Burn patient characteristics and outcomes following resuscitation with albumin

Amalia Cochran*, Stephen E. Morris, Linda S. Edelman, Jeffrey R. Saffle

Burn Center at the University of Utah, Department of Surgery, University of Utah Health Sciences Center, Salt Lake City, UT, United States

1. Introduction

Resuscitation from burn shock remains one of the essential challenges of modern burn care. Improved understanding of the physiologic derangements resulting from burn shock has improved patient survival during the period after injury. In spite of widespread understanding of this physiology, resuscitation protocols for burn-injured patients vary greatly between institutions [1,2]. Perhaps most importantly, the impact of different resuscitation protocols on late organ dysfunction and clinical outcomes in burn patients is largely unknown.

The aim of resuscitation of the burn patient is to support the patient during an initial period of relative hypovolemia driven by massive shifts from the intravascular compartment to the interstitium. The most commonly used resuscitation fluids during the first 24 h following severe burn are crystalloids; lactated Ringer’s in particular is widely accepted as appropriate for initial resuscitation [1,3]. The role of colloids in burn resuscitation is less well defined [1,2]. A 1998 Cochrane review demonstrated increased relative risk of mortality in burn patients who received albumin versus patients who did not receive albumin [4]. Although the Cochrane reviewers called for urgent review of human albumin administration in critically ill patients, many burn units continue to use albumin as a component of their resuscitation strategy [5]. In fact, little further evaluation of the role of albumin in burn resuscitation has occurred.

* Corresponding author at: Department of Surgery, University of Utah School of Medicine, 30 North 1900 East, Room 3B313, Salt Lake City, UT 84132, United States. Tel.: +1 801 581 7508; fax: +1 801 587 9149.
E-mail address: amalia.coehran@hsc.utah.edu (A. Cochran).
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The goal of this case-control retrospective study was to compare outcomes in patients who did and did not receive albumin during their burn shock resuscitation. The primary outcome measure was mortality. Secondary clinical outcomes included time to resuscitation, ventilator days, and length of hospital stay. This study also compared complications between the two groups; these complications included development of ARDS, SIRS/sepsis, acute renal failure, and multisystem organ failure.

2. Materials and methods

The University of Utah Health Science Center Institutional Review Board provided approval for this project. All patients in the institution’s TRACS/ABA™ burn registry from 1998 to 2002 with greater than 20% total body surface area (TBSA) burn injury were reviewed. Patients who survived fewer than 48 h or who were not resuscitated on compassionate grounds were excluded. Patients who received albumin during their acute resuscitation from burn shock provided the primary study group (ALB). All inpatient burn admissions during the same time period that were within 10 years of age of each patient resuscitated with albumin were considered possible controls (CON). Controls were then selected from these age-defined subgroups based upon most similar TBSA burnt. We were unable to include inhalation injury in the matching due to a paucity of control patients with inhalation injury who matched albumin resuscitation patients appropriately by age and TBSA burnt.

Patient data acquired through chart review included age, TBSA burnt, admission serum lactate and base deficit, length of time to complete resuscitation, and fluid volume required for resuscitation. Serum lactate and base deficit were used as proxies for perfusion status in study patients, consistent with prior burn and critical care literature [6,7]. Baux index (age + TBSA burn injury) was calculated from chart review data. Chart review also provided outcome data including mortality, number of ventilator days, and hospital length of stay. Outcome data on presence of inhalation injury and development of ARDS or SIRS/sepsis were acquired from the institutional TRACS/ABA™ registry.

2.1. Resuscitation protocol

The resuscitation protocol used was derived from Parkland formula calculations, and Lactated Ringer’s (LR) was the primary resuscitative fluid. The protocol followed by nursing staff is shown in Fig. 1. Once patients were more than 12 h from the estimated time of their burn, those whose ongoing fluid requirement exceeded twice the volume calculated by the Parkland formula were considered candidates for resuscitation with albumin at the discretion of the attending burn surgeon. This usually consisted of altering the composition of resuscitation fluid to consist of 5% albumin at one-third the previous rate, and ongoing LR at two-thirds the current rate. As urine output improved, the total infusion rate was reduced, maintaining the ratio of albumin to LR (1:2). Albumin was stopped when patients were able to maintain urine output at their calculated hourly maintenance require-ment. For the purpose of this study, patients were considered resuscitated when maintenance fluids were initiated at the patient’s calculated rate (basal fluid requirement + evaporative water loss), as shown in Fig. 1. The volume of fluid required to achieve resuscitation was the amount of fluid received less urine output during the time period from admission to fluid conversion. Albumin was initiated within 24 h of injury in all patients who received albumin during resuscitation.

Presence of inhalation injury was defined by bronchoscopic evidence of carbonaceous particles in the airway, airway erythema or edema, or sloughing of tracheal or bronchial mucosa. ARDS and SIRS/sepsis were based upon identification in the institution’s TRACS/ABA™ registry which included any note of ARDS, SIRS/sepsis in the attending burn physician notes.

2.2. Statistical evaluation

Mean values are reported as mean ± standard deviation. Admission values of serum lactate and base excess, total hours to resuscitation, and total resuscitation volume in cases and controls were compared using paired Student’s t-tests. Paired Student’s t-test was also used to compare ventilator days and hospital length of stay between cases and controls. Chi square and odds ratios were used for the comparison of dichotomous outcome data between cases and controls. Multivariate logistic regression was used for the development of a mortality model. All data analysis was performed using SPSS 13.0 (SPSS, Inc., Chicago, IL). p-Values of 0.05 or less were considered significant.

3. Results

During the 5-year period of this review, 101 patients eligible for inclusion received albumin during resuscitation from their burn injury. All 101 patients were matched with controls based upon age and TBSA burnt. Baux index was calculated as age + TBSA burnt. The differences in age, total TBSA burn injury, and Baux index between the two groups were not statistically significant (See Table 1). Patients who received albumin had a larger mean full-thickness burn size (p < 0.001). Inhalation injury is another known risk for mortality in burn patients, and ALB and CON did not match well on this parameter. While 52 of the patients who received albumin were found to have inhalation injury, only 18 of the controls had evidence of inhalation injury (p < 0.001). Thirty-nine patients in the study were women, 20 of whom were in the group who received albumin.

Admission serum lactate and base deficit were used as proxies for tissue perfusion, with findings presented in Table 2. Admission serum lactate was significantly higher in patients who ultimately received albumin during resuscitation than it was in controls. However, mean base deficit did not differ significantly between the two groups.

Resuscitation variables compared between the cases and controls were the length of time to resuscitation and the mean fluid volume required for resuscitation (Table 2). Mean time to complete resuscitation in ALB was significantly
longer than in CON. In addition, ALB required more volume to achieve resuscitation than CON patients. On average, the control patients exceeded Parkland estimates of their resuscitation needs by 67%. The average resuscitation of the albumin patients was 137% over Parkland estimates. No control patient received albumin during the time frame that is encompassed by the extended resuscitation period of the study patients.

Fig. 1 – Acute burn resuscitation protocol for adults, university of Utah Burn center.

Table 1 – Demographic data

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<thead>
<tr>
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<th>CON</th>
<th>ALB</th>
</tr>
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<tbody>
<tr>
<td>Age (mean ± S.D.)</td>
<td>35.9 ± 21.0</td>
<td>37.9 ± 21.2</td>
</tr>
<tr>
<td>TBSA (mean ± S.D.)</td>
<td>39.9 ± 16.6</td>
<td>42.3 ± 18.4</td>
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<tr>
<td>TBSA full-thickness* (mean ± S.D.)</td>
<td>14.3 ± 20.6</td>
<td>22.8 ± 15.9</td>
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<tr>
<td>Baux index (mean ± S.D.)</td>
<td>75.9 ± 22.7</td>
<td>80.2 ± 25.6</td>
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</table>

* p < 0.001.
Number of ventilator days and length of hospital stay were secondary outcomes examined in this study. Ventilator days differed significantly between the cases and controls, with patients in the albumin group having a mean of 0.53 ventilator days per %TBSA burn and those in the control group having a mean of 0.39 ventilator days per %TBSA burn ($p < 0.001$). Patients who received albumin also demonstrated a longer length of stay in days per %TBSA burn than did those patients who did not receive albumin during resuscitation (1.05 versus 0.84, $p < 0.01$).

Development of SIRS/sepsis and the development of ARDS provide secondary clinical outcomes. As shown in Table 3, the rate of development of SIRS and sepsis did not differ between patients resuscitated with albumin and their matched controls. However, patients resuscitated with albumin were more than three times more likely than controls to develop ARDS (Table 3). In a multivariate logistic model of the development of ARDS that included use of albumin and resuscitation volume received, only inhalation injury was independently predictive of the development of ARDS (OR 7.2, 95% CI 3.2–15.9).

The primary outcome measure for this study was mortality. The study group of patients who received albumin during resuscitation had a mortality rate of 18.8%. The mortality rate of the control patients was 10.9%. This difference failed to achieve statistical significance (odds ratio 1.9, 95% CI 0.8–4.2). Due to the limited number of deaths in the study population, only three independent variables could be selected for the development of a multivariate logistic model. Therefore, the Baux index was used to incorporate both age and TBSA into the model as a single variable. The most intriguing mortality-related finding is the association of albumin use during resuscitation with decreased mortality that was demonstrated in a multivariate logistic model of mortality (Table 4). This model includes Baux index and inhalation injury as well, and demonstrates the statistical significance of these factors in the study patient population. The Nagelkerke $R^2$ for the model is 0.54; thus, 54% of the variability among observed deaths are explained by the model. In addition, the model correctly predicts 90% of all survivals and deaths in the study group.

### Table 2 – Perfusion and resuscitation variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Albumin</th>
<th>Control</th>
<th>$p$-Value</th>
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<tr>
<td>Admission serum lactate (mg/dL, mean ± S.D.)</td>
<td>3.6 ± 2.3</td>
<td>2.3 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission base excess (mg/dL, mean ± S.D.)</td>
<td>−4.8 ± 4.7</td>
<td>−4.2 ± 2.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Time to resuscitation (h, mean ± S.D.)</td>
<td>52.8 ± 39.9</td>
<td>36.3 ± 24.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume/kg/TBSA for resuscitation (mL, mean ± S.D.)</td>
<td>9.4 ± 6.4</td>
<td>6.4 ± 4.4</td>
<td>&lt;0.001</td>
</tr>
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### Table 3 – Development of preventable clinical events

<table>
<thead>
<tr>
<th>SIRS/sepsis rate (N)</th>
<th>ARDS rate (N)</th>
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<tbody>
<tr>
<td>Albumin patients</td>
<td>Control patients</td>
</tr>
<tr>
<td>56.4% (57/101)</td>
<td>53.5% (54/101)</td>
</tr>
<tr>
<td>1.12 (0.65–1.69)</td>
<td>3.13 (1.76–5.55)</td>
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4. **Discussion**

Due to a paucity of evidence-based literature, burn shock resuscitation remains an area of clinical practice driven primarily by local custom of treating units. Administration of colloids during resuscitation has been fraught with controversy in terms of therapeutic appropriateness and optimal timing. The 1998 Cochrane Review meta-analysis demonstrated increased mortality in burn patients who received human albumin during resuscitation, resulting in a call for an urgent review of albumin use during burn shock resuscitation [4]. The rhetorical impact of this review is troubling in light of the fact that only three burn studies were included, the total number of burn patients in these studies was only 163, and the principles used to justify albumin administration differed greatly among the studies. A more recent meta-analysis showed a reduction in major morbidity, including mortality, in critically ill patients who receive albumin for resuscitation in a variety of settings [6]. A 2001 review of burn units in the U.K. showed that albumin-based protocols persisted in 18 of 22 contacted facilities, and confirmed the absence of consensus about the use of albumin in resuscitation from burn shock [5]. The present study adds to the controversy over the role of albumin in burn shock resuscitation with the demonstration of an association of albumin with decreased mortality in burn patients. These results also add further credence to calls for systematic evaluation of the use of albumin in burn shock resuscitation, ideally through a multicenter prospective randomized trial.

This study has two substantial methodologic shortcomings, both predicated upon the limited number of patients available for matching during the time period of study. Matching was based upon TBSA injury, resulting in a disparity in the full-thickness injury between cases and controls. Had matching been based upon full-thickness injury, the controls would not have matched the albumin patients as well on TBSA. Although TBSA burn injury plays an identified role in mortality following burn injury, extent of full-thickness injury is generally considered indicative of injury severity [7,8]. Since the outcome of interest for this study is mortality, matching...
was based upon TBSA. Interestingly, the resuscitation volumes did not differ significantly between those patients who sustained full-thickness injury and those who did not (8.18 mL/kg versus 7.89 mL/kg, p = 0.80).

The most significant shortcoming of this study is the poor matching of cases and controls for inhalation injury. Inhalation injury remains the best predictor of mortality in burn patients besides age and TBSA burn [7,8]. Age and burn size were controlled in this study by successfully matching patients who received albumin with those who did not receive albumin during the resuscitation phase of the management of their burn injury. Matching patients for inhalation injury status was not possible in the matching process because it would have compromised the overall quality of the matches achieved using only age and TBSA burn. Inhalation injury was associated with the use of albumin, the development of ARDS, the number of ventilator days, and mortality in simple bivariate analysis. Further, the increased number of ventilator days in patients who underwent resuscitation with albumin is likely driven by the increased incidence of inhalation injury and ARDS in this patient group. The multivariate logistic model controls for each independent variable during model creation, thus minimizing the matching problem for inhalation injury. In addition, the multivariate logistic model demonstrates that inhalation injury was an independent risk factor for mortality in the study group.

A variety of factors in addition to inhalation injury are known to complicate resuscitation of burn patients, only some of which were addressed in the design of this study. Delay in resuscitation not only complicates resuscitation, but also increases mortality [9–11]. Paradoxically, excessive early resuscitation is also related directly to mortality, typically via mechanisms like secondary abdominal compartment syndromes [12–15]. Due to the large catchment area of our burn center and the great number of pre-hospital providers and referring hospitals involved in the care of these patients, precise data on time of injury, time of initiation of resuscitation, and early fluid volumes were often not available. Associated traumatic injuries may also complicate fluid resuscitation of burn patients and result in increased mortality [16,17]. Alcohol or drug intoxication at the time of injury can significantly impact the systemic inflammatory response seen with severe burn and subsequent mortality, and thus impact fluid volumes required for resuscitation and subsequent resuscitation [18,19]. Toxicology screens are not routinely obtained at admission to this burn center, so relevant data are not consistently available.

This study also demonstrated the presence of a significant difference between the admission serum lactate of patients who received albumin during resuscitation and those who did not. Elevated serum lactate suggests inadequate resuscitation, and the elevated admission lactate values in those patients who ultimately received albumin may be indicative of a need for more aggressive resuscitation. Admission base excess values were not significantly different between the albumin patients and the controls. Base deficit clearly provides an important indicator of tissue hypoperfusion and underresuscitation during the shock state in burn-injured patients, and may also serve as a marker for severity of injury, magnitude of physiologic insult, or both [22,23]. However, subsequent re-evaluation of the use of base excess and serum lactate values in prediction of mortality from burn injury has shown that only serum lactate had predictive value [24]. Although serum lactate and base excess may correlate well in hemorrhagic or septic shock, they remain independent variables in other forms of shock that are less congruent with systemic acidosis [24,25]. In burn patients, serum lactate likely provides the superior indicator of systemic hypoperfusion and underresuscitation.

Patients who received albumin in this study required more fluid and longer times to resuscitate than those who did not, again illustrating that albumin treatment may be indicative of increased injury severity or the need for more intensive fluid management. It is important to note that these are patients who were failing resuscitation prior to the addition of albumin to their resuscitation fluid regimen. The patients who received albumin also had a significantly higher incidence of inhalation injury than controls, with inhalation injury providing a known risk factor for increased fluid requirements during resuscitation [26,27]. A surprising finding in this analysis was the use of 6.4 mL/kg%TBSA for resuscitation in the control group, which amounts to 160% of Parkland estimate. Engrav et al. previously suggested that resuscitation in burn patients often far exceeds the Parkland estimate [20]. Further, although “fluid creep” – the use of excessive volumes for resuscitation – is deplored in some burn circles, this phenomenon is being documented with increasing frequency at many burn centers [20,28,29]. Explanations for the increased volume beyond Parkland estimates are multiple. The nature of severe burn may have changed significantly since the development of the Parkland formula; resuscitation of very large burns is now viable, and an increasing number of burns are associated with methamphetamine use [29,30]. In addition, burn care providers have become more aggressive with the administration of benzodiazepines and narcotics for sedation and pain control, which may result in additional fluid demands [21].

The multivariate logistic model of mortality including Baux index, inhalation injury, and albumin provides the most provocative finding of this study. Although the model does not completely explain mortality following burn injury, it does confirm that age, TBSA burn, and inhalation injury all provide significant increased risks for mortality in burn patients. When these factors were controlled, receipt of albumin during resuscitation demonstrated an association with decreased mortality. The patients who received albumin had more extensive full-thickness burn, increased incidence of inhalation injury, had higher admission serum lactate levels, and were more difficult to resuscitate than the controls. These differences may indicate that patients who received albumin were more severely injured than controls, yet their survival was not significantly different. Thus, receipt of albumin may have resulted in improved survival through some means not elucidated in the present study.

The ideal avenue for assessment of the question of the impact of albumin on mortality in burn injury remains a prospective randomized trial of albumin use in burn shock resuscitation. Any prospective evaluation should also include a cost analysis of albumin use. Until a prospective trial of the use of albumin in resuscitation of burn patients is conducted, the influence of this practice on patient mortality will remain ambiguous.
REFERENCES