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Review

Hypertonic saline with furosemide for the treatment of acute congestive heart failure: A systematic review and meta-analysis ☆

Sumeet Gandhi [a,b,*], Wassim Mosleh [c], Robert B.H. Myers [b]

[a] McMaster University, Division of Cardiology, Hamilton, ON, Canada
[b] Sunnybrook Health Sciences Centre, Division of Cardiology, University of Toronto, ON, Canada
[c] Trinity College, Dublin, Ireland

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ABSTRACT

Background: Advanced congestive heart failure (CHF) therapies include intravenous inotropic agents, change in class of diuretics, and venous ultrafiltration or hemodialysis. These modalities have not been associated with improved prognosis and are limited by availability and cost. Compared to high-dose furosemide alone, concomitant hypertonic saline solution (HSS) administration has demonstrated improved clinical outcomes with good safety profile.
Methods: A literature search was conducted for randomized controlled trials that investigated the use of HSS in patients admitted to hospital with acute CHF.
Results: 1032 patients treated with HSS and 1032 controls, demonstrated decreased all-cause mortality in patients treat with HSS with RR of 0.56 (95% CI 0.41–0.76,$p = 0.0003$). 1012 patients treated with HSS and 1020 controls, demonstrated decreased heart failure hospital readmission with RR of 0.50 (95% CI 0.33–0.76,$p = 0.001$). Patients treated with HSS also demonstrated decreased hospital length of stay ($p = 0.0002$), greater weight loss ($p < 0.00001$), and preservation of renal function ($p < 0.00001$).
Conclusion: The results of this meta-analysis demonstrate that in patients with advanced CHF concomitant hypertonic saline administration improved weight loss, preserved renal function, and decreased length of hospitalization, mortality and heart failure rehospitalization. A future adequately powered, multi-centre, placebo controlled, randomized, double dummy, blinded trial is needed to assess the benefit of hypertonic saline in patients with renal dysfunction, in diverse patient populations, as well using a patient population on optimal current heart failure treatment. Pending further validation, there is promise for hypertonic saline as an advanced therapy for the management of acute advanced CHF.

1. Introduction

Therapy for the management of acute congestive heart failure (CHF) includes loop diuretics such as furosemide (Lasix™), with the goal of relieving pulmonary and systemic vascular congestion [1]. Diuretic resistance may result from escalating doses of furosemide and is characterized by diuretic ineffectiveness and exposure of patients to hypotension and acute kidney injury. Diuretic resistance results from a reduction in renal blood flow secondary to renal afferent arteriolar vasoconstriction, due to activation of the renin–angiotensin–aldosterone system (RAAS). Advanced heart failure therapies include intravenous inotropic agents, change in class of diuretics, and venous ultrafiltration or hemodialysis [2]. Despite short-term benefit, these modalities have not been associated with improved prognosis and are limited by availability and cost [3,4].

2. Diuretic resistance

Diuretic resistance is a reduction in natriuretic response that requires the use of escalating doses and/or combinations of loop and non-loop diuretics, often at the consequence of worsening renal function [5]. The body's perception of intravascular volume depletion with rapid diuresis in acute CHF results in activation of the RAAS and sympathetic nervous system [6]. Elevation in central venous pressure in CHF results in increased renal venous pressure and reduction in glomerular filtration rate. The response to this is intra-renal vasoconstriction, further reduction in glomerular filtration rate, decreased net filtration of salt and water, and reduction in renal blood flow. Patients with CHF

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* Corresponding author at: A-217, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada. Tel.: +1 416 480 4746; fax: +1 416 480 5251.
E-mail address: Sumeet.gandhi@medportal.ca (S. Gandhi).

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also have comorbidities that lead to chronic medical renal disease such as hypertensive nephropathy, diabetic nephropathy, and renal vascular disease, which over time results in nephron loss and reduction in GFR. This vulnerable substrate, combined with the activation of the neurohormonal cascade and reduction in glomerular filtration rate, results in decreased delivery of diuretics to the renal tubules requiring escalating doses of diuretics.

3. Hypertonic saline in CHF

Recent studies have proposed the use of intravenous (IV) hypertonic saline solution (HSS) in combination with high-dose furosemide for the management of advanced CHF. HSS alters renal and cardiac hemodynamics by increasing intracellular NaCl concentration, resulting in instantaneous mobilization of extravascular fluid into the intravascular space through the osmotic action of HSS [7]. Through the baroreceptor reflex, plasma volume expansion leads to a reduction in systemic vascular resistance [5]. Through these mechanisms, the small increase in preload and significant decrease in afterload results in increased cardiac output, renal blood flow and enhanced organ perfusion. This maintains a *therapeutic* furosemide concentration in renal tubules along with the continued delivery of sodium. Further studies in animal models suggest that HSS can increase myocardial contractility directly through hypertonicity [8] and decreases inflammatory markers such as tumour necrosis factor-α and interleukin-6, which are associated with adverse outcomes in patients with CHF [8].

Compared to IV high-dose furosemide alone, concomitant HSS administration has demonstrated improved diuresis, preservation of renal function, improvement in cardiac biomarkers and echocardiographic parameters [9–11], reduction in length of hospitalization, reduced readmissions to hospital for CHF, and reduced mortality with good safety profile. We have performed a systematic review of studies assessing the efficacy of HSS in combination with furosemide for the treatment of acute advanced CHF.

4. Methods

4.1. Study selection

A systematic search was conducted to retrieve studies that investigated the use of hypertonic saline with furosemide for treatment of acute advanced congestive heart failure. We identified potential English-language sources from the Pubmed, Medline, EMBASE, and Cochrane databases from 1950 to November 2013. Keywords used were (hypertonic saline) and (heart failure). Electronic search of abstracts available online were also reviewed from the annual congresses of the Canadian Cardiovascular Congress, European Society of Cardiology, American College of Cardiology, the American Heart Association, and the American Society of Nephrology.

4.2. Inclusion/exclusion criteria

Studies were included if they met the following criteria: (i) subjects included patients with acute advanced congestive heart failure treated with hypertonic saline and adjuvant furosemide; (ii) control group included patients with acute advanced heart failure treated with furosemide; and (iii) published abstract or full article in the English language. Eligibility assessment and data extraction were carried out independently by two investigators (SG and WM) with discrepancies resolved by consensus in consultation with the senior author.

4.3. Outcomes of interest

Primary outcomes of interest were the pooled relative risk ratio (RR) of (i) all-cause mortality and (ii) heart failure hospital readmission in patients. Secondary outcomes were length of hospitalization, weight loss, and change in serum creatinine.

4.4. Study quality and data extraction

Quality assessment was carried out independently by two investigators (SG and WM) using the Newcastle–Ottawa quality assessment scale. We assessed eligibility by three criteria: the selection of the study groups (0–4 points), the comparability of the groups (0–2 points), and the ascertainment of either the exposure or outcome of interest (0–3 points), with a total score of 9. A score ≥5 was adequate for inclusion in the meta-analysis. Discrepancies in interpretation of data and inclusion of studies were resolved in consultation with the senior author.

4.5. Statistical analysis

Meta-analysis was conducted by combining the risk ratios of individual studies into a pooled risk ratio using a random-effect model. Relative risk ratios are reported with 95% confidence intervals and a p value <0.05 was considered to be statistically significant. We tested for heterogeneity using the chi-squared test and the I^2 test. The I^2 test describes the percentage of variability in effect estimates that is due to heterogeneity rather than chance. A value of 25% suggests low variability, 50% suggests moderate variability, and 75% suggests high variability between studies [12]. Mean difference was calculated for continuous variables using a random-effect model, reported with 95% confidence intervals. Comparison of mean difference was calculated using generic inverse variance method. Funnel plots were constructed to assess for publication bias. Analyses were performed with RevMan 5.1 (Review Manager (RevMan) [Computer program] Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

5. Results

5.1. Search results

Our search strategy yielded 107 studies, of which 87 were excluded on review of the title and abstract (Fig. 1). A further 10 studies were excluded after careful review of the full text. Where only partial information on the outcomes of interest was reported, the authors were contacted and asked to provide additional information. Five review articles were excluded as no new patient data was offered [5,13–16]. One case report of a patient with cardiogenic shock who was administered 10% NaCl hypertonic saline with improvement in dyspnea was also excluded [17]. Ventrella et al. treated patients with *cardiorenal syndrome* with intravenous hypertonic saline and high-dose furosemide; this study was excluded as the authors could not provide an English language translation of their article [18]. Paterna et al. conducted a randomized control trial treating patients with acute heart failure with hypertonic saline with high dose furosemide compared to hypertonic saline and torasemide [19]. This study was excluded due to lack of a

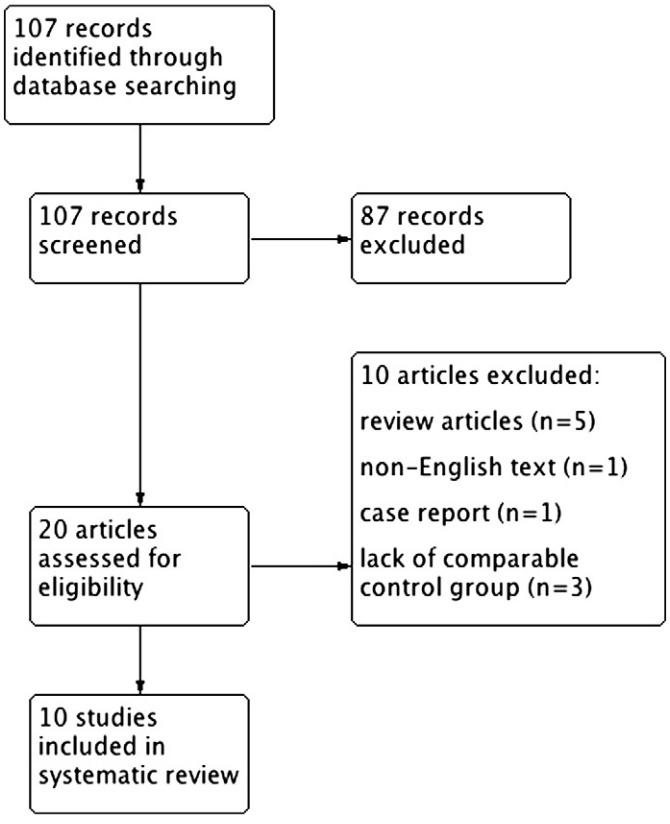

Fig. 1. Flow diagram of studies included in systematic review.