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ABSTRACT

Background: The concept of multinephron segment diuretic therapy (MSDT) has been recommended in severe diuretic resistance with only expert opinion and case-level evidence. The purpose of this study was to investigate the safety and efficacy of MSDT, combining 4 diuretic classes, in acute heart failure (AHF) complicated by diuretic resistance.

Methods and Results: A retrospective analysis was conducted in patients hospitalized with AHF at a single medical center who received MSDT, including concomitant carbonic anhydrase inhibitor, loop, thiazide, and mineralocorticoid receptor antagonist diuretics. Subjects served as their own controls with efficacy evaluated as urine output and weight change before and after MSDT. Serum chemistries, renal replacement therapies, and in-hospital mortality were evaluated for safety. Patients with severe diuretic resistance before MSDT were analyzed as a subcohort. A total of 167 patients with AHF and diuretic resistance received MSDT. MSDT was associated with increased median 24-hour urine output in the first day of therapy compared with the previous day (2.16 L [0.95–4.14 L] to 3.08 L [1.74–4.86 L], P = .003) in the total cohort and in the Severe diuretic resistance cohort (0.91 L [0.43–1.43 L] to 2.08 L [1.13–3.96 L], P < .001). The median cumulative weight loss at day 7 or discharge was −7.4 kg (−15.3 to −3.4 kg) (P = .02). Neither serum sodium, chloride, potassium, bicarbonate, or creatinine changed significantly relative to baseline (P > .05 for all).

Conclusions: In an AHF cohort with diuretic resistance, MSDT was associated with increased diuresis without changes in serum chemistries or kidney function. Prospective studies of MSDT in AHF and diuretic resistance are warranted. (J Cardiac Fail 2021;00:1–10)

Key Words: Acute heart failure, heart failure, diuretic, diuretic resistance, multinephron segment diuretic therapy.

Failure to achieve clinical decongestion by hospital discharge occurs in a substantial proportion of acute heart failure (AHF) hospitalizations.1,2 Patients discharged with signs and symptoms of hypervolemia are at higher risk for mortality and readmission.1,4 Diuretic resistance is a frequent complication of AHF and contributes to inadequate decongestion.5,6 Stepwise increases in decongestive therapy intensity are recommended to overcome diuretic resistance, including increasing loop diuretic doses, diuretic combinations, and extracorporeal renal therapies such as ultrafiltration.5,7,8 There is a paucity of evidence to guide therapy when combinations of high-dose loop and thiazide diuretics do not result in diuretic efficacy.7,9,10 Ultrafiltration has not demonstrated decongestive superiority over diuretic therapy in randomized AHF trials and was associated with more complications.11,12 The modern diuretic armamentarium consists of many diuretic agents that could work synergistically to overcome diuretic resistance while mitigating the electrolyte and acid–base imbalances associated with each individual diuretic agent alone.13,14 Multinephron segment diuretic therapy (MSDT), defined as the simultaneous use of 4 diuretic classes with actions along the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct, is a potential method to overcome severe diuretic resistance in AHF.

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We report our experience with MSDT in AHF complicated by diuretic resistance as hypothesis-generating data in a real-world cohort at a single US medical center.

**Methods**

We retrospectively identified hospitalized patients receiving MSDT at Vanderbilt University Medical Center (VUMC) from November 2017 to July 2019. This study was approved by the VUMC Institutional Review Board. Adult patients (age ≥18 years) with simultaneous active orders for carbonic anhydrase inhibitor, loop, thiazide, and mineralocorticoid receptor antagonist diuretics were identified within the EPIC electronic medical record and verified to have received these medications using the medication administration record. A standard MSDT regimen is recommended by consultant nephrology and heart failure specialists at VUMC for patients with hypervolemia and diuretic resistance (acetazolamide 250mg orally every 8 hours, intravenous [IV] furosemide 200 mg every 6 hours, metolazone 10 mg orally every 12 hours, and spironolactone 100 mg orally twice daily), yet clinicians can order any adaptation of MSDT without restriction. Therefore, we included any dosing or medication variations of this quadruple diuretic class MSDT regimen in this analysis. A carbonic anhydrase inhibitor diuretic included either IV or oral acetazolamide. An IV loop diuretic included either furosemide or bumetanide administered as an IV bolus or continuous infusions. Thiazide diuretics included oral metolazone or IV or oral chlorothiazide. Other thiazides were included if the dose was adequate to cause diuresis, excluding low-dose thiazides prescribed for hypertension. Mineralocorticoid receptor antagonists included either oral spironolactone or eplerenone. We excluded patients currently receiving renal replacement therapies (RRT), including intermittent hemodialysis, ultrafiltration, and continuous RRT. Patients with a history of RRT use could be included if they were no longer receiving RRT on the day of MSDT prescription and were not planned to continue RRT in the future.

We defined the MSDT initiation date as the first calendar date all 4 diuretics were simultaneously prescribed and administered. If the time of MSDT initiation was later than 18:00 hours, we considered the following date the MSDT initiation date. From the MSDT initiation date (day 1), we analyzed data 2 days before MSDT initiation (day −2) followed by day 2, day 4, and day 7 or the date of discharge or death if sooner. If the patient was not admitted to the hospital 2 days before MSDT initiation, we used data from 1 day before MSDT initiation. The daily cumulative mineralocorticoid receptor antagonist diuretic doses include both spironolactone and eplerenone as equivalent milligrams. Daily cumulative loop diuretic doses are expressed in furosemide equivalents, with 1 mg of IV bumetanide equal to 40 mg of IV furosemide.

**Outcomes**

Diuretic response was quantified by urine output and weight change. Cumulative urine values for the date were the sum of all urine output values charted on a given calendar date. For days with multiple recorded weights, we prioritized the standing weight over a bed weight and the first measurement of the day. If a weight value was missing for the calendar date, we used a weight from the previous or following day when available. Safety was assessed by vital signs, serum chemistries, electrolyte repletion, diuretic efficiency was calculated as the total daily urine output per 40 mg of IV furosemide administered.15

MSDT responders were classified a priori as patients with a urine output of 2 L or more on the date of MSDT initiation or 1 day after MSDT initiation and no RRT during the hospitalization. This designation was chosen to identify patients whose diuretic response would result in at least a net even 24-hour fluid balance with a standard 2-L fluid restriction.
Continuous data are shown as mean ± standard deviation or median (quartile 1—quartile 3) according to observed distribution. Categorical data are shown as frequency (percentage). Categorical variables were compared with the χ² test. Statistical analyses of differences in means for continuous variables in the same patient were performed using a paired samples t test between 2 measurements or repeated measure analysis of variance for multiple measurements. Continuous variables were compared between responder groups using an independent t test for normal distribution and the Mann—Whitney U for a skewed distribution. Statistical significance was defined as a 2-tailed P value of less than 0.05. Statistical analyses were performed using R version 4.0.0 and IBM SPSS Statistics version 26 (IBM Corp, Armonk, NY).

Results

We identified 167 patients hospitalized for AHF with diuretic resistance and treated with simultaneous MSDT, comprising an oral carbonic anhydrase inhibitor, IV loop diuretic, oral or IV thiazide, and oral mineralocorticoid receptor antagonist. Baseline characteristics of the total and severe diuretic resistance cohorts are presented in Table 1. The mean time from hospital admission to MSDT initiation was 9 ± 8 days, with 16% within the first 2 days. The majority of patients (87%) had a previous diagnosis of HF, whereas 13% of patients had new hypertensive AHF secondary to a preexisting renal disease. Approximately one-half of patients had a reduced left ventricular ejection fraction. Kidney dysfunction (median serum creatine 2.3 mg/dL [interquartile range (IQR) 1.5—3.1 mg/dL]) was common at baseline. In the severe diuretic resistance cohort (n = 75), the median baseline 24-hour urine output was only 0.91 L (IQR 0.43—1.43 L) to a median IV furosemide daily dose of 480 mg/d (IQR 200—720 mg/d), resulting in a median diuretic efficiency of 70 mL/40 mg (IQR 35—138 mL/40 mg) IV furosemide.

The doses and medications used during MSDT are shown in Table 2. MSDT included high-dose IV loop diuretic therapy (median daily IV furosemide equivalent dose 800 mg [IQR 400—1400 mg]) and moderate to high doses of thiazide, acetazolamide, and mineralocorticoid receptor antagonist therapies. Most patients (91%) received a variation of the standard MSDT regimen recommendation. Patients did not receive concomitant diuretics from other diuretic classes except one patient who received empagliflozin 10 mg once daily. MSDT was continued for 2 days in 55% of patients and 28% remained on MSDT at day 4 (Table 2). MSDT doses for the severe diuretic resistance cohort were similar to the total cohort (Supplementary Table 1).

MSDT was associated with increased urine output in the first day of therapy. The median 24-hour urine output increased from 2.16 L (0.95—4.14 L) to 3.08 L (1.74—4.86 L) (P = .003) on the day of MSDT initiation compared with the previous day (Fig. 1). Thirty percent of patients made more than 4.5 L of urine per day with the top decile producing more than 5.8 L of urine per day and a maximum 24-hour urine output of 10 L. In the severe diuretic resistance cohort, median 24-hour urine output increased 2-fold from 0.91 L (0.43—1.43 L) on the previous day to 2.08 L (1.13—3.96 L) with MSDT initiation (P < .001). Despite decreasing diuretic therapies on subsequent days, diuretic response was maintained with a cumulative weight loss of −7.4 kg (IQR −15.3 to −3.4 kg) (P = .02) from baseline to day 7 or discharge in the total cohort, with similar trends in the severe diuretic resistance cohort (Fig. 1).

A total of 62% of patients (n = 104) were MSDT responders (Fig. 2). MSDT nonresponders had higher rates of chronic kidney disease, higher BUN, and higher serum creatinine than responders at baseline. (Supplementary Table S2) MSDT diuretic regimens were similar between responders and nonresponders with the exception that nonresponders received a higher median daily dose of spironolactone (100 mg [IQR 25—100 mg] vs 50 mg [IQR 25—100 mg], P < .05) compared with responders (Supplementary Table 3) MSDT responders experienced a significant increase in UOP (3.2 ± 2.2 L to 4.0 ± 1.9 L, P = .007) compared with the previous day and weight loss from baseline to day 7 (102 ± 29 kg to 93 ± 28 kg, P = .045, respectively). Nonresponders were less likely to continue MSDT at day 2 than responders (44% vs 62%, P = .02, respectively). Nonresponders had insignificant improvements in urine output and, among those not undergoing RRT for volume removal, no significant weight loss (Fig. 3). Of the MSDT nonresponders (n = 63), new RRT was initiated in 63% (n = 40) of patients in 2 days (IQR 1—5 days) of MSDT initiation. RRT was predominantly comprised of continuous RRT or intermittent透析。
hemodialysis, with only 3 patients receiving isolated ultrafiltration. Of the 40 patients prescribed new RRT, 25% (n = 10) died during the index hospitalization, 35% (n = 14) were discharged requiring chronic hemodialysis, and 40% (n = 16) were discharged alive without RRT. In the total population, the length of stay was 19 days (IQR 11–32 days) and the inpatient mortality rate was 19.8% (n = 33) with n = 28 dying before day 7. The inpatient mortality among MSDT nonresponders was 29% (n = 18) and 14% (n = 15) among MSDT responders. The serum sodium, potassium, chloride, and bicarbonate did not change appreciably from the pretreatment baseline during MSDT (P > .05 for all) (Fig. 4 and Table 3). At day 7 or discharge, the median change in serum creatinine was 0.0 mg/dL (IQR −0.3 to 0.3 mg/dL) and median eGFR change was 0 mL/min/m² (IQR −5 to 10 mL/min/m²). Approximately three-fourths of patients required potassium repletion with a median daily potassium dose of 100 mEq (IQR 50−153 mEq), which was not different from the preceding days (Table 3). Vital signs were stable during MSDT despite decreasing rates of IV inotrope and vasopressor therapy. When divided into responders and nonresponders, vital signs and IV vasoactive medication trends over time were similar to the total cohort trends (Supplementary Table 4). Serum chemistry trends over time relative to baseline values were also similar when divided by responder status. (Supplementary Fig. 1).

Discussion

This retrospective analysis of MSDT in a real-world AHF population a single US medical center serves as hypothesis-generating data for future investigations of multinephron segment diuretic therapies. MSDT was associated with a significant diuretic response in approximately two-thirds of the total cohort and one-half of patients with severe diuretic resistance without substantial changes in serum electrolytes, extreme electrolyte repletion, or worsening kidney function. In the cohort of patients with severe diuretic resistance, MSDT was associated with a 2-fold increase in urine output. Collectively, these observations indicate that the existing diuretic armamentarium can be leveraged into a MSDT regimen to augment diuretic response and relieve congestion.

Intrarenal mechanisms involving tubular sodium reabsorption are the predominant drivers of diuretic resistance in patients with AHF.\textsuperscript{5,17,18} The nephron has great plasticity and nephron segments can significantly increase their resorptive capacity over normal conditions in the presence of chronic diuretic therapy. Therefore, MSDT uses diuretics in action in multiple nephron segments to counter the nephron’s adaptations.

The concept of MSDT has been recommended previously in severe diuretic resistance.\textsuperscript{5,7,19} The median daily IV loop diuretic dose before MSDT in our total and severe diuretic resistance cohort (480 mg/d IV furosemide) exceeded the daily loop diuretic doses in high-dose arm of the DOSE trial (median 258 mg/d IV furosemide) and the CARRESS-HF and ROSE-AHF trials (median approximately 200 mg/d IV furosemide).\textsuperscript{20−22} Our experience substantially increases the limited supporting evidence to date on MSDT’s safety and efficacy.\textsuperscript{23,24} Despite producing limited natriuresis as monotherapy, carbonic anhydrase inhibitors (acetazolamide) increased natriuresis when added to loop diuretics in small HF cohorts.\textsuperscript{25−27} Loop diuretics are the backbone of decongestion by MSDT, and our experience adds to recent literature, suggesting safety when using high doses to overcome diuretic resistance.\textsuperscript{28} Thiazide diuretics and mineralocorticoid receptor antagonists inhibit solute and water reabsorption distal to the site of action of the loop diuretics. In HF, evidence for diuretic doses of mineralocorticoid receptor antagonists is limited.\textsuperscript{29−31} In our cohort, only 32% of the spironolactone daily doses administered were at least 100 mg, which may have limited the diuretic impact.

Table 2. MSDT Regimen

<table>
<thead>
<tr>
<th>Diuretic regimen</th>
<th>Day 2 (n = 165)</th>
<th>Day 1 MSDT initiation (n = 167)</th>
<th>Day 2 (n = 165)</th>
<th>Day 4 (n = 150)</th>
<th>Day 7 or discharge (n = 139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FE, furosemide; IV = intravenous; MSDT, multisegment diuretic therapy consisting of loop, thiazide, acetazolamide, and aldosterone antagonist. Furomide equivalents where 40 mg IV furosemide = 1 mg IV bumetanide</td>
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<tr>
<td>*Not applicable (N/A) because patients could not receive MSDT before the initiation (day 0).</td>
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<tr>
<td>1Not applicable because on MSDT initiation date (day 1) all patients were on 4 diuretic medications.</td>
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</table>

All data are presented as median (IQR) or number (%).
Fig. 1. Total urine output and weight change with multinephron segment diuretic therapy (MSDT). (A, B) The 24-hour urine output on the first day of MSDT initiation is shown in 500-mL increments with a red vertical line at the 2 L indicating the urine volume needed to produce a net neutral fluid balance on a 2-L fluid restriction for the total cohort (A) and the severe diuretic resistance cohort (B). (C, D) The 24-hour total urine output (mean ± SD) starting 2 days before MSDT initiation (day 1) through day 7 or the last day of the hospital stay if the patient was discharged or deceased before day 7 is plotted on the y-axis for the total cohort (C) and the severe diuretic resistance cohort (D). After the day of MSDT initiation (day 1), diuretic therapy was consistently de-escalated, with a corresponding decrease in total urine output. (E, F) Trends in standing weights starting 2 days before MSDT initiation (day 1) through day 7 or the last day of the hospital stay if the patient was discharged or deceased before day 7 for the total cohort (E) and the severe diuretic resistance cohort (F).
If spironolactone is used for diuretic augmentation in a spironolactone naïve patient, a 300- to 400-mg loading dose or 100 mg doses 2 to 3 times daily may be required to maximize the diuretic contribution. More than 60% of patients challenged with MSDT produced a urine output to facilitate a net negative fluid balance, despite severe heart failure and kidney dysfunction, thereby avoiding potential RRT. In contrast, the majority of nonresponders required hemodialysis in the next few days. Another tertiary care medical center analyzed the outcomes of patients hospitalized with AHF unable to achieve decongestion with combination loop and thiazide diuretic therapy with similar baseline serum creatinine (2.2 ± 0.9 mg/dL) and IV inotropic therapy use (38%) to our cohort. Using ultrafiltration instead of MSDT for decongestion, patients experienced no improvement in kidney function and 59% required transition to hemodialysis. Challenge with MSDT may rapidly identify patients responsive to decongestive medical therapies from those at high risk of requiring RRT, but this hypothesis requires testing in a randomized study. A major barrier to MSDT is the absence of safety data. Concerns include hyponatremia, hypokalemia, hypochloremia, metabolic alkalosis, and worsening kidney function. We found serum electrolytes, serum bicarbonate, and kidney function did not worsen with MSDT. The combination of diuretics in MSDT have counteracting effects on electrolytes, minimizing adverse electrolyte events. Diuretics acting distal to the proximal tubule cause chloride loss and can increase serum bicarbonate, but the addition of acetazolamide mitigates these effects by decreasing bicarbonate reabsorption. Hypokalemia is a profound adverse effect from loop and thiazide combination therapy, but the addition of a higher dose of mineralocorticoid receptor antagonists decreases urine potassium excretion. Mineralocorticoid receptor antagonists are typically
contraindicated with an estimated glomerular filtration rate of less than 30 mL/min/m², owing to the risk of hyperkalemia. However, the median baseline estimated glomerular filtration rate in our cohort was less than 30 mL/min and hyperkalemia did not occur. In contrast, most patients still required potassium repletion. A trial of MSDT could be ordered in most hospital general medicine rooms, provided twice daily serum chemistry monitoring, continuous telemetry monitoring, and urine output measurements can be performed.

The concept of MSDT allows the incorporation of newer diuretics and customization of the diuretic combinations to the individual patient. Amiloride could provide similar potassium-sparing natriuresis as mineralocorticoid receptor antagonists while avoiding spironolactone’s long metabolite half-life, which delay the onset of action. Amiloride also inhibits the aldosterone-independent epithelial sodium channel activity, potentially providing additional benefits in AHF complicated by diuretic resistance. Vasopressin antagonists such as tolvaptan could be added to MSDT when decreases in serum sodium or chloride are limiting diuresis or causing adverse events. SGLT2 inhibitors have a synergistic diuretic response when combined with loop diuretics in patients with HF without evidence of electrolyte abnormalities. The estimated glomerular filtration rate threshold below which SGLT2 inhibitors have negligible additional diuretic action is currently unknown but is likely lower than previously defined. Because many of the diuretic agents are readily available at low costs, the implementation of various diuretic combinations of MSDT is only limited by the lack of evidence.

Our experience is retrospective and has the limitations of all retrospective observational studies, such as selection bias from provider MSDT prescription decisions and inability to establish a cause-and-effect relationship between observations. Although the patient population was severely ill with diuretic resistance, the decision to use MSDT was at the individual provider level with no formal criteria for use. Many patients were identified as diuretic resistant by cardiologists and standardized MSDT recommended by consultant nephrologists. The definition of severe diuretic resistance was limited by retrospective data lacking urine sodium measures, but this cohort clearly demonstrated a poor response to high-dose loop diuretics and combination diuretic therapies. Net fluid status calculations were not possible owing to missing intake measures, but changes in weight are also used in clinical practice to measure net fluid losses. Diuretic doses were decided by the treating provider and often changed.
Table 2. Laboratory values

<table>
<thead>
<tr>
<th></th>
<th>Day -2 (n = 165)</th>
<th>Day 1 MSDT Initiation (n = 167)</th>
<th>Day 2 (n = 165)</th>
<th>Day 4 (n = 150)</th>
<th>Day 7 or Discharge (n = 139)</th>
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</thead>
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<td><strong>Vital signs</strong></td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>112 (99–125)</td>
<td>109 (98–121)</td>
<td>107 (96–122)</td>
<td>108 (96–124)</td>
<td>111 (97–129)</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>66 (57–74)</td>
<td>66 (58–74)</td>
<td>64 (56–72)</td>
<td>65 (58–72)</td>
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<td><strong>Laboratory values</strong></td>
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<td>Serum sodium (mEq/L)</td>
<td>136 (133–140)</td>
<td>136 (132–140)</td>
<td>136 (132–140)</td>
<td>136 (132–140)</td>
<td>136 (131–140)</td>
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<tr>
<td>Hyponatremia</td>
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<td>64 (38)</td>
<td>65 (39)</td>
<td>63 (42)</td>
<td>56 (40)</td>
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<tr>
<td>Serum potassium (mEq/L)</td>
<td>3.9 (3.5–4.3)</td>
<td>3.9 (3.4–4.2)</td>
<td>3.8 (3.5–4.2)</td>
<td>3.7 (3.4–4.1)</td>
<td>3.9 (3.6–4.2)</td>
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<tr>
<td>Hypokalemia</td>
<td>33 (20)</td>
<td>42 (25)</td>
<td>34 (21)</td>
<td>42 (28)</td>
<td>23 (16)</td>
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<td>Serum chloride (mEq/L)</td>
<td>96 (91–103)</td>
<td>95 (88–101)</td>
<td>94 (87–101)</td>
<td>94 (87–104)</td>
<td>96 (86–103)</td>
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<td>Serum bicarbonate (mEq/L)</td>
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<td>28 (23–33)</td>
<td>27 (23–33)</td>
<td>27 (23–32)</td>
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<tr>
<td>BUN (g/dL)</td>
<td>48 (31–69)</td>
<td>55 (38–78)</td>
<td>56 (41–80)</td>
<td>62 (41–78)</td>
<td>54 (37–83)</td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.0 (1.3–3.0)</td>
<td>2.3 (1.5–3.1)</td>
<td>2.4 (1.6–3.3)</td>
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<tr>
<td>eGFR (mL/min/m²)</td>
<td>31 (20–52)</td>
<td>29 (19–42)</td>
<td>28 (19–42)</td>
<td>27 (17–45)</td>
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<td><strong>Vasoactive medications</strong></td>
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<td>IV Inotropic therapy</td>
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<td>IV vasopressor therapy</td>
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<tr>
<td>Supplemental potassium</td>
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<td>120 (72)</td>
<td>119 (72)</td>
<td>104 (69)</td>
<td>87 (63)</td>
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<tr>
<td>Potassium (mEq/d)</td>
<td>100 (50–140)</td>
<td>100 (50–153)</td>
<td>80 (40–152)</td>
<td>64 (40–140)</td>
<td>40 (20–80)</td>
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<tr>
<td>Supplemental magnesium</td>
<td>51 (32)</td>
<td>60 (36)</td>
<td>47 (29)</td>
<td>35 (23)</td>
<td>37 (27)</td>
</tr>
<tr>
<td>Magnesium (g/d)</td>
<td>2.3 (0.8–4.0)</td>
<td>2.0 (0.8–4.0)</td>
<td>2.0 (0.8–4.0)</td>
<td>0.8 (0.8–2.0)</td>
<td>1.0 (0.4–4.0)</td>
</tr>
</tbody>
</table>

All data are presented as median (interquartile range) or number (%).
The change in all variables from the pretreatment baseline during MSDT was not statistically significant. (P > .05 for all).
BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate by the Modification of Diet in Renal Disease equation. Other abbreviations as in Table 2.

Hyponatremia is a serum sodium of <135 mEq/L; hypokalemia is a serum potassium of <3.5mEq/L.

simultaneously with the addition of concomitant diuretics, prohibiting conclusions on dose–response relationships or the effect of individual diuretic agents. Patients had a poor diuretic response before MSDT, but diuretic response on day 1 could be impacted by prior multiple diuretic combinations or the length of hospital stay before MSDT. Although we did not identify safety concerns, the small sample size, retrospective design, absence of MSDT prescription for multiple days in all patients, lack of vasopressor or inotrope doses, and inability to measure subclinical changes in adverse events such as ototoxicity prohibit definitive conclusions on the safety of MSDT. As such, these data should be considered as hypothesis generating for future prospective, randomized investigations.

Conclusions

In a retrospective AHF cohort complicated by diuretic resistance, MSDT was associated with increasing diuretic response without worsening electrolyte abnormalities or kidney function. MSDT is an understudied decongestive strategy that can be tailored to the diuretic and electrolyte needs of the individual patient. Future studies should investigate the efficacy and safety of MSDT in a prospective AHF cohort complicated by diuretic resistance.

Lay Summary

Using a combination of 4 medications that work in different ways in the kidney to help patients with heart failure to get rid of extra fluid may help patients who are not responding to traditional diuretic medication combinations. We found that 2 out of every 3 patients responded to the combination of 4 medications. Patients did not experience serious complications or changes in kidney function. More research is needed before this can be widely recommended.

Application of this work to patients:

- MSDT could help remove extra fluid in patients with AHF unresponsive to combination diuretic therapy.
- MSDT could be tailored to minimize electrolyte disturbances from diuresis.
- MSDT could help avoid invasive procedures to remove excess fluid.

Disclosures

ZC reports research funding from AstraZeneca. KU reports being a consultant to AstraZeneca and research funding from Astra Zeneca. JT reports grants from Novartis, personal fees from Novartis, and AstraZeneca. JT reports research funding from AstraZeneca. JD reports consulting fees from AstraZeneca, research fees from Cardinal Health, and research funding from Sequana Medical, grants and personal fees from AstraZeneca, personal fees from Novartis, and grants and personal fees from Roche. JT reports grants and personal fees from Novartis, grants and personal fees from Roche, and grants and personal fees from Sanofi. JD reports consulting fees from AstraZeneca, Bayer, and Boehringer Ingelheim, and Sanofi, and research fees from AstraZeneca. JD reports funding from CSL and Boehringer Ingelheim, without other on No. 00 2021.
Acknowledgments

The authors thank Thomas G. Stewart, PhD, for his assistance with statistical analysis.

Funding Source

This work did not have financial support.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2021.07.016.

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