The AFR was adjusted according to urine output as follows:

1. If urine output was less than 0.5 mL per kg in the preceding hour, the AFR fluid volume and BR fluid volume for that hour were added and given as a bolus over 30 minutes. BR fluid infusion was left unchanged at its initial rate per hour.
2. If urine output was 0.5 to 1.0 mL per kg per hour for 2 consecutive hours, the AFR was reduced by 25 percent from the preceding hour's rate.

3. If urine output was 1.0 to 1.5 mL per kg per hour for 2 consecutive hours, the AFR was reduced by 50 percent from the preceding hour's rate.
4. If urine output was more than 1.5 mL per kg per hour for 2 consecutive hours, the AFR was reduced by 50 percent from the preceding hour's rate.

At 24 hours after injury (the beginning of the stabilization period), AFR was reduced by subtracting 125 mL per hour from the final AFR at the end of the resuscitation period. AFR adjustments were made according to the clinical judgment of the investigator. Attempts to decrease AFR by a minimum of 10 percent every 12 hours were recommended as a guideline provided that increased or ongoing fluid requirements

due to inhalation injury, surgery, or infection were either not present or anticipated. When AFR was not greater than 100 mL per hour for at least 12 hours, treatment fluid was discontinued as a continuous infusion. If additional fluid was subsequently required, it was given according to randomization until wound closure (defined as total open, ungrafted area of <5 percent TBSA).

Cointerventions during the study period. Standardized approaches to the critical care of the study population included a protocol for mechanical ventilation¹⁸ and for the administration of sedation, analgesia,¹⁹ and paralysis.²⁰ Enteral feeding was initiated at the beginning of the stabilization phase at 25 mL per hour and increased every 4 hours until the calculated target rate was achieved. If hypotension (mean arterial pressure <70 mmHg) or oliguria (<0.5 mL/kg/hr) persisted beyond 2 hours despite adjustment of the AFR, hemodynamic therapy with a pulmonary artery catheter according to a standardized hypotension protocol was recommended. Likewise, if patients demonstrated signs of excessive fluid resuscitation, such as atrial dysrhythmias, increase of FiO_2 of greater than 0.20 within a 24-hour period, decrease of PaO_2 -to- FiO_2 ratio by more than 25 percent of admission value, new onset of bilateral pulmonary infiltrate on chest radiograph or hypertension (defined as systolic blood pressure of >150 and diastolic blood pressure of >100 mmHg in the absence of stimulation) for 6 consecutive hours a standardized "overresuscitation" protocol was used.

Recommended wound care procedures were topical antimicrobial agents two times per day until early (2–5 days after injury) surgical excision of the burn wound. Management of the burn wounds with autograft, synthetic skin substitutes, or allograft, and subsequent wound care

were left to the discretion of the burn surgeons at each participating center. During surgery, the anesthesiologists were directed to continue fluid administration with the fluid to which the patient had been assigned at randomization and to avoid the use of synthetic colloid starches for volume resuscitation. Conservative red cell and blood product transfusion strategies were also recommended.²¹

Evaluation of patients

The *a priori* primary efficacy endpoint was the difference in the worst MODS between the treatment and control groups during Treatment Days 0 through 14, excluding the cardiovascular component. The full MODS score evaluates six organ systems with laboratory and simple clinical observations. These are PaO₂-to-FiO₂ ratio, serum creatinine, serum bilirubin, pressure-adjusted heart rate (heart rate times right atrial pressure/mean arterial pressure), platelet count, and the Glasgow coma scale. When entering data for MODS, study coordinators were instructed to use the worst values observed for each organ system during a given treatment day. A score, ranging from 0 to 4, quantifies dysfunction in each organ system. The score value corresponds to ranges of increasingly abnormal results in each organ system. The threshold corresponding to "failure" of an organ system is a score of 3. Delta MODS is the difference between baseline and subsequent daily worst values during the intensive care unit (ICU) stay. MODS is strongly correlated with ICU mortality. MODS scores between 9 and 12 are associated with mortality of approximately 25 percent and scores between 13 and 16 with 50 percent mortality.¹⁰ Secondary outcomes were mortality, duration of mechanical ventilation, length of ICU stay, local infection events, systemic infection events, percentage of graft take, and oxygenation failure (PaO₂-to-FiO₂ ratio), all evaluated up to and including Day 28.

Inhalation injury was diagnosed if patients had a history of smoke inhalation, physical signs, or carboxyhemoglobin levels of more than 20 percent on cooximetric blood gas analysis.²² Fiber-optic bronchoscopy was recommended as a confirmatory test but not mandated by the protocol. APACHE II and III scores were calculated according to published methods.^{15,23} Duration of mechanical ventilation was defined as the interval between intubation and successful completion of a 3-minute spontaneous breathing trial.²⁴ Percentage of graft take was assessed on the fifth day after autogenous skin graft by the surgeon. Graft take was defined as

$$[\Sigma(\% \text{BSA pink, good take areas}) / \% \text{BSA all grafted areas}] \times 100,$$

according to a validated scale for assessment of the grafted wound.²⁵ Local infection was defined as wound site infection requiring surgical intervention, a change in the type of dressing, or medical management. Systemic infection

was defined as bacteremia in two of two peripheral blood cultures.

Statistical analysis

The lowest MOD score recorded at any time from enrollment to Study Day 14 was the dependent variable. Data for calculation of the cardiovascular component of MODS (the pressure adjusted rate) were inconsistently collected, a deficiency noted during the study period by other investigators with the score.²⁶ Rather than impute normal values for missing data, we omitted the cardiovascular component of MODS in our calculations of total MODS.

Multiple regression was used for an exploratory analysis on the primary variable. The worst MOD score from enrollment to Day 14 was the dependent variable. Independent variables included treatment, center, baseline MODS, and mortality risk. Mortality risk was assessed in our analysis with the formula published by Ryan and coworkers²⁷ because (in contrast to the formula used for risk stratification at randomization) it incorporates inhalation injury as a risk factor for mortality. The chi-square test, Fisher's Exact test, Wilcoxon two-sample test, and analysis of covariance (ANCOVA) examined secondary efficacy variables, as appropriate.

RESULTS

The trial was suspended in June 2001 owing to slow enrollment, when 42 of 90 (the denominator was target) patients had been randomly assigned. No safety or good clinical practice issues were identified by Bayer Inc. monitoring committees before suspension of the trial. All randomly assigned patients were followed for the entire 28-day study observation period.

Baseline characteristics of the patients (Table 1)

The treatment (albumin and Ringer's) and control groups were comparable with respect to age and body habitus. Blood ethanol levels were zero in both groups at randomization, making interpretation of urine output during resuscitation free from confounding diuretic effects. The majority of patients were Caucasian men (79% treatment, 91% control). Predicted mortality (median) was 18.6 percent (95% confidence interval [CI], 9.9-38.2) for the treatment group and 9.4 percent for the control group (95% CI, 4.9-12.8). The difference in median predicted mortality was almost significant ($p = 0.06$). The lack of a difference in predicted mortality persisted in the two risk strata we used. The majority of patients in the treatment (16/19) and control (21/23) groups were stratified to the low-risk strata during block randomization. APACHE III (median) scores were comparable between groups and indicated moderate illness severity. Median baseline

TABLE 1. Baseline characteristics of the patients*

Characteristic	Treatment group, albumin and Ringer's (n = 19)	Control group, Ringer's (n = 23)
Age (years)	36 (24-45)	31 (25-39)
Height (cm)	177 (170-183)	178 (168-180)
Weight (kg)	80 (70-100)	82 (75-90)
TBSA (m ²)	2 (1.9-2.2)	2.0 (1.8-2.1)
Blood ethanol (mmol/L)	0 (0-0)	0 (0-0)
Race†		
Caucasian	13 (68)	18 (78)
African	1 (5)	2 (9)
Asian	0	1 (4)
First nations	1 (5)	0
Hispanic	2 (11)	1 (4)
Other	2 (11)	1 (4)
Sex†		
Male	15 (79)	21 (91)
Female	4 (21)	2 (9)
Predicted mortality (%)	18.6 (9.9-38.2)‡	9.4 (4.9-12.8)‡
Low risk†	16 (84)	21 (9)
High risk†	3 (16)	2 (9)
APACHE II	15 (11-27)	10 (10-14)
APACHE III	69 (44-89)	50 (41-85)
MODS	3 (1-5)	2 (0-2)
Burn injury cause†		
Flame	16 (84)	21 (91)
Scald	2 (11)	1 (4)
Other	1 (5)	1 (4)
Burn size (TBSA%)	39 (32-53)	32 (26-34)
Partial-thickness	14 (6-32)	20 (12-26)
Full-thickness	15 (0-43)	12 (0-20)
Inhalation injury†		
Yes	12 (63)	11 (48)
No	7 (37)	12 (52)
Mean arterial pressure (mmHg)	92 (77-113)	108 (95-129)
Urine output (mL)	68 (40-100)	100 (50-200)

* Data are reported as median (95% CI), except where noted.

† Data are reported as number (%).

‡ $p = 0.06$.

MODS indicated trivial organ dysfunction score: treatment group MODS 3 (95% CI, 1-5) and control MODS 1.5 (95% CI, 0-2). The mechanism of burn injury was similar between the treatment groups; flame burn was the most common type. TBSA burn and degree of full-thickness burn wound were similar: median full-thickness wound, treatment group 15 percent (95% CI, 0-43) and control group 12 percent (95% CI, 0-20).

Inhalation injury and diagnostic bronchoscopy were equally distributed between the two groups. Although a higher proportion of the treatment group had inhalation injury than the control group (treatment group, 12/19, 63%; control group, 11/23, 48%), the difference was not significant ($p = 0.37$). Mean arterial pressure (at enrollment) and urine output (total preceding enrollment) were comparable. No patients exhibited hypotension or oliguria according to American Burn Association definitions at time of enrollment.

Cointerventions during study (Table 2)

Treatment with study fluids (treatment group, Plasbumin-5; control group, Ringer's lactate) continued for a median duration of 3 days in both groups. The lowest daily values for mean arterial pressure and hourly urine output did not differ between groups and exceeded resuscitation endpoints from Day 0 to Day 14. There was no significant difference in the volume of fluid used for concomitant medications between the two groups (Plasbumin-5, median 8207 mL, 95% CI 2,941-23,948; Ringer's lactate, median 5277 mL, 95% CI 2,960-10,729; $p = 0.91$). Only one of the entire study cohort received treatment with an adrenergic agent. Use of H₂ receptor antagonists, proton pump inhibitors, and systemic corticosteroids (for any indication) did not differ between the treatment and control groups. Use of antibiotics for systemic infection did not differ significantly between groups (treatment, 13/19; control, 18/23; $p = 0.50$). Surgery for burn wound excision and grafting occurred on Day 6 (95% CI, 5-7) for the treatment group and Day 5 (95% CI, 5-6) for the control group. The percentage of body surface area excised and grafted at this operation approached 50 percent of the total burned area and did not differ significantly between groups.

Study fluid administration (Table 3)

In the resuscitation phase, total BR infusion volumes were not significantly different between the treatment and control groups ($p = 0.27$). There was a nonsignificant trend ($p = 0.42$) to administration of less total additional fluid as study drug in the treatment group (3355 mL; 95% CI, 2588-9183) compared to the control group (6178 mL; 95% CI, 3435-9481). Volume of additional "other" fluid for medications during the resuscitation phase was low in both groups and did not differ between them.

In the stabilization phase, the treatment group received less total BR infusion volume (1649 mL, 95% CI 0-2660 vs. 3358 mL, 95% CI 1875-4250) than the control group ($p = 0.02$). Total study fluid volumes also tended to be lower in the treatment group (232 mL, 95% CI 0-6079 vs. 2769 mL, 95% CI 0-14,314), but the trend was not significant ($p = 0.39$). The treatment group appeared to receive more total "other" fluid volume (7544 mL, 95% CI 1595-16,865 vs. 3194 mL, 95% CI 1642-23,085) but again this trend was not significant ($p = 0.58$).

Efficacy

Primary outcome measures

Worst MODS Day 0 to Day 14. Figure 2 shows a plot of daily aggregate MODS for the treatment (solid circles) and control (open circles) groups. There was no effect of treatment group ($p = 0.73$), center ($p = 0.97$), treatment by

TABLE 2. Cointerventions during the study*

Variable	Treatment group, albumin and Ringer's (n = 19)	Control group, Ringer's (n = 23)
Days on treatment	3 (3-6)	3 (3-5)
Other fluids (mL)	8,207 (2,941-23,948)	5,277 (2,960-10,729)
Adrenergic agents†		
Yes	1 (5)	0
No	18 (95)	23 (100)
H2-receptor antagonists†	13 (68)	18 (78)
Proton pump inhibitors†	0	3 (13)
Systemic corticosteroids†	2 (11)	4 (17)
Antibiotics†		
Topical	8 (42)	16 (70)
Systemic	13 (68)	18 (78)
Narcotics†	16 (84)	22 (96)
Benzodiazepines†	16 (84)	23 (100)
Blood transfusions†	1 (5)	3 (13)
Day‡ of surgery	6 (5-7)	5 (5-6)
Percentage of burned BSA excised§	45 (25-99)	42 (20-54)

* Data are reported as median (95% CI), except where noted.

† Data are reported as number (%).

‡ After injury, first wound debridement.

§ During first wound debridement.

TABLE 3. Study fluid administration*

Variable	Treatment group albumin and Ringer's (n = 19)	Control group Ringer's (n = 23)	P value
Resuscitation-phase infusions (mL)			
Basal	1,308 (480-1,980)	1,500 (720-2,450)	0.27
Treatment fluid	3,355 (2,588-9,183)	6,178 (3,435-9,481)	0.42
Other	1,820 (300-5,197)	1,039 (517-2,400)	0.67
Stabilization-phase infusions (mL)			
Basal	1,649 (0-2,660)	3,358 (1,875-4,250)	0.02†
Treatment fluid	232 (0-6,079)	2,769 (0-14,314)	0.39
Other	7,544 (1,595-16,865)	3,194 (1,642-23,085)	0.58

* Data are reported as median (95% CI).

† Wilcoxon two-sample test.

TABLE 4. Secondary outcomes*

Variable	Treatment group, albumin and Ringer's (n = 19)	Control group, Ringer's (n = 23)
28-day mortality†	3 (16)	1 (4)
Mechanical ventilation (days)	8.5 (3-14)	3 (0-14)
Length of ICU stay (days)	14 (7-31)	13 (10-29)
Local infection (events)	1 (1-2)	2 (1-3)
Systemic infection (events)	1 (1-2)	1 (1-1)
Percent graft take‡	95 (0-100)	54 (0-100)
Oxygenation failure†		
PaO ₂ -to-FiO ₂ ratio < 300	2 (11)	2 (9)
Oxygenation index (OI)‡		
OI > 25	4 (67)	2 (17)
OI ≤ 25	2 (33)	10 (83)

* Data are reported as median (95% CI), except where noted.

† Data are reported as number (%).

‡ OI = mean airway pressure × (FiO₂/PO₂) × 100. See Materials and methods for definition.

center ($p = 0.33$), or baseline MOD score ($p = 0.12$) when considered as sources of covariance in an ANCOVA model. When exploratory multiple regression analysis was performed, there was no significant difference between the treatment and control groups, considering baseline MODS ($p = 0.35$), treatment ($p = 0.77$), center ($p = 0.31$), or mortality risk ($p = 0.071$). Because we were concerned that the equation used for stratification might have underestimated baseline mortality risk, we repeated the regression analysis with the risk prediction model of Ryan and coworkers.²⁷ When the regression analysis was repeated, only mortality risk emerged as a significant source of variance ($p = 0.011$).

Delta MODS baseline to worst value at any time. Delta MODS, the daily differences between the day's MODS and baseline, are shown in Fig. 3. Differences in this variable, which quantifies worsening (positive delta MODS) or improvement (negative delta MODS) in organ dysfunction, were significant only on Day 5. At this time only, the treatment group demonstrated significantly more worsening of MODS than the control group (3.0 vs. 1.0; $p < 0.05$).

Secondary outcomes (Table 4)

Twenty-eight-day mortality was 3 of 19 in the treatment group and 1 of 23 in the control group ($p = 0.313$). Causes of death in the treatment group were 1 from acute respiratory distress syndrome and 2 from multisystem organ failure. The cause of death in the control group was multisystem organ failure. Median duration of mechanical ventilation in the treatment group was not significantly different from the control group (8.5 days vs. 3 days; $p = 0.27$). There were no significant differences in any of the secondary outcome variables. Median length of ICU stay was 14 days (95% CI, 7-31 days) in the treatment group and 13 days (95% CI, 10-29 days) in the control group. Rates of local and systemic infection were comparable. The treatment group had fewer episodes of bacteremia (3/19 vs.

Fig. 2. Worst daily MODS. Total daily MODS for the treatment (●) and control (○) groups. By use of worst MODS to Day 14 as the outcome variable, there was no effect of treatment group ($p = 0.73$), center ($p = 0.97$), treatment by center ($p = 0.33$), or baseline MODS ($p = 0.12$) when considered as sources of covariance in an ANCOVA model. * $p < 0.05$.

Fig. 3. Delta MODS. Differences in this variable that quantifies worsening (positive delta MODS) or improvement (negative delta MODS) in organ dysfunction were significant only on Day 5 (p value not adjusted for multiple comparisons). At this time, the treatment group demonstrated significantly more worsening of MODS than the control group (3.0 vs. 1.0) ($p < 0.05$). * $p < 0.05$.

12/23) than the control group ($p = 0.02$).

Complications

In the study's safety analysis the overall incidence of adverse events was comparable between groups. There were trends to fewer complications in some organ systems for the treatment group (Table 5). Both the treatment and the control groups demonstrated abnormal PaO_2 -to- FiO_2 ratio from Day 0 to Day 14 (Fig. 4). Median values were close to 300 for this period.

DISCUSSION

In this study, the use of 5 percent albumin as a component of a standardized fluid resuscitation protocol for adult, thermally injured patients was compared to standardized fluid resuscitation with Ringer's lactate alone. Our major findings are: 1) treatment with 5 percent albumin had no effect on the study's prospectively defined primary outcome, worst MODS from enrollment to Day 14; 2) temporal changes in MODS over the same period did not differ between groups; and 3) there was no significant difference in 28-day mortality between treatment and control groups. Our results therefore do not demonstrate improved efficacy as reduction in organ dysfunction with the use of 5 percent albumin in the resuscitation of adult burn patients. They also demonstrate that safety, whether framed as mortality or other complications, was not significantly impacted by the use of 5 percent albumin in adult burn shock resuscitation. Our finding that mortality was increased threefold in the 5 percent albumin group is of concern, however. Finally, because enrollment accumulated slowly at five centers over 2 years and the majority of the patients were at low mortality risk, we have demonstrated that clinical trials of fluid therapy in adult patients with high mortality risk (those most in need of innovative therapy) are unlikely to be feasible unless the scope of the investigation is much larger than the present.

TABLE 5. Adverse events*

Variable	Treatment group, albumin and Ringer's (n = 19)	Control group, Ringer's (n = 23)
Any event	13 (68)	18 (78)
Body as a whole		
Any	8 (42)	16 (70)
Edema	1 (5)	5 (22)
Sepsis	3 (16)	12 (52)
Cardiovascular		
Any	4 (21)	9 (39)
Hypotension	2 (11)	6 (26)
Tachycardia	1 (5)	6 (26)
Respiratory		
Any	10 (53)	13 (57)
Acute respiratory distress syndrome	2 (11)	2 (9)
Abdominal syndrome, acute	1 (5)	2 (9)
Renal		
Any	3 (16)	3 (13)
Failure	2 (11)	1 (4)
Oliguria	0	1 (4)
Infection	4 (21)	7 (30)
Metabolic hypoproteinemia	0	1 (4)

* Data are reported as number (%).

Fig. 4. Daily worst PaO₂-to-FiO₂ ratio. Both the treatment and the control groups demonstrated abnormal PaO₂-to-FiO₂ ratio from Day 0 to Day 14. Significant differences were observed on Treatment Days 1 and 7 only. *p < 0.05.

Treatment with 5 percent albumin has no effect on worst daily MODS or temporal changes in MODS from baseline (daily delta MODS)

We chose MODS rather than mortality as our primary outcome measure for two reasons. The first was pragmatic, based on the difficulties in conducting and supporting a large randomized controlled trial in burn patients with

mortality as the primary endpoint. If an absolute mortality risk reduction of 6 percent is taken as a clinically important benefit for adult burn patients with three validated risk factors for mortality,²⁷ the sample size required for a trial with a power of 80 percent with $\alpha = 0.05$ is 581 patients per group. For the more prevalent scenario, patients with one or two risk factors, the required sample size is even larger. The second reason for choosing MODS was that multiple organ dysfunction is a clinically relevant surrogate outcome and a common mode of death and morbidity in critically ill burn patients.¹¹⁻¹³ In critically ill burn patients, inadequate fluid resuscitation leading to base deficit is strongly associated with MODS.¹⁴ On the basis of evidence such as the effect of protein colloids on edema of nonburned tissues,²⁸ ischemia-reperfusion injury,²⁹ and bacterial translocation,³⁰ we speculated that the benefits, if any, of albumin over crystalloid-based resuscitation would manifest as a decreased burden of organ dysfunction.

Baseline MODS at enrollment on Day 0 was balanced between the treatment and control groups ($p = 0.1107$). Both groups demonstrated a progressive increase in organ dysfunction, followed by improvement to baseline by the end of the assessment period. We speculate our observation of an improvement in organ dysfunction in both groups reflects the effect of burn wound excision,³¹ which occurred at a median of 5 days after injury. When multiple regression analysis was applied to our primary outcome (worst MODS to Day 14), we found no effect of treatment, center, or treatment and center. In our initial analysis, mortality risk was calculated in the regression model with the equation we used for enrollment risk stratification.¹⁶ Mortality risk, then, was not a significant predictor of vari-

ance. Because this was unexpected, we repeated the regression analysis with a risk prediction model that incorporates inhalation injury.²⁷ Baseline mortality risk then became a significant predictor of variance in MODS. These observations; the temporal pattern of organ dysfunction and recovery in burn patients and the association of baseline mortality risk with subsequent severity of

organ dysfunction, are among the first to be presented in the literature to date with MODS in burn patients.

Limitations of our study

Our findings should be interpreted with awareness of the limitations in our study design. First, it is underpowered both for mortality and for our primary outcome. Our trial is one of the first to examine the incidence of MODS in burn patients. During its design, we could not perform an estimation of sample size for the primary endpoint. Next, open-label treatment fluid administration in our study could have introduced bias in study fluid administration and/or in outcome assessment. There were nonsignificant trends toward differences in the total treatment and other fluid volumes administered during the stabilization period (Table 3); in general, these were toward lower volumes of administration in the treatment (albumin and Ringer's) group. These results may represent operator bias in fluid rate adjustment owing to our open-label design. Study coordinators were instructed to enter the worst daily values of the individual components of MODS into the case report form. Because MODS (with the exception of the central nervous system component) is a score based on laboratory and physiological criteria, we are less concerned that open label administration of the study drug could have introduced bias into the outcome assessment. Although it is undeniable that their knowledge of treatment allocation could have introduced bias, the results do not show a significant difference in our primary outcome measure between the treatment and control groups. Our primary outcome assessment with MODS is limited by problems with its component scores. Marshall and coworkers¹⁰ noted in their study describing the MODS score that in half of all patients there was no central venous pressure measurement. Later, Cook and colleagues²⁶ abandoned the MODS cardiovascular score and replaced it with a simplified score that does not require measurement of central venous pressure in an investigation of baseline and serial component MODS scores. In our own study, we found that baseline MODS data were incomplete for this reason in 13 of 19 patients in the treatment group and 16 of 23 patients in the control group. We decided not to impute normal values for central venous pressure (CVP), and our data for MODS therefore exclude the cardiovascular component of the score. Finally, the generalizability of our findings is limited because we did not collect data on the screened but excluded population. This restricts our ability to make statements about the feasibility of future studies and the characteristics of our study population in relation to patients who were excluded or chose not to participate.

Our study sample is similar to other burn cohorts, such as the development and validation sets by Ryan and associates.²⁷ In a chart audit of all patients admitted from

1990 to 1994, the investigators found only 133 of 1665 patients with two or three risk factors for mortality. Similarly, the majority of our patients was young and had "critical" (>30 percent TBSA) burns that, nevertheless, were smaller than the defined cutoff for an increase in mortality risk. We sought to study patients with a moderate to severe burden of illness because we hypothesized that the special benefits of fluid resuscitation would have their greatest impact in such a population. Despite enrollment at five centers for a period of 2 years, our clinical trial failed to accumulate many with these criteria. This finding speaks to the difficulty of obtaining evidence of the efficacy and safety of albumin in a moderate to high-risk sample of patients.

In conclusion, we found no benefit from the use of 5 percent albumin resuscitation over crystalloid resuscitation in adults with moderate size major thermal injury. Treatment of these patients is likely to remain "evidence-guided" rather than "evidence-based" because a clinical trial of patients at greater risk is not feasible.

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