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Approaches to Decongestion in Patients with Acute Decompensated Heart Failure

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Abstract

Loop diuretics remain a mainstay in the pharmacologic treatment of acute decompensated heart failure (ADHF). Recent randomized trial results have challenged existing clinical dogma about the optimal manner of intravenous diuretic administration in hospitalized patients. The Diuretic Optimization Strategies Evaluation (DOSE) trial, while technically a neutral study, suggested some advantages of a high-dose diuretic strategy as compared with low dose administration without evidence of long term safety concerns. The DOSE study additionally showed no difference in efficacy or safety between continuous infusion or bolus diuretic therapy. Venovenous ultrafiltration (UF) holds promise as an alternative approach to volume removal in ADHF, but significant work remains in characterizing the relative risks and benefits of this technique, as well as the degree to which it can be broadly utilized. This review highlights current approaches and future directions in mitigating congestion and volume overload in the ADHF population, with a particular focus on novel diuretic dosing strategies and on the emerging role of UF.

Keywords

Loop diuretic; Ultrafiltration; Heart failure; Acute renal failure; Electrolytes; Decongestion; Acute decompensated heart failure

Introduction

Despite advances in our collective understanding of its pathophysiology and treatment, heart failure remains a common disease imparting significant individual suffering and societal cost. In the United States, more than 5 million patients suffer from heart failure, a condition that results in more than 1 million hospitalizations annually [1]. Hospitalization for heart failure is associated with a high rate of recurrence and is a primary driver of rising health care costs, and as such has become a focus of health care reform efforts aimed improving quality and cost-effectiveness.

Hemodynamic and clinical congestion, as manifest by elevated ventricular filling pressures and clinical symptoms (dyspnea, orthopnea) and signs (edema, elevated JVP) is the primary cause of most heart failure hospitalizations [2, 3]. Moreover, there is evidence to suggest

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that inpatient success at achieving measurable gains against congestion is at best mixed [4], and substantial proportion of patients may still have signs or symptoms of congestion at the time of hospital discharge [5]. Finally, a large body of data increasingly suggests that successful resolution of congestion is the key factor in reducing post discharge events, especially rehospitalization [6–8].

Multiple fundamental questions arise in the clinical management of congestion and volume overload resulting from ADHF: 1) What acute therapies are effective in producing symptomatic relief, and 2) What is the optimal manner of delivering those therapies? 3) Do differences in acute management of congestion have an impact on downstream (i.e., post discharge) clinical outcomes? Recent trials have helped shed new light on the answers to these questions and suggest novel approaches to optimal use of these proven therapies. The role of loop diuretics in relieving congestion has long been established and remains a mainstay in the treatment of ADHF. A variety of adjunctive approaches to loop diuretics have been used in clinical practice but have not generally been rigorously tested. More recently, ultrafiltration (UF) has emerged as an alternative means of congestion relief in ADHF population. We describe the existing evidence for how best to deliver each of these therapies, and further address the established and presumed strengths and drawbacks of each.

Loop Diuretic Therapy

Loop diuretics exact their pharmacologic effect via inhibition of the $\text{Na}^+/\text{2Cl}^-/\text{K}^+$ cotransporter in the ascending Loop of Henle. This ultimately results in natriuresis and diuresis via the decrease in sodium and chloride reabsorption [9]. Because of their rapid onset and effect, intravenous loop diuretics have long been the mainstay of ADHF therapy, and clinical experience has generally demonstrated improvements in ventricular filling pressures, congestion and important symptoms such as dyspnea.

Despite the tangible short-term benefits of loop diuretic administration, there are important potential downsides and limitations. Loop diuretics can activate the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), physiologic phenomena that play a key role in heart failure progression [10–12]. Via effects on RAAS and SNS, diuretics can produce a decrease in glomerular filtration rate (GFR) and worsening renal function. A variety of electrolyte abnormalities can occur after diuretic administration, including hypokalemia, hypomagnesemia and hyponatremia. These metabolic derangements potentially increase the occurrence of dangerous arrhythmias [13]. Finally, multiple observational studies had previously suggested that loop diuretics, especially when used at higher doses, were associated with increased risk of heart failure progression, renal failure, and mortality [14, 15].

The Diuretic Optimization Strategies Evaluation (DOSE) trial was designed in an effort to better understand the answer to the following question: what is the most clinically beneficial way to deliver intravenous loop diuretics to the hospitalized ADHF patient population [16••]? In this prospective, double-blind randomized trial conducted by the NHLBI Heart Failure Clinical Research Network, patients with ADHF were randomized into one of four treatment arms using a 2-by-2 factorial design: low-dose diuretics delivered in twice daily intravenous boluses, low-dose diuretics delivered by continuous infusion, high-dose diuretics delivered in twice daily intravenous boluses, and high-dose diuretics delivered by continuous infusion. This design permitted controlled comparison of high versus low dose strategies and of continuous versus bolus administration strategies.

Selected key results of the DOSE study are summarized in Table 1. Based on the co-primary endpoints of relief of symptoms based on patient global assessment and change in creatinine

at 72 hours, the DOSE study was neutral with regard to both the comparison of dose and route of administration. More detailed review of the data, however, suggests some important “take-home” messages. First, the high-dose strategy (HDS) appeared to offer some clinically important advantages relative the low-dose strategy (LDS), as measured by statistically and clinically significant improvements in global self-assessed dyspnea scores, change in weight at 72 hours, and net fluid loss at 72 hours. The HDS and LDS groups performed similarly, as measured by hospital length of stay, days alive and out of hospital, and serum creatinine at 60 days. The only clinical metric by which the LDS group performed favorably relative to the HDS group was in the proportion of patients experiencing a serum Cr increase of > 0.3 mg/dl. However, this difference in rates of acute renal failure was no longer present at discharge from the index hospitalization or at 60 days. Second, despite the classic dogma that continuous infusion of diuretic offers advantages over bolus administration, the results from the DOSE trial refute this assumption in the patient population studied. Across a spectrum of clinical metrics (global self-assessed overall symptoms, global self-assessed dyspnea, change in weight at 72 hours, net fluid loss at 72 hours, renal function at 72 hours, renal function at 60 days, hospital length of stay, alive and out of hospital days), the continuous infusion group and the bolus administration group performed similarly.

Taken as a whole, the results of DOSE suggest that in ADHF patients, higher doses of diuretic may offer clinical advantages in terms of greater diuresis, weight loss, and relief of dyspnea, without any identified long-term disadvantages. These specific advantages take the form of patient reported symptoms as well as evidence for more effective decongestion as measured by volume loss, weight loss, and decreases in natriuretic peptide levels. Although the HDS group had higher rates of worsening renal function at 72 hours, these effects were transient and not associated with any signal for worsening long term outcomes. These results suggest that clinicians should consider adequate decongestion a critical goal of ADHF therapy, and that transient changes in renal function may be an acceptable price to pay in order to achieve greater short-term fluid removal and symptom relief. Additionally, for hospitalized ADHF patients requiring relief of congestion and volume overload, continuous diuretic infusion offered no significant advantages over IV bolus administration when assessed across a variety of clinical end-points.

Thiazide-Type Diuretics

In ADHF patients who continue to exhibit signs and symptoms of congestion, despite an adequate trial of loop diuretics, adjunctive use of thiazide diuretics may help augment diuresis by inhibiting the Na/Cl co-transporter in the distal tubule, thus blocking sodium resorption [17]. As described by Jentzer et al., this leads to two important effects: 1) antagonism of the renal adaptation to chronic loop diuretic therapy, and 2) improvement or reversal of loop diuretic resistance due to rebound sodium resorption. This enhanced diuresis could potentially lead to faster achievement of symptom relief, more effective overall weight reduction, and shorter length of stay with fewer subsequent re-admissions, especially in patient demonstrating a substantial degree of diuretic resistance and or with significant renal dysfunction. Importantly however, these questions have not been carefully evaluated in prospective controlled clinical trials, and the risk benefit ratio of adjunctive thiazide diuretics remains uncertain.

The potential benefits imparted by the addition of a thiazide diuretic must be balanced against the potential risks, specifically the risk of resulting electrolyte and metabolic abnormalities. Hypokalemia is a frequent consequence of the sequential nephron blockade that results from combining a thiazide diuretic such as metolazone with a loop diuretic [18]. Hypomagnesemia, hypochloremic metabolic acidosis, and hyponatremia are also potential

concerns. Frequent monitoring of electrolyte and metabolic status is a critical part of preventing the morbidity and mortality associated with arrhythmic events [13].

Ultrafiltration

Ultrafiltration (UF) has emerged as an alternative approach to volume removal in the congested ADHF patient population, particularly with the introduction of peripheral venovenous techniques. UF permits the extracorporeal removal of plasma water from the whole blood across a semi-permeable membrane, a membrane across which there exists a pressure gradient [9].

UF has several potential advantages over a pharmacologic strategy. UF permits precise selection of the hourly rate of net fluid removal, thus potentially yielding a more accurate accounting of net fluid removal per diem relative to traditional quantification methods. A UF-based approach potentially avoids diuretic associated electrolyte abnormalities, namely hypokalemia. Because the ultrafiltrate is isotonic, UF removes less potassium than diuretics, instead removing more sodium for a given amount of net fluid removal and potentially leading to greater overall decongestion. Finally, by establishing a steady state of net fluid removal, whereby net fluid removal is in concert with the interstitial fluid mobilization rate, UF may limit significant fluctuations in intravascular volume. Doing so potentially avoids worsening neurohormonal activation that can limit an aggressive diuretic approach.

The presumptive disadvantages of UF relative to a traditional loop diuretic approach are important to recognize. There are unavoidable labor and capital commitments necessary for its effective use [19]. UF cannot occur without ample availability of exchange filter systems and of appropriately trained staff members able to run the system and troubleshoot when necessary. In an attempt to prevent circuit clotting, UF requires some systemic anti-coagulation, with the theoretic potential for excess bleeding. The historical invasiveness of vascular catheters necessary for the performance of UF has given way to a less invasive alternative in the form of a peripheral venovenous approach.

The evidence base for the use of UF in ADHF has been primarily based on two trials, Relief for Acutely-Fluid Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) and Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD).

The RAPID-CHF trial was designed as a proof-of-concept study to assess both the safety and efficacy of UF in a small population of patients hospitalized with ADHF [20]. Forty patients were enrolled, each randomized to either an 8-hour session of UF or to usual care. Though there was no significant difference between UF and usual care when it came to weight loss at 24 hours, UF performed favorably relative to usual care when it came to: 1) cumulative fluid removal at 24 hours, 2) improvements in dyspnea at 48 hours, and 3) improvements in heart failure symptoms at 48 hours. Two of the 20 patients randomized to the UF arm did not successfully receive UF therapy, due to difficulty obtaining intravenous access and due to inability to withdraw blood from a successfully inserted venous catheter, respectively. The results from RAPID-CHF set the stage for the UNLOAD study, assessing the relative efficacy of UF versus usual care in ADHF.

Building upon the results from RAPID-CHF, the UNLOAD trial was designed to provide more data comparing the safety and efficacy of venovenous UF and usual diuretic-based care as a primary strategy in ADHF patients [21]. Two-hundred patients were enrolled and randomized to one of two primary treatment arms. In the first 48 hours of their hospitalization, patients randomized to the UF arm received UF exclusively, with diuretics

prohibited during this time window. Key selected results of the trial are summarized in Table 2.

The co-primary endpoints were weight loss at 48 hours and patient self-assessed dyspnea score. While UF provided clinically and statistically significant improvements in weight loss compared to standard diuretic therapy when it came to weight loss at 48 hours, there was no significant difference in dyspnea scores at 48 hours. There were no appreciable differences in renal function assessed at various time points both during and following the index hospitalization although creatinine tended to be numerically higher in the UF arm. UF performed better when it came to avoidance of hypokalemia. Despite the anti-coagulation regimen used for UF delivery, less bleeding was observed in the UF group than in the standard diuretic therapy group. Finally, UF performed better when it came to two outcomes: 1) freedom from heart failure (HF) hospitalization at 90 days, 2) unscheduled office and emergency department visits. Importantly, limitations exist which may limit the conclusions from the UNLOAD study. The study was non-blinded, HF re-hospitalization was investigator-reported, and re-hospitalization criteria were not explicitly defined. Enthusiasm for a UF approach to congestion and volume overload is further tempered by uncertainty regarding the cost-effectiveness implications of this therapy. Even if the reductions in re-admission and unscheduled office visits are indeed validated by larger studies designed to primarily assess these outcomes, it remains unclear whether downstream cost-savings are sufficient to offset the relative resource-intensity of providing upfront UF therapies.

Next Steps

In the current era of comparative effectiveness, the attempts to better define optimal approaches to decongestion using diuretics represent an example of applying the principles of evidence based medicine even to well established therapies. Despite this promising step, many potentially important clinical questions remain unanswered. In clinical practice, a common use of UF therapy is in patients who develop worsening renal function during diuretic therapy with evidence of persistent congestion (the type I cardiorenal syndrome as defined by Ronco) [22]. The safety and efficacy of UF vs. stepped pharmacology care in this population is being tested in the NHLBI sponsored Cardiorenal Rescue in Acute Decompensated Heart Failure (CARRESS-HF) randomized trial, which will report results soon[23].

Additionally, ongoing research continues into whether either alternatives or adjuncts to loop diuretics as a therapy for congestion. The ongoing NHLBI sponsored Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE) study (NCT01132846) is evaluating the efficacy of either “renal dose” dopamine or low dose nesiritide as adjuncts to diuretics in patients with ADHF. Research continues into the potential use of tolvaptan, a vasopressin V₂ receptor antagonist that is FDA approved for hyponatremia, as an adjunct for diuretics therapy in ADHF. Although the long term EVER-EST study did not show a long term benefit with tolvaptan therapy [24], short term data suggest the possibility of important effects on dyspnea [25]. The ongoing Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure (TACTICS) (NCT01644331) and Short Term Clinical Effects of Tolvaptan in Patients Hospitalized for Worsening Heart Failure With Challenging Volume Management (Secret of CHF) (NCT01584557) studies are assessing the adjunctive use of tolvaptan in addition to diuretic regimens in the short term management of congestion in heart failure.

An important limitation of existing data on decongestion strategies in hospitalized heart failure patients has been the focus on “soft” endpoints (e.g., symptom relief, net fluid loss,

and biomarkers) rather than “hard” outcomes (e.g., rehospitalization or mortality). As noted above, the one study of a decongestion intervention sufficiently powered to address morbidity and mortality (EVEREST) did not show any significant difference between tolvaptan and placebo. The UNLOAD study with ultrafiltration showed an unexpected effect of heart failure hospitalizations, but this was not a planned endpoint and the number of events were small. Future studies will ideally focus on both shorter term signs and symptoms as well as post discharge morbidity and mortality, although the sample size required to demonstrate downstream effects remains a challenge for trial design in the context of generic therapies (such as diuretics) with limited funding sources.

Conclusion

Though ADHF patients continues to experience a high burden of morbidity and mortality, there have been encouraging developments in how to improve delivery of acute therapies targeting congestion and volume overload. Through a rigorous, randomized approach, the DOSE trial has provided important guidance on how to effectively and safely deliver diuretic therapy and has helped reinforce the important principle that delivery of existing therapies should continue to be informed by trial-based evidence. Ultrafiltration as a primary means of fluid removal in ADHF patients has shown promise but clearly needs more study characterizing and clarifying its cost and benefit profile and informing optimal patient selection. Ideally, future studies will need to address the effects of decongestion strategies on both short term and post discharge morbidity and mortality endpoints. Ultimately, this work will serve to better inform how we achieve maximal therapeutic benefit at minimal risk for patients hospitalized with congestion due to ADHF.

Clinical Trial Acronyms

DOSE	Diuretic optimization strategies evaluation
RAPID-CHF	Relief for acutely-fluid overloaded patients with decompensated congestive heart failure
TACTICS-HF	Targeting acute congestion with tolvaptan in congestive heart failure
UNLOAD	Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated congestive heart failure

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Table 1

Loop diuretic administration in ADHF: a tabular presentation of key results and potential management lessons from the DOSE trial

Key endpoints	High-dose strategy versus low-dose strategy	P value
Patient self-assessments		
Global self-assessment of overall symptoms over 72 hr (co-primary endpoint)	No difference (<i>trend favors high-dose</i>)	0.06
Global self-assessment of dyspnea over 72 hr	High-dose performed better	0.04
Congestion and clinical assessment		
Change in weight at 72 hrs	High-dose performed better	0.01
Net fluid loss at 72 hrs	High-dose performed better	0.001
Change in NTproBNP	No difference (<i>trend favors high-dose</i>)	0.06
Resolution of clinical congestion at 72 hours	No difference (<i>trend favors high-dose</i>)	0.09
Patients with worsening or persistent heart failure	No difference	0.40
Impact on renal function		
Mean change in serum Cr at 72 hr (Co-primary endpoint)	No difference	0.21
Proportion of patients with serum Cr increase >0.3 mg/dl within 72 hr	Low-dose performed better	0.04
Process & outcome measures		
Hospital length of stay (days)	No difference	0.55
Alive and out of hospital (days)	No difference	0.42

Cr=creatinine; mg/dl=milligrams per deciliter

(Adapted from Table 2 from: Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. New England J Med 2011;364:797–805) [16••]

Table 2

Ultrafiltration (UF) in ADHF: a tabular presentation of key results and potential management lessons from the UNLOAD trial

Key endpoints	UF vs. standard care (diuretics)	P value
Metrics during index hospitalization		
Weight loss at 48 hr (co-primary)	UF performed better	0.001
Mean dyspnea score at 48 hr (co-primary)	No difference	0.35
Renal function & electrolytes		
Rise in serum Cr>0.3 mg/dL at 48 hours	No difference	0.53
Avoidance of hypokalemia ($K^+ < 3.5$)	UF performed better	0.018
Process & outcome measures		
Adverse event: bleeding	UF performed better	0.03
Freedom from heart failure hospitalization at 90 days	UF performed better	0.037
Unscheduled office and ED visits	UF performed better	0.009

Cr=creatinine; ED=emergency department; UF=ultrafiltration

(Adapted from: Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *Journal of the American College of Cardiology* 2007;49:675–83) [21]