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Loop diuretic strategies in patients with acute decompensated heart failure: A meta-analysis of randomized controlled trials☆,☆☆

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ABSTRACT

Purpose: The safety and efficacy of continuous infusion vs bolus injection of intravenous loop diuretics to treat acute decompensated heart failure were debated. Our aim is to compare the administration routes of diuretics in hospitalized patients with acute decompensated heart failure.

Methods: A systematic review and meta-analysis of randomized controlled trials was performed to evaluate the effects of continuous infusion vs bolus administration of loop diuretics in patients with acute decompensated heart failure. The primary end points were urine outputs, body weight loss, all causes of mortality, and death from cardiovascular causes. Secondary end points were electrolyte imbalance, change in creatinine levels, tinnitus or hearing loss, and days of hospitalization.

Results: Ten randomized controlled trials with 518 patients were identified. Continuous infusion of diuretics was associated with a significantly greater weight loss (weighted mean difference, 0.78; 95% confidence interval, 0.03-1.54) compared with bolus injection. Urine output, the incidence of electrolyte imbalance, change in creatinine level, length of hospitalization, the incidence of ototoxicity, cardiac mortality, and all-cause mortality showed no significant differences between the 2 groups.

Conclusion: Meta-analysis of the existing limited studies did not confirm any significant differences in the safety and efficacy with continuous administration of loop diuretic, compared with bolus injection in patients with acute decompensated heart failure.

1. Introduction

Acute decompensated heart failure is a common condition associated with morbidity and mortality worldwide [1]. Diuretic therapy is the mainstay of treatment of heart failure. Approximately 90% of patients who are hospitalized with acute decompensated heart failure received intravenous diuretic therapy [2]. Common adverse effects of diuretics include abnormalities of intravascular water homeostasis, worsening kidney function, and electrolyte disturbances. Administration of loop diuretics to patients with heart failure may result in a significantly decreased glomerular filtration rate, presumably because of activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system [3]. Developing effective and safe diuretic treatment strategies that would provide symptom relief is important [4].

Loop diuretics inhibit the reabsorption of sodium and water and increase the urinary excretion of chloride, calcium, and magnesium; these characteristics result in a prompt diuretic effect that peaks at 1.5 hours after administration [5]. Many clinicians treat acute decompensated heart failure with bolus diuretic therapy because of convenience. However, bolus delivery may lead to marked fluctuations in intravascular volume and to high-peak serum levels of the

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diuretic agents, thereby increasing their toxicity [4,6]. Thus, the role of continuous infusion in diuretic therapy has been investigated for the treatment of acute decompensated heart failure [7]. Continuous delivery of the drug to the nephron avoids the compensatory renal sodium reabsorption that occurs when blood levels of the diuretic agent are low [8]. However, debate on the safety and efficacy of the 2 modes of administration is ongoing.

Several small studies have investigated the optimal mode of diuretic administration in patients with acute decompensated heart failure, but these studies have lacked the power to address clinical questions decisively [7,9]. The most recent meta-analysis from the Cochrane Collaboration suggested that continuous infusion of diuretics resulted in greater urine volume and a better safety profile compared with intermittent bolus injections [10]. However, several large randomized controlled trials (RCTs) evaluating diuretic strategies in acute decompensated heart failure were published recently; the efficacy of continuous infusion was challenged in the recent 3 RCTs [11-13]. Moreover, the Cochrane review pooled various research outcomes, including the measurement of urine output, in a nonuniform manner, which increased the possibility of heterogeneity. Therefore, we performed a systematic literature review and meta-analysis of RCTs comparing continuous infusion with bolus injection of diuretics in patients with acute decompensated heart failure. Our meta-analysis contributes to medical understanding of the efficacy and safety of the optimal route of diuretic administration.

2. Methods

2.1. Literature search

Studies were identified by computer search in the MEDLINE, PubMed, EMBASE, SCOPUS, and Cochrane databases up to and including August 2013. The following MeSH search headings were used: *heart or cardiac or congestive*, *failure*, *loop diuretics*, *furosemide*, *torsemide*, *bumetanide*, and *lasix*. These terms and their combinations were also searched as text-words. The "related articles" facility in PubMed was used to broaden the search, and all retrieved abstracts, studies, and citations were reviewed. In addition, we attempted to identify other studies by hand-searching the reference sections of the accessed articles and by contacting known experts in the field. Finally, unpublished studies were sought in the ClinicalTrials.gov registry (http://clinicaltrials.gov/). No language restrictions were applied. The systematic review described herein was accepted by the online PROSPERO international prospective register of systematic reviews of the National Institute for Health Research (CRD42012002061).

2.2. Study selection

To be included in our analysis, studies were required to meet the following criteria: randomized, controlled studies that evaluate the efficacy and safety of continuous infusion vs bolus injection of diuretics in patients with acute decompensated heart failure from any etiology; clearly states the inclusion and exclusion criteria used for patient selection; and adequately describes the delivery procedures for the experimental drugs. Studies were excluded from our analysis if any one or more of the following conditions applied: the outcomes of interest were not clearly reported for each of the 2 administrative methods, and extraction or calculation of the appropriate data was not possible from the published results after the authors of the studies were contacted. When duplication articles using overlapping data sets were published, the study with the larger population was included.

2.3. Data extraction and quality assessment

Two reviewers (M.Y. Wu and K.W. Tam) independently extracted the following information from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, matching criteria, drug administration methods, urine output, body weight loss, parameters of renal function, and complications including electrolyte imbalance, change in creatinine levels, tinnitus or hearing loss, days of hospitalization, and cardiac and all-cause mortality. The retrieved studies were assessed for eligibility by the 2 reviewers according to the inclusion criteria specified. The individually recorded decisions of the 2 reviewers were compared, and any disagreements were resolved by a third reviewer (N.C. Chang). The authors of the studies were contacted for additional information when necessary.

The quality of studies was assessed using the "risk of bias" method recommended by the Cochrane Collaboration [14]. Several domains were assessed, namely, allocation generation; allocation concealment; blinding of participants, personnel, and outcome assessors; completeness of outcome data; freedom from selective reporting; and freedom from other bias.

2.4. Data synthesis and analysis

We used the following outcomes to evaluate the efficacy and safety of continuous and bolus diuretics for congestive heart failure (CHF): (1) urine output; (2) body weight loss; (3) complications including electrolyte imbalance, increase in creatinine, and tinnitus or hearing loss; (4) duration of hospitalization; and (5) cardiac mortality and all-cause mortality.

Urine output (in milliliters) was measured for 24, 48, or 72 hours. Weight loss was calculated by accurate measurement of body weight (in kilograms) before and after treatment, from the patient's admission until day 3 or discharge from hospital. *Electrolyte imbalance* was defined as the observation of hypokalemia or hypomagnesemia during treatment. Hypokalemia refers to a serum potassium level less than 3.5 meq/L, and hypomagnesemia means a serum magnesium level less than 1.5 mg/dL. Serum creatinine was measured from admission to day 3 or discharge, and changes were calculated accordingly. Tinnitus or hearing loss was as reported by patients. Cardiac mortality refers to cardiac arrest, sudden death, or death from cardiogenic shock.

We conducted the analysis using the statistical package Review Manager, Version 5 (Cochrane Collaboration, Oxford, England, UK). Meta-analysis was performed according to recommendations in the PRISMA guidelines [15]. When necessary, SDs were estimated from the provided confidence interval (CI) limits, SE, or range values [16].

We statistically analyzed the dichotomous outcomes using risk ratios (RRs) as the summary statistic. Continuous outcomes were analyzed using the weighted mean difference (WMD). Both types of summary statistics were reported with 95% CIs. Data were pooled only for studies that reported sufficiently similar clinical and methodological variables. A pooled estimate of the RR and WMD was computed using the DerSimonian and Laird random-effect model [17]. This calculation provides an appropriate estimate of the average treatment effect when studies are statistically heterogeneous; it yields relatively wide CIs, resulting in a relatively conservative statistical claim. Heterogeneity among the studies was assessed by the I^2 test and a null hypothesis test, in which $P < .1$ was considered to indicate significant outcome heterogeneity. Subgroups analyses were also performed by pooling estimates for similar subsets of patients across trials, where available. The Egger test was used to assess the funnel plot for significant asymmetry, indicating possible publication or other bias [18].

3. Results

3.1. Characteristics of the studies

Fig. 1 shows a flowchart for the selection of studies. Our initial search strategy yielded 1010 citations, 907 of which were ineligible