Albumin Dialysis for Liver Failure: A Systematic Review

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Albumin dialysis is the best-studied extracorporeal nonbiologic liver support system as a bridge or destination therapy for patients with liver failure awaiting liver transplantation or recovery of liver function. We performed a systematic review to examine the efficacy and safety of 3 albumin dialysis systems (molecular adsorbent recirculating system [MARS], fractionated plasma separation, adsorption and hemodialysis [Prometheus system], and single-pass albumin dialysis) in randomized trials for supportive treatment of liver failure. PubMed, Ovid, EMBASE, Cochrane's Library, and ClinicalTrials.gov were searched. Two authors independently screened citations and extracted data on patient characteristics, quality of reports, efficacy, and safety end points. Ten trials (7 of MARS and 3 of Prometheus) were identified (620 patients). By meta-analysis, albumin dialysis achieved a net decrease in serum total bilirubin level relative to standard medical therapy of 8.0 mg/dL (95% confidence interval [CI], −10.6 to −5.4) but not in serum ammonia or bile acids. Albumin dialysis achieved an improvement in hepatic encephalopathy relative to standard medical therapy with a risk ratio of 1.55 (95% CI, 1.16-2.08) but had no effect survival with a risk ratio of 0.95 (95% CI, 0.84-1.07). Because of inconsistency in the reporting of adverse events, the safety analysis was limited but did not demonstrate major safety concerns. Use of albumin dialysis as supportive treatment for liver failure is successful at removing albumin-bound molecules, such as bilirubin and at improving hepatic encephalopathy. Additional experience is required to guide its optimal use and address safety concerns.

Key Words: Liver failure, Albumin dialysis, MARS, Prometheus, First-pass albumin dialysis

INTRODUCTION

Over the past several decades, a number of extracorporeal liver support therapies have been conceived to either bridge patients with liver failure to transplantation or serve as potential destination therapies for patients with acute or fulminant hepatic failure while awaiting tissue regeneration and recovery of liver function. These extracorporeal therapies are divided in 2 major categories, biologic and nonbiologic support systems. Biologic systems incorporate liver cells or tissues that simulate the excretory, synthetic, and metabolic functions of the liver,[1,2] whereas nonbiologic systems use artificial membranes and adsorbents to detoxify the blood in patients with liver failure. Albumin dialysis is the best-studied and most promising nonbiologic system and is based on the removal of unwanted albumin-bound and water-soluble substances, such as bilirubin, bile acids, ammonia, nitrotyrosine, and fatty acids. There are 3 available albumin dialysis systems (Fig 1)[3]: the molecular adsorbent reticulating system or MARS (Teraklin, Rostock, Germany), single-pass albumin dialysis (SPAD), and the Prometheus system (Fresenius, Bad Homburg, Germany).

MARS is a commercially available albumin dialysis system that removes protein-bound and water-soluble toxins. It comprises 2 separate dialysis circuits (Fig 1A); the first circuit contains exogenous human serum albumin, which is in contact with the patient's blood through a semipermeable membrane (molecular weight cutoff of 50-60 kDa). Water-soluble and protein-bound toxins in the blood pass through this membrane. The toxin-enriched albumin solution is then passed through another dialyzer to remove water-soluble toxins using a counter-current bicarbonate-based dialysate. Albumin-bound toxins are removed by 2 adsorbent cartridges that contain activated charcoal and an anion exchanger. The regenerated albumin solution is then ready for new uptake of toxins from the blood. Although MARS has been used in Europe for the treatment of acute-on-chronic liver failure, severe alcoholic hepatitis, severe pruritus because of cholestasis, and intoxication with protein-bound substances, in the United States, it has been cleared for use in the treatment of drug overdose, poisoning, and hepatic encephalopathy but is not indicated for the treatment of chronic liver disease or as a bridge to liver transplantation.[4,5] Relative contraindications to the use of MARS include severe sepsis, coagulopathy, and bleeding. A previous meta-analysis of small, randomized, and quasi-randomized trials published in 2012 demonstrated a clinical benefit of MARS compared with standard medical therapy in terms of lowering serum total bilirubin levels (net change −7.0 mg/dL; 95% confidence interval [CI], −10.4 to −3.7; $P < .001$) and improving hepatic encephalopathy (odds ratio, 3.0; 95% CI, 1.9-5.0; $P < .001$); however, there was no observed mortality benefit (odds ratio, 0.91; 95% CI, 0.64-1.31; $P = .62$).[6] Two randomized controlled trials of MARS have since been completed.[7,8]

Single-pass albumin dialysis is an extracorporeal liver support system that uses a conventional dialysis circuit in which an exogenous albumin solution is passed once

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through the dialysate compartment and then discarded.[9] This liver support system has shown some promise in a case series of children with acute liver failure.[10]

The Prometheus system is a variant of albumin dialysis and combines fractionated plasma separation, adsorption, and hemodialysis.[11] It uses a 250-kDa semipermeable membrane generating an albumin-containing plasma-like solution. The patient's albumin-containing plasma solution is then adsorbed on 2 albumin-detoxifying columns before reuniting with blood cells. Diffusive hemodialysis is then performed to remove water-soluble solutes. This system is advantageous as it relies on endogenous rather than exogenous albumin. The HELIOS trial represents the largest multicenter clinical experience using the Prometheus system.[12]

To provide an update on MARS and review the scarce literature on the other 2 albumin dialysis modalities, SPAD and the Prometheus system, we conducted a meta-analysis of all randomized controlled trials published to date that compared the efficacy and safety of any of the 3 albumin dialysis systems, including head-to-head comparisons.

METHODS

Literature Search and Study Selection

The literature search and study selection were performed independently by 2 authors (A.S. and E.T.). With the assistance of a medical librarian, the following electronic databases were searched for relevant citations: PubMed, Ovid, EMBASE, and Cochrane's Library (inception to October 2014). The terms and filters' syntax for each database are provided in the Supplementary Material. We also searched ClinicalTrials.gov using similar terms and the bibliographies of retrieved articles. The search strategy was limited to human studies with no restrictions on language, sample size, duration of study, or year of publication.

CLINICAL SUMMARY

- Use of albumin dialysis, including MARS and the Prometheus system, as supportive treatment for liver failure is successful at removing albumin-bound molecules, such as bilirubin and at improving hepatic encephalopathy.
- However, survival benefit has not been established yet.
- Additional experience is required to guide its optimal use and address safety concerns.

Data Extraction and Assessment of Bias

We included parallel-arm randomized controlled trials that enrolled patients with acute liver failure, acute-on-chronic liver failure, or chronic decompensated liver disease, comparing the safety and efficacy of albumin dialysis systems (MARS, Prometheus, or SPAD) to standard medical therapy or to each other.

The following data were extracted in duplicate: country of origin, year of publication, population setting (acute, acute-on-chronic, and chronic liver failure), study design, study period, intervention groups, primary outcome, summary characteristics of study participants (sex, mean age, serum albumin, total bilirubin, creatinine, prothrombin time/international normalized ratio, and Model for End-Stage Liver Disease score), summary characteristics of the albumin dialysis system used (including percentage of albumin dialysate used, blood flow rate, anticoagulation use, duration of treatment, and number of treatment sessions), and duration of follow-up.

The efficacy end points of interest were changes in circulating levels of total bilirubin, ammonia, and bile acids; improvement in hepatic encephalopathy; and all-cause mortality. To assess these end points, we extracted the mean values of the solutes at baseline and at the end of the study period and the net change from baseline, the number of patients experiencing an improvement in the West-Haven grade of hepatic encephalopathy (as defined in individual trials), and the number of patients who died. Safety end points of interest included gastrointestinal bleeding, catheter-related bleeding, thrombocytopenia, infections and sepsis, pulmonary adverse events, and serious adverse events. Disagreements were resolved through consensus. The corresponding authors of 3 trials were contacted for data clarification. When indicated, values reported as medians with ranges were converted to estimates of means with standard deviations.[13]

The Cochrane's Collaboration tool was used to assess risk of bias, which covers 6 domains of bias (selection, performance, detection, attrition, reporting, and other bias). Two authors (A.S. and E.T.) independently rated each domain's risk of bias as low, high, or unclear, with the implication of a third author (B.J.) in case of disagreement.

Data Synthesis and Analysis

Random-effects model meta-analyses were used to calculate the pooled mean difference in net change in levels of the solutes of interest and the risk ratio (RR) for improvement in the grade of hepatic encephalopathy and all-cause mortality. All pooled estimates are displayed with a 95% CI. Existence of heterogeneity among study effect sizes was examined using the I^2 index and the χ^2 test P value. An I^2 index of 50% or more was used to indicate medium-to-high heterogeneity.[14] Subgroup analyses were performed according to certain study characteristics, including the albumin dialysis modality (MARS and Prometheus vs SPAD) and the number of dialysis sessions (<5 vs ≥ 5). All analyses were performed using the Cochrane's Collaboration Review Manager (version 5.3, Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration).

RESULTS

Characteristics of the Trials and Risk of Bias Assessment

A total of 3688 potentially relevant citations were identified and screened (Fig 2). Seventy articles were retrieved for evaluation, of which 10 randomized controlled trials fulfilled eligibility criteria comprising 7 trials of