

# Potential Use of Albumin Administration in Severe Sepsis

Tsann-Long Hwang\*

*Department of Surgery, Chang Gung Memorial Hospital, Chang Gung University, Taipei, Taiwan, R.O.C.*

## Introduction

Albumin administration for the treatment of critically ill patients is controversial, although it has been widely used by clinicians for more than half a century. A Cochrane review showed an increased rate of mortality in patients treated with albumin administration after a meta-analysis of 30 randomized controlled trials including 1,419 randomized patients.<sup>1</sup> However, when more studies were added into the meta-analysis, the adverse effect of albumin administration on mortality disappeared.<sup>2</sup> The reason for this was due to the inclusion criteria in studies being diverse and the infused fluid regimens varying widely among the included trials. A recent randomized controlled study (Saline versus Albumin Fluid Evaluation study) provided more data on 7,000 patients who were randomized to receive either albumin or normal saline as resuscitation fluid; the results showed that there was no significant difference in outcome between the 2 groups.<sup>3</sup>

## Hypoalbuminemia in Acute Illness

The normal serum concentration of albumin in healthy adults is approximately 3.5–5.0 g/dL. Hypoalbuminemia is quite common in critically ill patients, especially in severe sepsis. Increased mortality, morbidity, and prolonged ICU or hospital stay in acutely ill patients with hypoalbuminemia is well recognized.<sup>4,5</sup> The association between hypoalbuminemia and poor outcomes has caused most clinicians to administer exogenous albumin for their hypoalbuminemic patients.<sup>6</sup>

Several mechanisms may explain the protective effects of serum albumin. Serum albumin can maintain physiologic homeostasis. At reduced albumin levels, homeostatic functions may be impaired, resulting in the development or progression of pathologic processes

and poor outcome. The biologic actions of albumin have not been fully delineated. One action is the ability to maintain normal colloid osmotic pressure; reduction in osmotic pressure may cause edema.

The inflammatory processes during acute illness may induce hypoalbuminemia, and inflammatory mediators can increase vascular permeability to promote escape of circulatory albumin into the extravascular space. C-reactive protein is one marker of inflammation that has been proposed to account for the association between hypoalbuminemia and poor outcome.<sup>7</sup> It is possible that certain undetectable derangements in patients' inflammatory response may also cause the hypoalbuminemic effect.

Because of its high frequency in pathologic conditions, hypoalbuminemia is interpreted as a normal compensatory mechanism not requiring intervention. Albumin redistribution into the interstitial space may provide protection from the oxidative stress affecting extravascular tissues during disease states. Hypoalbuminemia-related reductions in osmotic pressure, intravascular antioxidative reserve, binding activity, and other protective effects of albumin in the plasma compartment still have difficulty to be a beneficial adaptation.

## Benefit of Albumin Administration in Patients with Hypoalbuminemia

There is not enough evidence to show that administering human albumin to replace the lost blood in critically ill or injured patients will improve survival when compared to giving normal saline. Trauma, burns or surgery can cause patients to lose large amounts of blood. Fluid resuscitation is used to help patients restore circulatory volume and hopefully reduce the risk of mortality. However, the results of previous clinical trials



\*Correspondence to: Dr Tsann-Long Hwang, Department of Surgery, Chang Gung Memorial Hospital, 199, Tunghwa North Road, Taipei 105, Taiwan, R.O.C.

E-mail: hwangtl@adm.cgmh.org.tw • Received: April 13, 2009 • Accepted: April 24, 2009

failed to show that albumin can reduce the risk of mortality. In addition, albumin is very expensive, and it may be better to use cheaper alternatives such as normal saline for fluid resuscitation.

Two types of evidence may support the adequacy of albumin replacement therapy for hypoalbuminemia. The first is the results from multivariate analysis of cohort study data collected for the purpose of evaluating the relationship between albumin level and outcome specifically in acutely ill patients, and the other is the findings of controlled trials evaluating the effects of correcting hypoalbuminemia on morbidity. Such evidence has not previously been systematically reviewed.

In one included cohort study of 9,352 cardiac surgical patients,<sup>8</sup> hypoalbuminemia was predictive of postoperative infection, and ICU stay increased more than fivefold in patients who developed infections ( $13.4 \pm 20.1$  days vs.  $2.5 \pm 3.8$  days;  $p < 0.001$ ). In another included cohort study of elderly hospitalized patients, hypoalbuminemia was associated with increased risk for delirium.<sup>9</sup> Mean hospital stay was 23.7 days for patients with delirium compared with 13.6 days for non-delirious patients. A morbidity benefit due to albumin therapy, if demonstrable, might improve the overall costs of care. Significant edema in patients with hypoalbuminemia may limit their mobility and prolong hospitalization. Savings resulting from a reduced morbidity rate may exceed the acquisition cost of albumin.

### Use of Albumin in Patients with Severe Sepsis

Administration of purified albumin is clearly effective in raising serum albumin levels. Even in patients with severe sepsis, a pathologic condition marked by increased vascular permeability, administration of albumin may produce a prompt and sustained rise in serum albumin concentration.<sup>10</sup> If serum albumin does indeed exert a protective effect, then exogenous albumin administration might benefit hypoalbuminemic patients. Furthermore, even if albumin level did reflect other upstream pathologic processes, albumin administration might be effective as a downstream intervention to interrupt the events culminating in poor outcome.

Chou et al<sup>11</sup> analyzed 143 patients with severe sepsis due to secondary peritonitis and found that albumin administration might reduce 28-day mortality in patients whose baseline albumin level was  $\leq 20$  g/L. They also concluded that albumin administration had no effect on patients whose baseline serum albumin

level was  $> 20$  g/L. Although their analysis was a retrospective study, they narrowed down the causes of patients with secondary peritonitis with sepsis. In addition, they found that albumin administration was helpful for these septic patients with severe hypoalbuminemia ( $\leq 20$  g/L). Their findings provide a clue for clinicians to make decisions on albumin administration for patients with severe sepsis.

### Future Prospects

Further prospectively well-designed, adequately powered, controlled clinical trials are necessary to determine whether or not correcting hypoalbuminemia is beneficial for acute illness. Before the results of such future studies, there does appear to be a coherent rationale for albumin administration therapy and no compelling basis to withhold albumin if it is clinically appropriate in severely hypoalbuminemic patients.

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