MELT-HF

MEtolazone as Early add on Therapy for acute decompensated Heart Failure.

A single center pilot study.

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INTRODUCTION

Background

- Heart failure is a major source of morbidity, mortality and growing public health cost.
- In US, the number of congestive heart failure patients is more than 4 million with more than 550,000 new annually reported cases.
- The annual cost of heart failure management exceeds 35 billion dollars per year.
- The heart failure readmissions and average length of hospital stay cost approximately $11,000 per patient.
- Loop diuretics are used alone in the majority of cases to promote diuresis.
- An association of increased creatinine and increased risk of renal dysfunction, the cardiorenal syndrome, in the face of high dose loop diuretics has raised questions regarding the safety and toxicity of high dose loop diuretics.
- While the dose of diuretics is ubiquitous, little data exists to guide their use and many clinicians are uncertain as to when and how to initiate and limit therapy.
- In many cases, a "stepped approach" with oral loop diuretics advancing to intravenous and finally combination high dose diuretics is employed.

PREVIOUS TRIALS

DOSE(Diuretic strategies in patients with ADHF) Trial

- Prospective, randomized double blinded trial of 308 patients with ADHF.
- Showed that high dose diuretics (2.5 times the outpatient daily dose) were associated with improved urine output at 72 hours (3575± 2635 in low dose group vs. 4899±3479 in high dose group).
- There was no significant difference between the high and low dose groups in mean creatinine change (0.08±0.3 mg per deciliter in high-dose group as compared to 0.04±0.3 mg per deciliter in low-dose group, P=0.21.

CARESS-HF (Ultrafiltration in ADHF patients with CRS) Trial

- Randomized non blinded study of 188 patients with ADHF.
- High dose loop strategy with stepped addition of metolazone was used. The combination approach compared favorably with renal ultrafiltration in patients with acute decompensated heart failure.

- At 96 hours, the mean change in the creatinine level was 0.04±0.53 mg per deciliter in drug therapy group, as compared with +0.23±0.70 mg per deciliter in the ultrafiltration group (P = 0.003).
- There was no significant difference in weight loss at 96 hours between patients in the pharmacologic-therapy group and those in the ultrafiltration group (a loss of 5.5±5.1 kg vs. 5.7±3.9 kg [12.6±8.5 lb], respectively; P = 0.58).
- There was a higher percentage of serious adverse events in the ultrafiltration group as compared with the pharmacologic-therapy group (72% vs. 57%, P = 0.03).

OBJECTIVES

THE PRIMARY OBJECTIVE OF THE STUDY IS TO DETERMINE EFFICACY OF METOLAZONE AS SYNERGISTIC THERAPY WITH LASIX IN PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE.

STUDY DESIGN

- A single center double blinded randomized placebo- controlled pilot study of the addition of 5 mg of metolazone per day for a total of 2 doses compared to placebo in patients admitted with acute decompensated heart failure (Class III-IV).
- All patients will receive standard heart failure therapy, including but not restricted to diuretics, digoxin, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, aldosterone antagonists, hydralazine, and/or nitrates, at the discretion of the treating physician.

ENDPOINTS

Primary Endpoint

- Total urinary output and negative fluid balance (in milliliters) at 48 hours following initial administration of first intravenous diuretic.

Secondary Endpoints

- Change in weight from admission to day 2.
- Degree of improvement in dyspnea at 6, 12, 24, 36, and 48 hours assessed with Modified Borg Scale (1-10) (Appendix 1).
- All-cause mortality at 30 days.

- Time difference between diuretic dose and study drug.
- Total dose of diuretics administered during first 48 hours from administration of first intravenous diuretic.
- Inotrope administration during hospital stay.

Exploratory Endpoints

- Length of hospital stay.
- All cause readmission occurring within 30 days after discharge.
- Heart failure readmission occurring within 30 days post discharge.

Safety Endpoints

- Severe electrolyte abnormalities requiring aggressive replacement defined as potassium levels less than 3.0 meq/L or magnesium levels less than 1.5 meq/L during the study.
- Severe hypotension following study drug administration (MAP less than 55 mm of Hg).

ADVERSE EFFECTS OF INVESTIGATIONAL PRODUCT

- Hypotension requiring intervention.
- Electrolyte imbalance requiring intervention.
- Acute kidney injury defined as a 30% rise from baseline.

The above adverse effects will be collected on each patient for 48 hours after enrollment in the MELT trial. No other adverse events will be reported unless deemed to related to the study by the Principal Investigator.

STUDY PROCEDURES

- This is a randomized, double blinded, placebo-controlled single center study of at least 200 patients who are admitted to Aultman Hospital with clinical decompensated Class III-IV congestive heart failure.
- All patients will receive standard heart failure therapy, including but not restricted to diuretics, digoxin, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, aldosterone antagonists, hydralazine, and/or nitrates, at the discretion of the treating physician.
- After informed consent is obtained, patients will be randomized 1:1 to the treatment arm or placebo arm.
- Two doses of study drug will be administered. The first dose will be given as soon as possible following enrollment, but within 6 hours of the first intravenous diuretic

administration. This will be considered Day 0. The second dose will be administered 24 hours after the first dose of study drug. This will be considered Day 1. Patients and physicians will be blinded to the administered drug (metolazone vs. placebo). In the event of unforeseen circumstances the patient does not receive both doses of study drug (i.e. early discharge or emergent surgery), they will be deemed inevaluable. See Analysis Populations section below.

- ⊡ Study drug assignment will be randomized and distributed by a delegated pharmacist after the patient is consented and enrolled in the trial.
- ⊡ Specific guidance/recommendations regarding diuretic therapy will be provided (documented in detail below) but will be at the discretion of the treating physician.
- ⊡ We will collect data on demographics, co-morbidities, clinical presentations and outcomes with Metolazone administration with patient follow up within seven (±3) days and 30 (±7) days post discharge.
- ⊡ BMP, magnesium and CBC will be collected daily or as clinically indicated at the discretion of the treating physician..
- ⊡ BNP will be collected on admission and Day 2. For the first ten (10) patients, a BNP will be collected at discharge.
- ⊡ Patients will be preferred to have an indwelling urinary catheter to collect accurate output measurements. If patient agreeable, the catheter will be placed upon enrollment unless already in place. Total urinary output will be measured at 48 hours after from administration of first intravenous diuretic.
- ⊡ Daily intake, urine output and standing weights will be measured for the entire length of the hospital stay. The total urine output and negative fluid balance will be measured at 48 hours from administration of first intravenous diuretic (primary endpoint).
- ⊡ Total dose of diuretics administered in both groups will be monitored and compared with total urine output at 48 hours (primary endpoint). Urine output will be adjusted based on total loop diuretic dose beginning from administration of first intravenous diuretic (analysis of covariance).
- ⊡ Study drug will be administered as soon as possible after enrollment in the study and this will be conveyed clearly to the emergency staff prior to starting the study to avoid unnecessary delays. The time interval between the administration of loop diuretic and the dose of study drug will be tracked as well and adjustments made accordingly in the final analysis.

Inclusion/Exclusion Criteria

Inclusion Criteria

- ⊡ Age 18 years or older

- ☐ Current hospitalization for chronic congestive heart failure with admission up to 48 hours prior to inclusion.
- ☐ Chronic heart failure will be defined as requiring treatment for a minimum of 30 days prior to current admission, NYHA Class III or IV at the time of hospitalization, and left ventricular ejection fraction less than or equal to 40% within one year or evidence of heart failure with preserved ejection fraction and evidence of diastolic dysfunction on echocardiogram.
- ☐ Admitted with clinical decompensated heart failure based on history, physical exam, and parameters indicating extracellular volume expansion such as including JVP ≥ 8 cm of water and 1+ or greater peripheral edema
- ☐ Is able to be dosed with study medication within six (6) hours of first dose of IV diuretics

Exclusion Criteria

- ☐ Baseline severe hypotension defined as mean arterial pressure (MAP) less than 55
- ☐ Creatinine clearance less than 20 ml/min or creatinine greater than 2.5 mg/dl.
- ☐ Serum sodium less than 128 meq/L.
- ☐ Serum Potassium < 3.0 meq/L.
- ☐ Known adverse reaction to metolazone
- ☐ Inability to take oral medications
- ☐ Severe Aortic Stenosis (AVA < 0.8cm2)
- ☐ History of Hypertrophic obstructive cardiomyopathy
- ☐ Metastatic Carcinoma per history
- ☐ Severe COPD, FEV < 1L
- ☐ Severe dyspnea requiring prolonged CPAP,BIPAP or intubation

Subject Population

Recruitment

- ☐ At least 200 patients who are admitted with acute decompensated heart failure will be identified in the Emergency Room, Outpatient Clinic, 4 South, or Cardiac Care Unit.
- ☐ Patients included in the study will receive standard heart failure therapy including but not restricted to digoxin, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, aldosterone antagonists, hydralazine, and/or nitrates, at the discretion of the treating physician.
- ☐ After informed consent is obtained patients will be randomized 1:1 to the treatment arm or placebo arm.

- For the participating patients, they will be recommended to at least receive their (total daily outpatient dose of furosemide) x1.25 intravenously.
- With equivalent conversion which would be 2:1 for torsemide and Lasix and 40:1 for bumex and Lasix, we will give at least 1.25 x intravenous dose of Lasix if they are taking torsemide or bumex as part of their outpatient regimen.
- If enrolled in the study, the first dose of study drug will be given as soon as possible following enrollment, but within 6 hours of the first IV dose diuretics. The second dose will be administered 24 hours after the first dose of study drug..
- Electrolytes will be repleted per the treating physician.
- Drug administration will be held in patients with severe hypotension (MAP less than 55).

STATISTICAL ANALYSIS

Statistical Methods

- Power Analysis: In the DOSE trial urine output at 72 hours was 4200ml with a standard deviation of 3200 ml.
- With 1:1 randomization, there is a power of more than 80% to detect a difference of 3000-4000 ml between the groups at 48 hours and at least 200 patients will be enrolled to achieve statistical significance.
- The demographics to the two groups will be compared with Fischer's exact T-test to ensure the validity of the randomization.
- Primary and secondary outcomes will be collected and compared with the Student's T-test.
- Appropriate subgroup analyses will be done and outcomes will be presented by Kaplan Meier plots.

Analysis Populations

- The Evaluable Population for the primary, secondary, and exploratory endpoints will include all randomized subjects who receive both doses of the study drug, and complete the 48 hour evaluation period. The efficacy analysis will be based on the Evaluable Population.
- If a patient does not receive both doses of study drug or complete the 48 hour evaluation period they will be considered inevaluable, however, this will not be classified as a protocol deviation.
- The Safety Endpoints will include all randomized subjects who receive at least one dose of the study drug.

Data and Safety Monitoring

A data safety monitoring committee will be assigned to review each case for eligibility, adherence to the protocol, occurrence of adverse events, and accuracy of data. This will be completed on a regular basis. The first review will be conducted after enrolling the first 100 patients. Regular reviews will be scheduled at increments of 50 randomized patients until enrollment goals are met. Unscheduled random chart audits will also be performed to ensure data integrity. Any deficiencies found during these reviews will be addressed and reported to necessary parties.

All study related data will be anonymized and secured via password access being strictly confidential to the investigators. The stored data will be kept in locked cabinets at all times with limited access.

Appendix 1: Modified Borg Scale

SCALE	SEVERITY
0	No Breathlessness* At All
0.5	Very Very Slight (Just Noticeable)
1	Very Slight
2	Slight Breathlessness
3	Moderate
4	Some What Severe
5	Severe Breathlessness
6	
7	Very Severe Breathlessness
8	
9	Very Very Severe (Almost Maximum)
10	Maximum

Appendix 2: New York Heart Association (NYHA) Heart Failure Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

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