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Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: A randomized double-blind study

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SUMMARY OF RESULTS:

Background & Aims

Episodic hepatic encephalopathy (HE) is frequently precipitated by factors that induce circulatory dysfunction, cause oxidative stress-mediated damage or enhance astrocyte swelling. The administration of albumin could modify these factors and improve the outcome of hepatic encephalopathy. The aim of this study is to assess the efficacy of albumin in a multicenter, prospective, double-blind, controlled trial.

Methods

A randomized, double-blind, controlled study was conducted in four tertiary care hospitals between March 2009 and July 2012. The protocol conformed to the Declaration of Helsinki and Guidelines for Good Clinical Practice in Clinical Trials and was approved by the Institutional Review Boards, in accordance to the Spanish legislation. Informed consent was initially given by next of kin and later confirmed by the patient. All data was collected in the medical history of each centre.

Patient selection: Patients were considered to be included in the study if fulfilled the following criteria: (1) liver cirrhosis (diagnosed by clinical data or liver biopsy); (2) development of an episode of HE that was initiated within 72 h of inclusion into the

study and persisted on grade P2 (West-Havenscale); (3) age between 18 and 85 years. Exclusion criteria were: (1) terminal illness with a performance status P3 prior to HE, (2) need for intensive support (ventilation, dialysis, vasopressors, etc.); (3) comorbid psychiatric or neurological conditions that make the assessment of HE difficult (e.g., Parkinson's disease, Alzheimer's disease, stroke, etc.); (4) disorders requiring treatment with albumin (hepatorenal syndrome, spontaneous bacterial peritonitis), (5) contraindications to albumin (cardiac failure, allergy), (6) active gastrointestinal bleeding in the previous 72 h, (7) acute-on-chronic liver failure defined by an acute decompensation associated with bilirubin >5 mg/dl.

Intervention: Prior to randomization, potential participants were assessed following a standardized protocol that established the diagnosis of HE, searched for precipitating factors and assessed inclusion and exclusion criteria. Those that fulfilled the criteria were randomized to (a) albumin group or (b) saline group. Albumin 20% was administered intravenously; drug dosing was adjusted by weight at approximate doses of 1.5 g/kg/d at inclusion (day 1) and 1.0 g/kg/d after 48 h (day 3). Saline was administered at equivalent volume. Treatment was infused at a rate of 5 ml/min. Allocation to each group was performed with a number sequence based on a list randomly generated by a computer, designed in blocks of 4, which was only available to the pharmacist who prepared the flasks for infusion.

Outcomes: Patients were followed during hospitalization up to day 14 and were visited at day 30 and day 90. The primary end point of the study was the presence of HE at day 4. HE was assessed in all patients of the four centres by the same neuropsychologist, who was unaware of any clinical data. The secondary end points included: (a) Daily assessment of the severity of HE (at 12 h intervals during the first 3 days and daily thereafter), using the following scales: West-Haven, Glasgow Coma Score, and Clinical Hepatic Encephalopathy Staging Scale (CHESS). (b) Length of hospital stay. (c) Survival at day 30 and day 90. (d) Ammonia at days 1, 2, 3, 4 and end of study (resolution of HE or day 14, whatever comes early). (e) Index of circulatory dysfunction: plasma renin concentration at baseline, day 4, and end of study (resolution of HE or day 14). (f) Oxidative stress markers and pro-inflammatory cytokines: at baseline and at end of study: TNF-a, IL-10, IL-6, and malondialdehyde. (g) Soluble CD163 was measured at baseline and at the end of study by ELISAs.

Results

Fifty-six patients were randomly assigned to albumin (n =26) or saline (n= 30) stratified by the severity of HE. Both groups were comparable regarding to demographic data, liver function, and precipitating factors. The percentage of patients without hepatic encephalopathy at day 4 did not differ between both groups (albumin: 57.7% vs. saline:

53.3%; p >0.05). However, significant differences in survival were found at day 90 (albumin: 69.2% vs. saline: 40.0%; p =0.02).

Conclusions

Albumin does not improve the resolution of hepatic encephalopathy during hospitalization. However, differences in survival after hospitalization suggest that the development of encephalopathy may identify a subgroup of patients with advanced cirrhosis that may benefit from the administration of albumin.

Flow diagram of participants in the study: