Targeted albumin therapy does not improve short term outcome in hyponatremic patients hospitalized with complications of cirrhosis, data from the ATTIRE trial.

Corresponding author and Chief Investigator: Alastair O'Brien, UCL Institute for Liver and Digestive Health, Upper 3rd Floor, Division of Medicine, Royal Free Campus, Rowland Hill Street London NW3 2PF. Email: a.o'brien@ucl.ac.uk

Authors: Louise China, M.D., Ph.D.*, Nick Freemantle, Ph.D.[‡], Ewan Forrest, M.D.[k], Yiannis Kallis, M.D., Ph.D.[‖], Stephen D. Ryder, D.M.[¶], Gavin Wright, M.D., Ph.D.[**] and Alastair O'Brien, M.D., Ph.D.*

Affiliations: *Institute of Liver and Digestive Health, University College London, United Kingdom; [‡]Comprehensive Clinical Trials Unit, University College London, United Kingdom; [k]Glasgow Royal Infirmary, Glasgow, United Kingdom; [‖]Barts and the London School of Medicine and Dentistry Queen Mary University of London; [¶]National Institute for Health Research Nottingham Biomedical Research Centre at Nottingham University Hospitals NHS Trust and the University of Nottingham, Queens Medical Centre, Nottingham; ** Mid and South Essex NHS Foundation Trust, Basildon & Thurrock University Hospitals NHS Foundation Trust, Honorary Consultant in Gastroenterology, Hepatology and Hepatobiliary Medicine, The Royal Free Hospital, Honorary Senior Lecturer, University College London, Honorary Senior Clinical Lecturer, Kings College London.

Abstract:

Introduction: Patients with decompensated cirrhosis and hyponatremia have a poor prognosis. We investigated ATTIRE trial data to determine whether targeted albumin infusions improved outcome in patients with hyponatremia at baseline.

Methods: We examined the interaction between targeted albumin and standard care for the composite primary endpoint, stratifying by baseline sodium $\geq$ and <130 mmol/L.

Results: Randomisation to albumin was associated with a significant increase in sodium, however, there was no interaction between sodium category and treatment for the trial primary endpoint.

Discussion: Targeted intravenous albumin infusions raise serum sodium in hospitalized hyponatremic cirrhosis patients, but this did not improve outcome.

Introduction:

Hyponatremia is negatively associated with clinical outcomes in decompensated cirrhosis, yet there is scant evidence-based guidance for management[1, 2]. Treatment includes diuretic withdrawal and fluid restriction[3], with the expensive vasopressin receptor antagonist, tolvaptan rarely prescribed[4]. Intravenous human albumin solution (HAS) infusions are frequently used to treat hyponatremia in hospitalized patients, despite this not being one of the recommended uses of albumin in international guidelines. Indeed, in a large cohort of decompensated cirrhosis patients that were given albumin, 29% had hyponatremia as the primary indication for prescription[5]. This non-randomised retrospective cohort demonstrated that albumin use was associated with higher resolution of hyponatremia compared to no albumin and hyponatremia resolution led to improved 30-day survival. Therefore, this large study of 777 patients that received albumin and 349 that did not, provided substantial support for the use of albumin to treat hyponatremia. However, the comparator group received no albumin and it would be expected for many decompensated cirrhosis patients with hyponatremia to have complications such as spontaneous bacterial peritonitis or renal dysfunction or require large volume paracentesis during hospitalisation that are indications for albumin use, as per standard guidelines. Therefore, a more appropriate comparator might include patients in which albumin was prescribed for these well-established reasons to determine whether albumin infusions are specifically beneficial for hyponatremia. This has not been directly addressed in a large-scale prospective study and so we investigated data from the ATTIRE trial (Albumin to Prevent Infection in Chronic Liver Failure), in which albumin was given to the control group for these indications, to determine whether targeted albumin infusions improve clinical outcomes in decompensated cirrhosis patients with hyponatremia at baseline.

Methods:

The ATTIRE trial and protocol have been published previously[6, 7]. This was a randomized, multicenter, open-label, parallel-group trial in hospitalized decompensated cirrhosis patients with serum albumin <30 g/L. Patients received either targeted infusions of 20% HAS for up to 14 days or discharge, to raise albumin >30g/L, or standard care. Albumin was permitted for large-volume paracentesis (LVP), spontaneous bacterial peritonitis (SBP), or hepatorenal syndrome (HRS) in standard care (see Supplementary Material). The composite primary end point was new infection, renal dysfunction, or death between days 3-15 after commencement of treatment. 90% had alcohol-induced cirrhosis.

We examined the interaction between targeted albumin and standard care for the primary endpoint, its components and the Model for End-Stage Liver Disease (MELD) score during trial, stratifying by baseline sodium ≥ and <130 mmol/L, the threshold for hyponatremia[8]. Differences in sodium after 5 days of trial between groups were analysed accounting for baseline, stratification variables and site, as a mixed model with sodium level as response variable, parameterised to identify baseline, post baseline albumin randomisation and stratification variables. Sites and patient identification numbers were random intercepts.

Results:

568/777 patients (73%) had sodium ≥130 and 206 (27%) a sodium <130 mmol/L at baseline. In <130 mmol/L patients, the targeted albumin group (n=103) received a mean total 239.4g (SD 129.1) of albumin and standard care (n=103) 123.2g (SD 138.4). For ≥130 mmol/L patients, the targeted albumin group (n=277) received a mean 216.5g (SD 117.3) of albumin and standard care 65.5g (SD 104.3). There was a significant interaction between sodium category and treatment group for total amount of albumin infused (p=0.046) (**Table 1**).

Randomisation to albumin was associated with an overall 1.77 mmol/L increase in sodium, (95% CI:1.04-2.51; p<0.0001) at day 5 with 521/777 (67.1%) patients providing a value. This was greater in

hyponatremic patients (mean 2.84 mmol/L, 95% CI:1.10-4.57) compared to ≥130 mmol/L patients (mean 1.46 mmol/L, CI:0.67-2.25), although this did not reach significance (p=0.11) (**Table 1**).

For the composite primary endpoint, there was a non-linear response according to baseline sodium with the odds ratio of reaching this endpoint rising for both hypo and hypernatremia (**Figs 1A and B**). There was no interaction between sodium category and treatment for the primary endpoint, (p=0.1002; **Fig. 1C**). Examining the components, we found no interaction between sodium category and treatment for renal dysfunction or death within the trial (p=0.532 and 0.528; **Fig. 1C**). There was a significant interaction between sodium category and treatment for development of new infection (p=0.021; **Fig. 1C**), with odds ratio 0.62 (95% CI:0.32-1.19; p=0.149) favouring albumin in hyponatremic patients compared to 1.65 (95% CI:1.05-2.58; p=0.03) favouring standard care in ≥130 mmol/L patients. Finally, there was a significant interaction between sodium category and treatment for MELD score at trial end (p=0.0078). MELD was non-significantly lower in targeted albumin hyponatremic patients compared to standard care and significantly lower in standard care for ≥130 mmol/L patients compared to targeted albumin at end of trial (p=0.0018) (**Table 1**).

Discussion:

We confirm the increased risk of adverse outcomes in patients hospitalized with cirrhosis and hypo or hypernatremia at baseline. Targeted albumin infusions increased serum sodium by ~3 mmol/L compared to standard care at day 5 of trial in hyponatraemic patients. Albumin was given in standard care for LVP, SBP and HRS with more infused to patients with hyponatremia at baseline than those with sodium >130 mmol/L, which likely reflected a greater incidence of these indications in more unwell patients. Therefore, the effect of albumin on serum sodium is probably an underestimate.

However, there was no interaction between sodium category and treatment group for our primary endpoint. There was a significant interaction for development of new infection, but this was a combination of improved outcomes in hyponatremic patients at baseline that received targeted albumin (although confidence intervals crossed 1) and in patients with sodium ≥130 mmol/L treated with standard care (where confidence intervals did not cross 1). The significant interaction for difference in MELD score at end of trial treatment period between albumin and standard care for baseline sodium should be regarded as exploratory, as the overall analysis was non-significant.

We demonstrate the efficacy of targeted intravenous albumin infusions to raise serum sodium in hospitalized decompensated cirrhosis patients with hyponatremia at baseline, but this does not improve short-term outcome compared to standard care. It is possible that certain subgroups of hyponatremic patients that were not part of our analyses may have derived clinical benefit. However, these prospective data from our completed randomised trial do not support extending albumin use for treatment of hyponatremia in decompensated cirrhosis.

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Figure Legend

Figure 1. Odds ratio for primary composite outcome in ATTIRE according to baseline serum sodium in (a) Albumin and (b) Standard Care treatment groups. (c) Baseline Sodium subgroups and interactions by outcomes.

Table 1.

	Point Estimate	Lower 95% CI*	Upper 95% CI*	P	P$_{Interaction}$
Difference in total albumin infused between albumin and standard care for sodium <130 mmol/L	580.17	400.37	759.97	<0.0001	0.0460
Difference in total albumin infused between albumin and standard care for sodium ≥130 mmol/L	756.69	666.43	846.94	<0.0001	
Overall increase in sodium (mmol/L) when albumin compared to standard care	1.77	1.04	2.51	<0.0001	N/A
Increase in sodium for baseline sodium <130 mmol/L	2.84	1.10	4.57	0.0016	0.11
Increase in sodium for baseline sodium ≥130 mmol/L	1.46	0.67	2.25	0.0003	
Overall difference in MELD[#] score at end of trial treatment period between albumin and standard care	0.5863	-0.08918	1.2618	0.0888	N/A
Difference in MELD[#] score at end of trial treatment period between albumin and standard care for baseline sodium <130 mmol/L	-0.9405	-2.4675	0.5866	0.2257	0.0078
Difference in MELD[#] score at end of trial treatment period between albumin and standard care for baseline sodium ≥130 mmol/L	1.1672	0.4359	1.8985	0.0018	

*CI – Confidence Interval

[#]MELD – Model for End Stage Liver Disease