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# Chronic Albumin Infusions to Achieve Diuresis in Patients with Ascites Who Are Not Candidates for Transjugular Intrahepatic Portosystemic Shunt (TIPS)

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While transjugular intrahepatic portosystemic shunt (TIPS) is a common therapy for cirrhotic patients with diuretic-resistant or diuretic-refractory ascites, some patients are unsuitable for the procedure for technical or medical reasons. We report our experience with the use of chronic intravenous albumin infusions to achieve diuresis in this difficult patient population and review the historic experience of chronic albumin infusions as a treatment for ascites. Nineteen patients with cirrhosis and diuretic-resistant or diuretic-refractory ascites who were deemed unsuitable for TIPS received outpatient intravenous albumin infusions (50 g) weekly for at least 4 weeks. The following endpoints were retrospectively recorded: serum sodium, serum creatinine, blood urea nitrogen, hematocrit, bilirubin, albumin, international normalized ratio, body weight, and Model for End-stage Liver Disease (MELD) score. The contraindicatoins for TIPS included the following: portal vein thrombosis, two; advanced age, one; encephalopathy, nine; hyperbilirubinemia, five; and other, two. Compared to pretreatment, posttreatment weight decreased in 17 patients, remained unchanged in 0 patients, and increased in 2 patients. The overall mean change in body weight (before vs. after therapy) was 8 lb ($P < 0.05$). The only significant change in biochemistries was an increase in serum albumin from 2.5 g/dl before therapy to 3.5 g/dl after therapy ($P < 0.05$). We conclude that (1) recurrent intravenous weekly albumin infusions resulted in significant loss of edema and ascites as measured by loss of body weight, and (2) clinicians may want to consider chronic albumin infusions for selected patients with refractory ascites who are not candidates for TIPS.

**KEY WORDS:** ascites; cirrhosis; transjugular intrahepatic portosystemic shunt (TIPS); albumin; diuretics.

The standard treatment protocol for ascites caused by end-stage liver disease is typically a stepwise approach beginning with sodium restriction, diuretic therapy, and paracentesis (1, 2). For patients whose ascites is refractory to this approach a transjugular intrahepatic portosystemic shunt (TIPS) may be required. However, due to concurrent medical problems (advanced age, hyperbilirubinemia, encephalopathy) or abnormalities of the hepatic vasculature (portal vein thrombosis), some patients with refractory ascites are not able to undergo TIPS. Over the past several years, an increasing number of patients have presented to our center with refractory ascites and contraindications to TIPS. Since these patients had limited treatment options, we began to administer chronic, intermittent intravenous albumin infusions (50 g per week) as a potential therapy for refractory ascites. We have found this treatment to be efficacious in this group of patients and report our experience

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TABLE 1. LABORATORY VALUES AND WEIGHT BEFORE AND AFTER TREATMENT

| | *Na* | *Cr* | *BUN* | *Hct* | *Bili* | *Alb* | *INR* | *Weight* | *MELD* |
|---|---|---|---|---|---|---|---|---|---|
| Before | 133 | 1.08 | 19 | 36.0 | 3.9 | 2.5 | 1.6 | 187 | 15.1 |
| After | 135 | 1.06 | 21 | 33.7 | 5.4 | 3.5* | 1.6 | 179† | 16.3 |

*Note.* Na, serum sodium (mEq/L); Cr, serum creatinine (mg/dl); BUN, blood urea nitrogen (mg/dl); Hct, hematocrit (%); Bili, total serum bilirubin (mg/dl); Alb, serum albumin (g/dl); INR, international normalized ratio; weight, body weight (lb); MELD, Model for End-Stage Liver Disease score.
*$P = 0.005$.
†$P = 0.002$.

here. In addition, we review the literature documenting the experience of other groups demonstrating the efficacy of chronic albumin infusions as a treatment for ascites. Most of these studies were reported over 40 years ago and represent the initial experience with albumin as a therapeutic agent following its isolation and production in the 1940s.

## METHODS

This study was approved by the Colorado Multi-institutional Review Board (COMIRB). The medical records of all identifiable patients who received chronic, intermittent intravenous albumin infusions for the treatment of refractory ascites were reviewed. Patients were identified through review of patient charts, pharmacy records, and records of our outpatient infusion center. The following endpoints were measured before and after 8 weeks of therapy: serum sodium, serum creatinine, blood urea nitrogen, hematocrit, bilirubin, albumin, international normalized ratio (INR), body weight, and Model for End-Stage Liver Disease (MELD) score. Comparisons were made using Student's *t*-test with the Microsoft Excel (Microsoft Corporation, Redmond, WA) software.

## RESULTS

Complete clinical and laboratory data were available for 19 patients whose demographics were as follows: mean age, 54.5 years; male, 13; female, 6; HCV, 6; alcohol, 4; cryptogenic, 6; and other, 3. The indication for rejection for TIPS included the following: portal vein thrombosis, 2; advanced age, 1; encephalopathy, 9; hyperbilirubinemia, 5; and other, 2. Mean laboratory values and weight before and after treatment are listed in Table 1. The mean dose of aldactone pretreatment was 160 mg and furosemide was 90 mg. Compared to pretreatment, posttreatment weight decreased in 17 patients, remained unchanged in 0 patients, and increased in 2 patients. There were no apparent complications related to the infusions. The range of duration of treatment with albumin infusions was 4 weeks to 3 years.

## DISCUSSION

We found that chronic intravenous infusion of 50 g albumin per week was an effective therapy for many patients with refractory ascites who were unable to undergo TIPS. We believe that the most important endpoint is the loss of body weight after the initiation of therapy, which represents loss of ascites fluid and/or edema. However, the retrospective nature of this report did not allow us to prospectively record more sensitive measures of the physiologic effects of albumin such as urinary output and urinary sodium excretion.

The use of intravenous albumin as a treatment for ascites in patients with end-stage liver disease dates back 60 years. The military medical service initially developed albumin as a volume expander and was the first group to use albumin therapeutically. The first report of administration of albumin to patients with cirrhosis was published by Janeway *et al.*, who treated six patients with cirrhosis with 25 g albumin per day (3). The albumin solution used in their study was relatively high in sodium concentration, 0.3 M sodium chloride (compared to 0.14 M, the concentration of sodium in the blood). The range of treatment (described for only two of the six patients) was between 10 and 14 days and the total dose of albumin ranged between 250 and 350 g. These investigators were the first group to document that intravenous administration of albumin was associated with an increase in serum albumin level followed by a reduction in albumin levels to pretreatment values over a few weeks after cessation of therapy. Following this initial observation, a number of other physicians published their experience during the 1940s, 1950s, and early 1960s, describing the use of chronic albumin infusions in the treatment of ascites caused by end-stage liver disease, as reported in Table 2. During this era, the treatment options for ascites were limited to recurrent paracentesis, hospitalization for institution of strict dietary sodium restriction, and primitive mercurial diuretics. Thus, the use of albumin as a therapeutic agent for ascites was developed during a period of medicine when the treatment options for ascites were very limited. As noted below, the efficacy of albumin in the treatment of ascites was mixed, and with the development of effective and safe diuretics, the use of albumin in this setting largely disappeared after 1960. It is important to note that many of the early studies describing the use of albumin in the treatment of

TABLE 2. STUDIES OF CHRONIC ALBUMIN INFUSION IN PATIENTS WITH END-STAGE LIVER DISEASE

| *Author* | *Year* | *n* | *Duration of therapy* | *Response* |
|---|---|---|---|---|
| Janeway (3) | 1944 | 6 | — | Minimal |
| Faloon (4) | 1949 | 29 | Up to 8 mo | 44 immediate to delayed improvement, 56% failure or indeterminant |
| Havens (5) | 1950 | 8 | Up to 6 mo | 7/8 (88%) "varying degrees of disappearance of edema or ascites" |
| Patek (6) | 1948 | 3 | Up to 16 days | Negligible |
| Kunkel (7) | 1948 | 15 | Up to 16 mo | 14/15 (93%) resolution of ascites |
| Watson (8) | 1949 | 6 | Up to 11 days | Negligible |
| Dykes (9) | 1961 | 12 | Up to 32 mo | 7/12 (58%) "restored to normal life" |
| Thorn (10) | 1946 | 5 | Up to 27 days | 2/3 (67%), disappearance of "all clinical evidence of ascites" |
| Post (11) | 1954 | 34 | Up to 23 wk | 21/34 (62%) "loss of ascites and edema" |
| Schindler (12) | 1999 | 12 | Mean, 31 days | Significant body weight loss, 10.1 kg |
| Gentilini (13) | 1999 | 38 | Up to 2 years | Significant reduction in recurrence of ascites, readmission, and hospital days |

ascites are compromised by the following: primitive clinical descriptions of patients (associated with the limited diagnostic capabilities of medical care over 50 years ago), incomplete descriptions of treatment protocols, inclusion of patients with variable stages of liver disease, variable durations and doses of albumin, and concurrent administration of large amounts of intravenous fluid with the albumin (which may reduce the efficacy of albumin infusion). Despite these obvious limitations, these early studies, described below, are valuable, because they provide some insight into the potential efficacy of albumin as a treatment for ascites.

Faloon *et al.* described the treatment of 29 patients with cirrhosis and ascites with 25% albumin diluted with an equal volume of 5 to 10% dextrose solution (4). The goal of therapy was to raise the serum albumin to >3 g/dl until clinical improvement or death. Most patients received daily infusions of 75 g albumin and then, in the absence of a clinical response, 75 g albumin per week for up to 8 months. The range of treatment duration was 2 days to 8 months and the range of total albumin dose was between 150 and 4000 g. Patient responses were categorized as follows: 3 of 29 (10%) showed immediate improvement; 5 of 29 (17%), slow improvement; 5 of 29 (17%), delayed improvement or improvement only with low-sodium diet; 6 of 29 (21%), failure; and 9 of 29 (31%), indeterminate outcome.

Havens and Bluemle reported outcomes in eight patients with cirrhosis complicated by ascites and edema (5). These patients were administered 25 to 50 g of 25% albumin at intervals from daily to three times a week for up to 6 months. A mercurial diuretic (mercupurin; Campbell Products, New York) was given intravenously after each albumin administration at an unspecified dose. No restriction of sodium or fluid intake was specified. They judged that seven of eight (88%) of the patients had "improvement manifested by varying degrees of disappearance of peripheral edema or ascites," which occurred within 3 weeks in five patients and over many weeks in the remaining patients. Three of the eight patients developed hematemesis, which the authors speculated could have been due to increased blood volume from the albumin infusions.

Patek *et al.* treated three cirrhotic patients with albumin (200 ml of 25% albumin in 0.3 M sodium chloride) for up to 16 days (6). These patients had "persistent ascites, hypoalbuminemia and minimal edema" and had been hospitalized for between 7 and 21 months prior to initiation of therapy. During the period of albumin infusions, all of these patients underwent recurrent paracentesis, which compromises the assessment of the therapeutic benefit of albumin. Overall, these three patients showed negligible benefit, and according to the authors the patients "neither sustained diuresis nor disappearance of ascites."

Kunkel *et al.* reported the outcomes in 17 patients with cirrhosis, 15 of whom had ascites. The patients were administered 25 g of albumin in 100 ml of intravenous fluid (see below) for up to 80 administrations at unspecified time intervals (7). The range of treatment was 4 days to 16 months. The albumin solution included 0.6 to 0.9 g sodium per 100 ml for some patients and 0.3 g sodium per 100 ml for others. Salt was not restricted in the diet. Five of the patients were treated "soon after the onset of ascites," four had ascites "present constantly for more than 5 months," and six patients had albumin levels <2 g/dl and "extremely severe cirrhosis" or "fatal subacute infectious hepatitis with large amounts of edema associated with ascites." Fourteen of 15 (93%) experienced resolution of ascites. Two patients developed "esophageal hemorrhage" during albumin therapy, which the authors suggested could be a side effect of the treatment.

Watson *et al.* treated six patients (three with alcoholic cirrhosis, two with cirrhosis due to "sporadic infectious hepatitis," and one with "homologous serum hepatitis" (8). Albumin was administered at doses of 25 to 100 g, diluted in 500 to 1000 ml 5% dextrose at 250 ml/hr. The range

of treatment was between 5 and 11 days and the range of total dose of albumin was between 300 and 1000 g. These investigators reported no benefit attributable to albumin, although one patient had complete resolution of ascites that was ascribed to spontaneous recovery by the authors. In addition to the infusion of albumin, the treatment protocol for these patients included a large volume of intravenous fluid, which could have offset the diuretic effects of the albumin.

Dykes infused albumin doses of 25 to 100 g (in 100 ml 5% dextrose solution), up to 5400 g, at unspecified intervals, up to a duration of 32 months, in 13 patients with cirrhosis of whom 12 had "ascites or edema of disabling proportions which it had proved impracticable to control other than by keeping the patient in the hospital" (9). These patients were quite ill: mean serum albumin was 2.1 g/dl, and mean bilirubin 5.5 mg/dl. All but three patients were maintained on sodium restriction and only one patient received diuretics. Three patients died over the short term, but of the 10 remaining, 7 showed remarkable improvement and were "restored to their normal life." "Major episodes of gastrointestinal hemorrhage" were reported in three patients, two of which were due to esophageal varices during a total of 128 patient-months of follow-up. According to the authors, the contribution of the albumin infusions to these bleeding complications was not clear.

Thorn *et al.* described results of albumin infusion in five patients with cirrhosis complicated by hypoalbuminemia, edema, and ascites (10). Patients were maintained on a diet of 1–2 g sodium per day. Albumin was given as 50 g in a 10% albumin solution in 6% dextrose each day for 3 days and, in three patients, 50 g each day for up to 27 days, for a total dose of between 425 and 500 g albumin. Two of these three patients showed a disappearance of "all clinical evidence of ascites" and the remaining unresponsive patient was found to have peritoneal metastases at autopsy.

Post *et al.* reported clinical outcomes in 34 patients "critically ill with cirrhosis of the liver, hypoalbuminemia and ascites" who received albumin sufficient to maintain a normal serum albumin concentration for extended periods" (11). Dietary sodium was between 2.5 and 3 g daily. Albumin was administered at 25 g daily in 100 ml of intravenous fluid (not otherwise specified), then twice daily and thereafter to maintain serum albumin levels of between 4 and 5 g/dl. The range of treatment was between 1 and 23 weeks, and the range of total dose of albumin between 625 and 3600 g. All but eight patients received concomitant mercurial diuretics. The criteria for improvement were "gain in appetite, body tissue and strength, decreasing icterus and loss of ascites and edema. Excepting the changes in jaundice, by these standards 21 of the 34 patients improved during the period of therapy." Five patients experienced gastrointestinal bleeding during therapy, four from esophageal varices and one from gastric ulceration.

Schindler and Ramadori treated 12 patients with refractory ascites with a mean of 22.1 g/day of intravenous albumin for up to 31 days (12). The dosing of albumin was not specified. These investigators demonstrated a mean loss of body weight of 10.1 kg and a significant improvement in urine sodium excretion, urine output. and serum albumin levels (8). During treatment, the mean daily dose of aldactone decreased from 222 to 133 mg and the mean dose of furosemide from 32 to 5 mg.

The most definitive study measuring the effect of long-term albumin infusion was performed by Gentilini *et al.*; 81 patients who failed to respond to bedrest and sodium restriction were randomized to diuretic therapy or diuretic therapy with albumin infusions (25 g/week for 1 year followed by 25 g every 2 weeks for up to an additional 2 years) (13). Thirty-eight patients were randomized to diuretics only (group A), and 43 to diuretics with albumin infusions (group B). The recurrence of ascites was significantly higher in group A patients (82%) compared to group B (49%; $P < 0.03$). The cumulative probability of readmission for ascites and number of hospital days were also significantly higher in the patients not receiving albumin ($P < 0.03$). The incidence of complications of liver disease (24 vs. 28%) and mortality (24 vs. 26%) was not different between the two groups. No complications related to albumin infusion were noted. In the accompanying editorial, Blendis and Wong commented that despite the evidence of clinical improvement with long-term administration of albumin, "the benefit [of this treatment] is less clear since such management of ascites is just not practical and, together with albumin administration every 1–2 weeks, too expensive" (14).

What can one conclude from the experience reported in the clinical experience of albumin administration in patients with cirrhosis and ascites? There is only one randomized, controlled trial study which demonstrated a significant benefit associated with the long-term administration of albumin relative to clinically relevant endpoints (resolution of ascites, readmission, and hospital days). The remaining reports are case series from which no definitive conclusion can be made. However, the data suggest that short-term administration of albumin (less than 16 days) was uniformly associated with negligible clinical effect. However, a substantial proportion of the patients treated for longer periods of time (27 days to several years) showed clinical improvement (between 44 and 93%). We believe that collectively the data from all of these

studies suggest that long-term administration of albumin may be an effective therapy for selected patients with refractory ascites. However, definitive data are very limited and available from only one randomized, controlled study.

Some of the patients in our cohort reported an increased sense of well-being after receiving an albumin infusion which lasted up to 1 week following the infusion. In fact, some patients requested increased frequency of the infusions based on this response, which seemed to be independent of diuresis. Other investigators have made similar observations. Dykes reported: "The gain in well-being was much greater than could be accounted for by the hope generated by a new form of therapy, and indeed was independent of its success or failure, occurring as commonly in those who had a successful diuresis as in those who did not" (9). Kunkel *et al.* found that "a number of patients volunteered the information that they developed a feeling of well-being following the administration of albumin, despite the fact that no diuresis occurred" (7). Whether these observations have a physiologic basis or represent "the placebo effect" is not known.

The use of albumin for patients with cirrhosis began over 50 years ago, because of the absence of any of the modern treatments for ascites: effective oral diuretics, TIPS, and liver transplantation. Currently, many hepatologists are treating a growing number of patients waiting for liver transplantation in whom diuretics are ineffective or associated with serious side effects and TIPS may be contraindicated due to technical considerations or severity of underlying liver disease. In this desperate group of patients who have no options other than recurrent paracentesis, physicians may want to consider the chronic administration of albumin, thus reverting to therapy that was successfully used by their predecessors over a half-century ago.

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