Journal of Critical Care 29 (2014) 253–259

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Renal/Metabolic

Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: A meta-analysis ☆

Georgios D. Kitsios, MD PhD [a,b,*], Paolo Mascari, MD PharmD [a], Riad Ettunsi, MD MSc [a], Anthony W. Gray, MD [a]

[a] Department of Internal Medicine and Department of Pulmonary and Critical Care Medicine, Lahey Hospital and Medical Center, Burlington, MA, USA
[b] Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA

ARTICLE INFO

Keywords:
Albumin
Furosemide
Meta-analysis
Diuretic resistance
Hypoalbuminemia

ABSTRACT

Purpose: To systematically review clinical studies of co-administration of albumin and loop diuretics in hypoalbuminemic patients as a strategy to overcome diuretic resistance.
Materials and Methods: Systematic search of electronic databases up to October 2012. We included randomized clinical trials of adults with hypoalbuminemia, comparing co-administration of loop diuretics and albumin versus loop diuretics alone. Quantitative data were synthesized with meta-analytic techniques for clinical, surrogate (urinary volume and urinary sodium excretion) and intermediate (pharmacokinetic and hemodynamic parameters) outcomes.
Results: Ten studies were included, of which 8 trials with crossover design were synthesized with meta-analysis. A statistically significant increase in the amount of urine volume (increment of 231 mL [95% confidence interval 135.5-326.5]) and sodium excreted (15.9 mEq [4.9-26.8]) at 8 hours were found in favor of co-administration of albumin and furosemide. These differences were no longer statistically significant at 24 hours. Meta-analyses for intermediate outcomes (ie, furosemide excretion, distribution volume etc.) did not reveal statistically significant differences.
Conclusions: Synthesis of a heterogeneous body of evidence shows transient effects of modest clinical significance for co-administration of albumin with furosemide in hypoalbuminemic patients. Pragmatic, large-scale randomized studies are needed to delineate the role of this strategy.

1. Introduction

The loop diuretic furosemide constitutes the mainstay of treatment in patients with hypervolemic conditions, such as cirrhosis, nephrotic syndrome or congestive heart failure. However, its clinical use is hampered when "furosemide resistance" is encountered, i.e. increased doses of furosemide fail to induce adequate diuretic response, and such resistance is frequently observed in patients with hypoalbuminemia [1].

Compelling experimental data demonstrate that furosemide is dependent on adequate plasma albumin concentrations for exerting its biological action [2]. More than 95% of furosemide molecules in the plasma are bound to albumin, and this albumin-bound fraction reaches the proximal tubular epithelial cells to interact with an anion transporter and finally be translocated into the tubular lumen to exert its action in the ascending limb of Henle's loop. In hypoalbuminemia, the volume of furosemide distribution is increased because the drug cannot be retained in the plasma, leading to a diminished amount of albumin-bound furosemide presented to the proximal tubules. Based on initial experiments with analbuminemic rats in which the co-administration of albumin with furosemide significantly potentiated diuretic response compared to furosemide alone [2], this co-administration of albumin and furosemide (FUR-ALB) has been proposed as a strategy to overcome diuretic resistance in hypoalbuminemic patients.

Although the clinical efficacy of FUR-ALB has not been conclusively demonstrated [3], this is a frequently employed measure in clinical practice. Albumin is not without limitations though, including high cost, periodic shortages, and even potential adverse effects, such as anaphylaxis, risk of infection or detrimental transient volume expansion in hypervolemic patients [4], and thus routine use of FUR-ALB cannot be justified without strong evidentiary support.

We aimed to draw safer conclusions and clarify misconceptions on the efficacy of co-administration of albumin with loop diuretics for overcoming diuretic resistance in patients with hypoalbuminemia, by conducting a systematic review of the literature for randomized clinical trials (RCTs) comparing this co-administration strategy versus diuretics alone.

☆ Conflicts of interest: None.

* Corresponding author. Department of Internal Medicine, Lahey Hospital and Medical Center, 41 Mall road, Burlington, MA, 01805, USA. Tel.: +1 781 744 7000.
E-mail address: Georgios.Kitsios@Lahey.org (G.D. Kitsios).

0883-9441/$ – see front matter
http://dx.doi.org/10.1016/j.jcrc.2013.10.004

2. Methods

2.1. Data sources and searches

We conducted systematic searches of the literature in Ovid Medline, Cochrane Register of Controlled Trials, PubMed, CINAHL, and SCOPUS databases from inception up to October 2012 using keywords—and MeSH terms when appropriate—relating to albumin, furosemide (and all other loop diuretics, i.e., torsemide, ethacrynic acid, bumetanide) for RCTs published in full text in English. Potentially eligible studies were retrieved in full text for further assessment of eligibility. We hand-searched reference lists of eligible studies and also retrieved and evaluated for eligibility all studies included in a previous systematic review [3]. Details of our protocol can be found in the Appendix.

2.2. Study selection

Two investigators determined study eligibility against a set of predefined criteria. Eligible populations included patients with hypoalbuminemia of any cause, ≥18 years old, and requiring diuresis for hypervolemia. Interventions and comparators of interest included administration of loop diuretics with and without concurrent human albumin intravenous infusion. The outcomes of interest included both surrogate outcomes (such as urinary volume excretion, urinary sodium (Na) excretion, weight loss and improvement in oxygenation) and clinical outcomes (such as mortality, rehospitalization and resolution of hypervolemic symptoms) as reported by the original studies. We also specifically examined outcomes aiming to delineate the underlying pharmacokinetic or hemodynamic mechanisms of potentiated diuresis with albumin, adjudicated as intermediate outcomes (such as furosemide excretion, furosemide volume of distribution, change in glomerular filtration rate etc.). Eligible study designs included RCTs, of either parallel or crossover design.

2.3. Data extraction and synthesis

From eligible studies, we extracted detailed data regarding the demographics, index and comorbid conditions of included patients, baseline laboratory values, details on study design, description of protocols regarding intervention and comparator arms, and finally, outcome data (surrogate, clinical and intermediate outcomes). Data were extracted independently by 2 investigators and disagreements were resolved through consensus.

Outcome data for categorical variables were described as odds ratios (ORs) or other relative effect sizes available with their corresponding 95% confidence intervals (CIs); adjusted estimates were recorded when available, otherwise ORs (95% CI) were calculated from raw data. Continuous outcomes were described as net differences between the 2 arms with their 95% CIs. Among studies with similar populations, interventions and outcomes, we performed quantitative synthesis of outcome data of selected continuous variables with random effects meta-analysis, when there were at least 3 unique similar studies. Based on available data and our a priori assessment of the clinical importance of specific outcomes, we performed random effects model meta-analysis [5] for the surrogate outcomes of urinary volume and Na excretion, and the intermediate pharmacokinetic and hemodynamic outcomes. Meta-analyses were possible only for crossover RCTs investigating a single-time FUR-ALB versus furosemide alone, with the outcomes measured at 2 time points (at ≤8 and at 24 hours, respectively). In crossover studies, by definition, there is only one set of baseline values for the cohort of patients, and as these cancel out, we therefore utilized the net differences between the final values obtained with each intervention (ie, incremental urinary volume or Na excreted with FUR-ALB). When such net differences were not directly reported, we calculated these values and estimated their 95% CI from the standard errors of the final values [6]. For the pharmacokinetic and hemodynamic outcomes, we conducted meta-analyses after transformation of results to standardized effect sizes (Cohen's D), given differences in estimation and reporting of these parameters by individual studies [7]. Heterogeneity among effect sizes was assessed using the I^2 index and Cochran's Q test. An I^2 index ≥50% was used to indicate medium-to-high heterogeneity [8]. To explore potential treatment-effect heterogeneity, we performed a prespecified subgroup analysis for patients with nephrotic syndrome and also conducted meta-regression analyses in which the effect sizes of individual RCTs were regressed against the doses of albumin and furosemide used in each RCT, respectively. Analyses were performed with Open Meta-analyst [9] and StatsDirect.

2.4. Quality assessment

We assessed the risk of bias in included RCTs by using the predefined criteria from the Cochrane's Risk of Bias tool: adequacy of randomization, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, possibility of selective reporting, and possible other sources of bias, as previously described [10]. For crossover RCTs, we also specifically evaluated the adequacy of the washout period (defined as at least 48 hours). RevMan was used for construction of the risk of bias graphs. This report was designed and prepared according to the PRISMA statement [11].

3. Results

3.1. Study selection

A flowchart of the study selection process is shown in Fig. 1. Of a total of 331 abstracts screened, 21 articles considered to be potentially eligible were evaluated in full text, and 10 articles were finally included [2,12-20].

3.2. Descriptive characteristics

Sample sizes were generally small, ranging from 5 to 126 patients (median 11 patients) included (Table 1). Populations were heterogeneous in terms of their index disease, with 2 studies performed in patients with cirrhosis [17,19], 5 studies in patients with nephrotic syndrome [12-16], 1 study in patients with acute lung injury in an intensive care unit setting [20], 1 study in patients with chronic kidney disease [18], and 1 study in patients with various causes of hypoalbuminemia [2].

Two included RCTs were of parallel design [19,20] and the remaining 8 studies were of crossover design. Crossover and parallel RCTs had significant differences in included populations and primary aims, and thus, we evaluated their results separately. The 8 crossover studies had the mechanistic primary aim of delineating the mechanism of potentiated diuresis with albumin. Their patients were carefully selected after a roll-in period and an equilibrated state of hypervolemia was maintained in the experimental period (with intravenous or oral fluid repletion of volumes lost during diuresis) (Table E1). The 2 parallel studies were conducted in clinically decompensated patients requiring urgent diuresis.

Demonstrated resistance to diuretics was an inclusion criterion in only 1 of the 10 studies [2]. Furosemide was the single loop diuretic investigated (Table E1). The 8 crossover studies used a single time FUR-ALB, whereas the parallel studies randomized patients to titratable, sequential doses of diuretics and repeated, fixed-doses of albumin over the course of days [20] or weeks [19]. Among crossover studies, doses of furosemide ranged from 30 to 220 mg, and for albumin from 6 to 40 g (Fig. 2). The furosemide-albumin solutions were administered as a premixed solution in 3 studies.