Research Article

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Cirrhosis

Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial

Thierry Thévenot[1,*], Christophe Bureau[2], Frédéric Oberti[3], Rodolphe Anty[4], Alexandre Louvet[5], Aurélie Plessier[6], Marika Rudler[7], Alexandra Heurgué-Berlot[8], Isabelle Rosa[9], Nathalie Talbodec[10], Thong Dao[11], Violaine Ozenne[12], Nicolas Carbonell[13], Xavier Causse[14], Odile Goria[15], Anne Minello[16], Victor De Ledinghen[17], Roland Amathieu[18], Hélène Barraud[19], Eric Nguyen-Khac[20], Claire Becker[21], Thierry Paupard[22], Danielle Botta-Fridlung[23], Naceur Abdelli[24], François Guillemot[25], Elisabeth Monnet[1], Vincent Di Martino[1]

[1]*Service d'Hépatologie, hôpital Jean Minjoz, 25000 Besançon, France;* [2]*Service d'Hépato-Gastroentérologie, hôpital Purpan, clinique Dieulafoy, 31059 Toulouse, France;* [3]*Service d' d'Hépato-Gastroentérologie, hôpital d'Angers, 4 rue Larrey, 49100 Angers, France;* [4]*Service d'Hépato-Gastroentérologie, hôpital Archet, rue St Antoine Ginestier, 06200 Nice, France;* [5]*Service des Maladies de l'Appareil Digestif, CHRU de Lille, rue M. Polonovs.ki, 59037 Lille cedex, France;* [6]*Inserm U-773, Service d'Hépatologie, hôpital Beaujon, 100 boulevard du Général Leclerc, 92118 Clichy cédex, France;* [7]*Service d'Hépato-Gastroentérologie, hôpital Pitié-Salpétrière, 47-83 boulevard de l'Hôpital, 75651 Paris cedex 13, France;* [8]*Service d'Hépato-Gastroentérologie, hôpital Robert Debré, 51092 Reims cedex, France;* [9]*Service d'Hépato-Gastroentérologie, CHIC de Créteil, 40 avenue de Verdun, 94010 Créteil cedex, France;* [10]*Service d'Hépato-Gastroentérologie, centre hospitalier, 135 rue du Président Coty, 59 200 Tourcoing, France;* [11]*Inserm U-1075, Service d'Hépato-Gastroentérologie, hôpital de Caen, avenue de la Côte de Nacre, 14000 Caen, France;* [12]*Service d'Hépato-Gastroentérologie, hôpital Lariboisière, 2 rue Ambroise-Paré, 75010 Paris, France;* [13]*Service d'Hépato-Gastroentérologie, hôpital Saint-Antoine, 184 rue du Fbg St Antoine, 75571 Paris cedex 12, France;* [14]*Service d'Hépato-Gastroentérologie, hôpital de la Source, BP 6709, 45067 Orléans cedex 12, France;* [15]*Service d'Hépato-Gastroentérologie, hôpital de Rouen, 1 Rue Germont, 76000 Rouen, France;* [16]*Service d'Hépato-Gastroentérologie, hôpital du Bocage, BP 1542, 21034 Dijon cedex, France;* [17]*Service d'Hépato-Gastroentérologie, hôpital du haut Levêque, 33604 Pessac cedex, France;* [18]*Service d'Hépato-Gastroentérologie, hôpital Jean Verdier, av. du 14 juillet, 93143 Bondy cedex, France;* [19]*Service d'Hépato-Gastroentérologie, hôpital de Brabois, rue du Morvan, 54511 Vandoeuvre-les-Nancy cedex, France;* [20]*Service d'Hépato-Gastroentérologie, hôpital d'Amiens, 2 Place Victor Pauchet, 80080 Amiens, France;* [21]*Service d'Hépato-Gastroentérologie, hôpital de Lens, 99 route de la Bassée, SP-8, 62307 Lens cedex, France;* [22]*Service d'Hépato-Gastroentérologie, hôpital de Dunkerque, 130 avenue Louis Herbeaux, 59385 Dunkerque cedex 1, France;* [23]*Service d'Hépato-Gastroentérologie, hôpital de la Conception, 147 Bd Baille, 13005 Marseille, France;* [24]*Service d'Hépato-Gastroentérologie, hôpital de Chalons-en-Champagne, 51 rue du commandant Derrien, 51005 Chalons-en-Champagne cedex, France;* [25]*Service d'Hépato-Gastroentérologie, hôpital de Roubaix, 11-17 Boulevard Lacordaire, 59100 Roubaix, France*

Background & Aims: Albumin infusion improves renal function and survival in cirrhotic patients with spontaneous bacterial peritonitis (SBP) but its efficacy in other types of infections remains unknown. We investigated this issue through a multicenter randomized controlled trial.

Methods: A total of 193 cirrhotic patients with a Child-Pugh score greater than 8 and sepsis unrelated to SBP were randomly assigned to receive antibiotics plus albumin (1.5 g/kg on day 1 and 1 g/kg on day 3; albumin group [ALB]: n = 96) or antibiotics alone (control group [CG]: n = 97). The primary endpoint was the 3-month renal failure rate (increase in creatinine ⩾50% to reach a final value ⩾133 μmol/L). The secondary endpoint was 3-month survival rate.

Results: Forty-seven (24.6%) patients died (ALB: n = 27 *vs.* CG: n = 20; 3-month survival: 70.2% *vs.* 78.3%; $p = 0.16$). Albumin infusion delayed the occurrence of renal failure (mean time to onset, ALB: 29.0 ± 21.8 *vs.* 11.7 ± 9.1 days, $p = 0.018$) but the 3-month renal failure rate was similar (ALB: 14.3% *vs.* CG: 13.5%; $p = 0.88$). By multivariate analysis, MELD score ($p < 0.0001$), pneumonia ($p = 0.0041$), hyponatremia ($p = 0.031$) and occurrence of renal failure ($p < 0.0001$) were predictors of death. Of note, pulmonary edema developed in 8/96 (8.3%) patients in the albumin group of whom two died, one on the day and the other on day 33 following albumin infusion.

Conclusions: In cirrhotic patients with infections other than SBP, albumin infusion delayed onset of renal failure but did not improve renal function or survival at 3 months. Infusion of large amounts of albumin should be cautiously administered in the sickest cirrhotic patients.

Keywords: Liver cirrhosis; Sepsis; Renal failure; Portal hypertension; Prognosis.
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* Corresponding author. Address: Service d'Hépatologie et de Soins Intensifs Digestifs, University Hospital Jean Minjoz, 25000 Besançon, France. Tel.: +33 3 81 66 84 21; fax: +33 3 81 66 84 18.
E-mail address: tthevenot@chu-besancon.fr (T. Thévenot).

Abbreviations: AKI, acute kidney injury; IQR, interquartile range; LVP, large-volume paracentesis; MDRD, modification of diet in renal disease; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome.

Introduction

Bacterial infections are common in cirrhotic patients and dramatically increase one-year mortality; with mortality reportedly up to 38% after infection [1,2]. Once infection occurs, it may lead to systemic inflammatory response syndrome (SIRS) and subsequently, renal failure, multi-organ dysfunction and death [3]. The most common infection, accounting for around one quarter of all infections in hospitalized patients, is spontaneous bacterial peritonitis (SBP), which is mainly caused by bacterial translocation [4]. About one-third of these patients go on to develop renal failure despite the resolution of infection [5,6].

Renal failure in SBP is the most powerful independent predictor of in-hospital mortality, with a median death rate of 67% in patients with renal failure, versus only 11% in patients who maintained normal renal function [7]. Renal failure has also been reported to be a strong predictor of early death in cirrhotic patients with infections other than SBP [8–10]. Deterioration of renal function during sepsis proceeds from several causes: firstly, splanchnic vasodilation, due to increased production of pro-inflammatory cytokines and vasodilatory factors, such as nitric oxide, with a subsequent reduction in effective arterial blood volume; and secondly, vasoconstriction in non-splanchnic vascular beds, including the kidney [11].

Renal hypoperfusion is further exacerbated by sepsis-related cardiomyopathy, which has been shown to be improved by albumin infusion in cirrhotic rats [12]. Intravenous albumin administration has also been shown to have beneficial effects on systemic hemodynamics and renal function in cirrhotic patients with SBP, mediated by both an improvement in cardiac function and a decrease in arterial vasodilatation [13]. More importantly, the use of albumin together with antibiotic treatment in SBP was associated with a marked decrease in 3-month mortality compared to antibiotic treatment alone [6]. The beneficial effect of albumin infusion in the context of SBP is related mostly to its oncotic effect, but may also be due to its antioxidant, immune modulatory and scavenger properties [14].

The efficacy of albumin to prevent renal impairment and reduce mortality in patients with SBP was recently confirmed in a meta-analysis [15]. Its use is endorsed by current guidelines and well-integrated in clinical practice, although the benefit of this strategy remains questionable in low-risk SBP patients [16,17]. Conversely, little is known about the effects of albumin on renal function and survival in cirrhotic patients with infections other than SBP. Only one single-center study with a relatively small sample size has addressed this issue to date [18]. Although encouraging, the overall result of this study was negative, with no significant difference in survival between groups observed at 3 months, underlining the need for a larger trial [18].

We performed a randomized, multicenter trial to determine whether albumin infusion has a beneficial effect on renal function and 3-month survival in cirrhotic patients with infections other than SBP.

Patients and methods

Study oversight

The "Albumin Administration in Cirrhotic Patients With Bacterial Infection Unrelated to Spontaneous Bacterial Peritonitis (ALB-CIRINF)" study (registered with ClinicalTrials.gov under the number NCT01359813) was a randomized, open-label, controlled, multicenter clinical trial designed by a scientific committee and supervised by an independent oversight committee (Supplementary File 1). LFB laboratories (Courtaboeuf, France) provided the albumin vials (Vialebex®, LFB). All authors had access to the study data, critically reviewed the manuscript, and approved the final draft for submission. The trial was performed in 25 participating centers, in accordance with the Declaration of Helsinki and with the approval of our local ethics committee (CPP Est-II) on the 7th August 2008 (ref: 2008-A80478-45) (Supplementary File 2).

Patients

All consecutive cirrhotic patients with sepsis who were admitted to the participating centers were screened for eligibility. Full details of the inclusion and exclusion criteria, and the definitions of infection are given in Supplementary File 3. Briefly, inclusion criteria were: age $\geqslant$18 and $\leqslant$80 years, presence of sepsis or severe sepsis according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) guidelines [19], and cirrhosis with a Child-Pugh score >8. Exclusion criteria were: patients with serum creatinine level >160 μmol/L, SBP, septic shock, and use of antibiotics (except antibiotic prophylaxis) during the week prior to randomization. We excluded patients with a creatinine level >160 μmol/L because the Scientific Committee considered that randomization would be unethical and not feasible in these patients.

Randomization

Randomization was performed in blocks of 4, in a 1:1 ratio, by means of an interactive voice-system response (Ascopharm, Novasco group, Paris, France) with stratification by center. The number of subjects per block was known only to the methodologist.

Treatment allocation and follow-up

Eligible patients were randomly assigned to receive either antibiotics alone (control group) or antibiotics plus albumin 20% (ALB group: 1.5 g/kg on day 1 and 1 g/kg on day 3). Albumin administration was initiated in the first 12 h after randomization, and antibiotics were to be started as soon as possible without waiting for the randomization. During the 3-month follow-up period, eight visits were planned (at days 1, 3, 6, 9, 15, 30, 60, and 90) to record clinical and biological data (Supplementary Table 1). Complications of cirrhosis were managed according to standard protocols [20]. In septic patients with ascites, diuretics had to be stopped at the time of infection and re-introduced after resolution of infection. Large-volume paracentesis (LVP >3 liters) was not authorized until after resolution of infection, but paracentesis of lesser volumes without albumin administration was authorized in cases of abdominal discomfort. Proposals for the choice of antibiotics were given in the study protocol to assist physicians (Supplementary File 3).

Endpoints and definitions

Endpoints

The primary endpoint was the rate of renal failure during the 3-month follow-up period. The secondary end-point was 3-month mortality rate.

Renal failure

Renal function was assessed by measuring serum creatinine concentration at inclusion and throughout follow-up (see Supplementary Table 1 for measurement schedule). To define renal failure, a cut-off serum creatinine level of 133 μmol/L (15 mg/L) was used. For patients without pre-existing renal insufficiency, renal impairment was diagnosed whenever there was an increase in serum creatinine of $\geqslant$50%, reaching a final value of over 133 μmol/L. For patients with pre-existing renal insufficiency before infection, renal impairment was diagnosed by an increase in the serum creatinine level by more than 50% from baseline. Glomerular filtration rate was estimated according to the MDRD formula [21].

Statistical analysis

Quantitative variables are presented as mean ± SD or as median and interquartile range (IQR), and categorical variables as number (percentage).

The sample size was estimated based on a projected 27% renal failure rate at 3 months in the control group [9] and 10% in the albumin infusion group [6]. It was calculated that 186 patients (93 per group) would yield 80% power with a two-sided alpha risk of 5%. The sample size was increased by 10% to 206 patients