

Title of Project: Metolazone pre-dosing versus concurrent dosing with furosemide on 24-hour urine output: A pilot study

Research Team:

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Introduction and Supporting Literature:

Acute decompensated heart failure (ADHF) is the primary diagnosis for greater than 1 million hospitalizations per year.^[1] Intravenous (IV) loop diuretics prescribed at doses higher than a patient's home regimen are the treatment of choice for patients presenting with volume overload in ADHF.^[2] Diuretic resistance, defined as failure of diuretics to relieve congestion, is a complex process that occurs via pathophysiologic retention of sodium and decreased renal response to diuretic therapy and further complicates hospitalizations for ADHF. There are multiple mechanisms through which diuretic resistance can occur, including the "braking" phenomenon where decreased diuresis occurs with repeated doses of loop diuretics, the post-diuretic effect in which sodium reabsorption at the loop of Henle increases once the loop diuretic has worn off, and nephron remodeling including hypertrophy of the distal convoluted tubule that leads to increased sodium reabsorption.^[3,4] Neuberger *et al.* found diuretic resistance, indicated by greater total daily doses of furosemide, to be associated with increased mortality.^[5]

Sequential nephron blockade, or combination diuretic therapy, with a loop and thiazide-type diuretic is a frequently used strategy to overcome diuretic resistance caused by hypertrophy of the distal convoluted tubule.^[4] In healthy patients, approximately 25% of sodium is reabsorbed proximally at the ascending loop of Henle and 5% of sodium is reabsorbed at the distal convoluted tubule. With increasing doses of loop diuretics, a compensatory increase in sodium reabsorption occurs via the sodium chloride cotransporter at the distal convoluted tubule.^[4] Adding a thiazide-type diuretic, such as metolazone limits this distal reabsorption and therefore restores effectiveness of diuretic therapy. The majority of studies examining combination diuretic therapy in ADHF are retrospective and evaluate a limited number of patients (1 to 45 patients).^[6-13] Overall, combination diuretic therapy has been found to be safe and efficacious in increasing urine output and decreasing weight. The most common side effect noted in these studies is hypokalemia. Of the available thiazide diuretics, one has not been found to be more effective than another; however, metolazone is often used due to its potency and long duration of action (up to 20 hours).^[14]

Based on this observed synergy, combination therapy with furosemide and metolazone is routinely prescribed in patients presenting with ADHF without adequate diuresis from loop diuretics alone. It has been recommended to administer the thiazide-type diuretic one hour prior to the loop diuretic to allow the thiazide-type diuretic to achieve peak diuretic effect.^[16] This practice of pre-administration likely comes from pharmacokinetic and pharmacodynamic data that found the peak diuretic effect of metolazone to be delayed approximately 80 minutes after administration.^[17] However, this pharmacokinetic study was performed in two healthy volunteers that were administered metolazone alone. The administration time of metolazone in relation to furosemide dosing has not been studied and is not commented on in the observational and randomized controlled trials looking at combination

diuretic therapy. Given the long duration of effect of metolazone, it is unlikely that the delay in peak diuresis would be of clinical importance in terms of desired synergistic effect. Furthermore, the practice of staggering administration times complicates the regimen and puts a burden on nursing staff, especially in units with greater patient to nurse ratios or patients with contact precautions.

Therefore, the practice of administering metolazone 60 minutes prior to loop diuretic therapy increases the complexity for nursing staff and patients without proven clinical benefit. Despite this information, the practice remains common in clinical settings. The purpose of this study is to examine whether administering metolazone 60 minutes prior to furosemide increases urine output compared with administering metolazone and furosemide concomitantly.

Methods:

Study Design:

This will be a prospective, randomized, open-label, active control trial at the University of Maryland Medical Center (UMMC). The objective of this study is to examine whether administering metolazone 60 minutes prior to IV furosemide bolus increases urine output compared with administering metolazone and IV furosemide bolus concurrently. The study has been approved by the institutional review board at UMMC, and written informed consent will be obtained for all patients.

Study Participants:

Adults aged 18 to 89 years are eligible for enrollment if they present within the previous 48 hours with ADHF to the advanced heart failure service at UMMC. ADHF will be defined on the basis of the presence of at least one symptom (dyspnea, orthopnea, cough, or edema) and one sign (rales, peripheral edema, ascites, jugular venous distention, or pulmonary vascular congestion on chest radiography) of heart failure. Additional eligibility criteria are receipt of an oral loop diuretic prior to admission and plan to administer furosemide 120 – 200 mg IV bolus twice daily over the next 24 hours with additional diuresis deemed necessary. Patients are to be excluded if they have cirrhosis, an estimated glomerular filtration rate (GFR) less than 10 mL/min/1.73m², need for concurrent renal replacement therapy, or if they were prescribed metolazone prior to admission. Non-English speaking patients and patients that could not provide consent and do not have a legally authorized representative to provide consent will also be excluded.

Randomization and Treatment Assignments:

Patients will be randomized in a 1:1 ratio to a pre-dosing strategy (metolazone 5 mg orally dosed 60 minutes prior to furosemide 120 – 200 mg IV bolus) or a concurrent dosing strategy (metolazone 5 mg dosed simultaneously with furosemide 120 – 200 mg IV bolus). All treatment during the 24-hour study period will be open-label at the discretion of the treating physician. Patients enrolled in the study can receive additional IV boluses up to every 6 hours during the 24-hour study period. If per the treating physician, patients required additional doses of metolazone, switch to furosemide IV continuous infusion, titration of IV inotrope or IV vasodilator, or renal replacement during the 24-hour study period, the appropriate therapy will be ordered and the patient will be excluded from the study at that time. Patients will be followed until discharge.

Endpoints:

The primary endpoint will be total urine output (mL) 24 hours post-metolazone dose. The total urine output will be collected and entered into EPIC electronic medical record by nursing staff and the value will be collected by study investigator during chart review. Additional pre-specified secondary endpoints that will be assessed 24 hours post-metolazone dose include: net fluid balance (mL), change in weight (kg), change in SCr (mg/dL), proportion of patients with acute kidney injury (AKI) (defined as an increase in SCr by ≥ 0.3 mg/dL or $\geq 50\%$ from baseline), hypokalemia ($K < 4.0$ mEq/L), hypomagnesemia ($Mg < 2.0$ mEq/L), and hyponatremia ($Na\ 125 - 135$ mEq/L 24).

Statistical Analysis:

We calculated that 126 patients would have to be enrolled in order to achieve 80% power to detect an effect size of 500 mL. Given that this was a pilot study, our target patient enrollment will be 30 patients as this was felt to be a feasible number of patients to enroll during the study period. Descriptive statistics will be used to characterize data. When target enrollment is reached, the primary endpoint will be analyzed using student t-test. For other variables and outcomes, data will be analyzed using student t-test or chi-square/Fisher's exact test as appropriate.

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