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Review Article

Decongestion: Diuretics and other therapies for hospitalized heart failure

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ABSTRACT

Acute heart failure (AHF) is a potentially life-threatening clinical syndrome, usually requiring hospital admission. Often the syndrome is characterized by congestion, and is associated with long hospital admissions and high risk of readmission and further healthcare expenditure. Despite a limited evidence-base, diuretics remain the first-line treatment for congestion. Loop diuretics are typically the first-line diuretic strategy with some evidence that initial treatment with continuous infusion or boluses of high-dose loop diuretic is superior to an initial lower dose strategy. In patients who have impaired responsiveness to diuretics, the addition of an oral thiazide or thiazide-like diuretic to induce sequential nephron blockade can be beneficial. The use of intravenous low-dose dopamine is no longer supported in heart failure patients with preserved systolic blood pressure and its use to assist diuresis in patients with low systolic blood pressures requires further study. Mechanical ultrafiltration has been used to treat patients with heart failure and fluid retention, but the evidence-base is not robust, and its place in clinical practice is yet to be established. Several novel pharmacological agents remain under investigation.

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1. Introduction

Acute heart failure (AHF) is a potentially life-threatening clinical syndrome, usually requiring hospital admission. The syndrome is heterogenous, but the largest group of patients is those who develop peripheral and pulmonary congestion over days or weeks prior to hospitalization. AHF can occur de novo, or can occur in patients with chronic heart failure. In extreme cases, cardiogenic shock may be present, with symptoms and signs of poor organ perfusion due to low cardiac output and low blood pressure.

Although there is some variation internationally in the duration of hospitalization with AHF, in many countries, patients are admitted for at least 1 week, with an inpatient mortality of 5–10%, and up to 25% are readmitted within a month of discharge.[1] With the aging population, the burden of heart failure (HF) on health services is expected to rise, with increasing healthcare expenditure and activity.

The management of AHF has remained largely unchanged over the past 20 years. Across Europe, a quarter of patients hospitalized because of worsening HF have signs of inadequate decongestion at the time of discharge,[2] and this is

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Abbreviations: HF, heart failure; AHF, acute heart failure; UF, ultrafiltration.
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associated with increased risk of readmission and a poorer prognosis.[3] Furthermore, almost a third of patients hospitalized with HF with congestion have worsening renal function and have an impaired response to diuretics. Such patients frequently have more advanced HF, characterized by even longer lengths of hospital stay, more frequent readmissions, and high degree of morbidity and mortality compared to patients who are sensitive to diuretics.[4,5] Clinical management is challenging and variable, partially due to the lack of a robust evidence-base on which to base treatment decisions.[6]

Congestion not only has a significant effect on symptoms and quality of life, but is also associated with cardiac, renal, and liver injury, which are in turn associated with worse clinical outcomes.[7] Rapid relief of congestion is increasingly recognized as an important therapeutic target, not only to improve symptoms, but also to improve prognosis, reduce hospital length of stay, and to contain costs to the healthcare system.[8]

In this review, we highlight and discuss the appropriate management of congestion in patients with heart failure based on the (limited) evidence-base for diuretics and other pharmacological and nonpharmacological strategies currently available. Further research is urgently needed to optimize the outcome for patients, and to ensure best treatment at a sustainable cost to the healthcare system.

2. Decongestion with diuretics

The type, mechanism of action, and use of diuretics and their common side effects are summarized in Table 1. The clinical evidence for the efficacy of diuretics in reducing the symptoms of heart failure is based on clinical experience and relatively small-randomized studies. Most clinical practice guidelines on the management of heart failure have given diuretic therapy a 'Class I' recommendation (evidence and/or general agreement that a given treatment or procedure is beneficial, useful, or effective'), with consensus that diuretics help relieve symptoms of congestion in patients presenting with fluid retention.[9,10]

In the most recent European guidelines on heart failure,[10] diuretics are recommended for the relief of dyspnea and edema in patients with signs and symptoms of congestion, irrespective of left ventricular ejection fraction, with the stated aim of achieving and maintaining euvolemia with the lowest achievable dose of diuretic. It is acknowledged that the dose must be adjusted, particularly after restoration of 'dry body weight', to avoid the risk of intravascular volume depletion and dehydration, which can lead to hypotension, renal dysfunction, and the inability to introduce disease-modifying therapies, such as angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists.

2.1. *Placebo-controlled trials of diuretics*

Placebo-controlled randomized trials of diuretic therapy for the treatment of heart failure are limited to studies that include small number of patients (ranging from 3 to 247 patients). All of these studies reported that diuretics significantly improved symptoms in heart failure.[15–17] None was powered to estimate the effect on mortality, but a meta-analysis of three short-term studies (follow-up ranging from 1 to 12 months) reporting mortality suggested a 75% relative mortality reduction [95% CI 16–93% $p = 0.03$]; the number of deaths was low (12 in the placebo group and 3 in the diuretic group), and the majority of the patients within the meta-analysis were unlikely to have met the contemporary definition of AHF.[18]

2.2. *Trials of thiazide versus loop diuretic*

Several small studies suggest that loop diuretics are more effective than thiazides alone in the management of HF.[17,19,20] Furthermore, thiazides are also more likely to result in electrolyte abnormalities, such as hypokalemia and hyponatremia.[11,17] Thiazides as sole diuretic agents have a less abrupt onset and longer duration of action than loop diuretics.[21]

2.3. *Dose of loop diuretic*

The Diuretic Optimization Strategies Evaluation (DOSE) trial is the largest prospective, double-blind, randomized trial to evaluate initial diuretic strategies in patients with acute heart failure.[22] Using a 2×2 factorial design, the DOSE trial randomized 308 patients with acute heart failure to IV furosemide given as twice-daily boluses or continuous infusion, and to either a low-dose strategy (IV dose numerically equivalent to the patient's oral dose) or a high-dose strategy (2.5 times oral dose given intravenously), with specified dose adjustments permitted after the first 48 h.

There was no significant difference in either of the co-primary endpoints of global assessment of symptoms, or change in serum creatinine over 72 h, with diuretic administration by bolus or continuous infusion or with a low-versus a high-dose strategy. However, patients randomized to the higher dose strategy had a more favorable outcome with regard to several secondary measures, including relief of dyspnea ($p = 0.04$), reduction in weight ($p = 0.01$), and net fluid loss ($p = 0.01$), albeit with a greater risk of serum creatinine increasing by >0.3 mg/dL within 72 h (23% versus 14%, $p = 0.04$). There was no difference in length of initial hospital stay, or in days alive and out of hospital at day 60.

The trial data therefore suggest that a strategy of using higher doses of diuretics on admission to hospital with AHF is likely to more rapidly control fluid retention and relieve symptoms at the cost of a slightly higher risk of renal dysfunction. Such a strategy does not, however, appear to affect initial length of stay in hospital or the readmission rate. Importantly, the DOSE trial[22] demonstrated that there was no difference between giving diuretics as a continuous infusion versus boluses.

2.4. *Decongestion with hypertronic saline to facilitate effect of loop diuretics*

A single group has reported several randomized single-blind studies that demonstrate that the combination of hypertronic saline infusion (150 ml of 3% NaCl) with a furosemide 250 mg infusion is superior to furosemide infusion alone in terms of increasing diuresis and serum sodium levels, and in reducing the length of hospital stay. Mortality (12.9% versus 23.8%; $p < 0.0001$) and readmission rate (18.5% versus 34.2%; $p < 0.0001$) were both reported to be reduced over a median

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