Milrinone as Compared with Dobutamiune in the treatment of Cardiogenic Shock

Reviewer: Rebecca Wahrmund, PharmD

Background:

Cardiogenic shock is associated with significant morbidity and mortality. Hemodynamic stability with vasopressor and inotrope therapy is the mainstay of treatment for cardiogenic shock. While norepinephrine has emerged as the vasopressor of choice in patients with cardiogenic shock, the preferred inotrope remains debatable. When it comes to inotrope therapy, selection is often determined by institution and provider preference. The authors of this study previously published a systematic review and meta-analysis comparing effectiveness and safety of milrinone and dobutamine in low cardiac output states, including cardiogenic shock. Their review found favor with milrinone in the primary outcome of all-cause mortality – however this review did not reach statistical significance. In the current study, tagged the DOREMI trial, the safety and efficacy of milrinone and dobutamine are compared in a parallel, randomized, double-blinded, controlled clinical trial.

What They Did:

- Patients were recruited between September 17, 2017 and May 17, 2020.
- A total of 192 patients admitted to the CICU between the above enrollment period were identified by the treating medical team as requiring inotrope therapy, and thus included in the study.
- Patients were randomized in a 1:1 fashion to receive either milrinone or dobutamine.
- Inotrope dosing was initiated according to a blinded protocol.
- Identified possible differences in atrial and ventricular arrhythmias, hepatic and renal function, markers of end-organ perfusion (lactate, urine output, mentation status), use of vasopressors, sustained hypotension, need for mechanical ventilation, cardiac transplant, total length of stay in CICU, and mortality in patients with cardiogenic shock treated with dobutamine vs. milrinone.

Outcomes:

- Primary: In-hospital death from any cause, resuscitated cardiac arrest, receipt of cardiac transplant, mechanical circulatory support, or renal replacement therapy, and non-fatal myocardial infarction, transient ischemic attack, or stroke.
- Secondary: Each individual component of the composite primary outcome.

Inclusion:

Patients $\geq$ 18 years admitted to the CICU plus $\geq$1 of the following:

- Low cardiac output state
- Clinical evidence of systemic and/or pulmonary congestion despite use of vasopressors and/or diuretics
- ACS complicated by cardiogenic shock
- Augmentation of cardiac output while on maximum vasopressor therapy
- Medical team decision of patient's need for inotropic therapy

Exclusion:

- Milrinone or dobutamine initiated prior to randomization
- Patients presenting with an out-of-hospital cardiac arrest
- Pregnant females
- Healthcare team preference for specific inotrope

Results:

- Primary outcome of the composite of in-hospital death from any cause, TIA, stroke, or cardiovascular or renal events
    - 47 (49%) patients in the milrinone group
    - 52 (54%) patients in the dobutamine group
    - RR = 0.90; 95% CI (0.69-1.19, p = 0.47)
- In-hospital death
    - 35 (37%) patients in the milrinone group
    - 41 (43%) patients in the dobutamine group
- TIA/stroke
    - 1 (1%) patient in the milrinone group
    - 2 (2%) patients in the dobutamine group
- Cardiac arrest
    - 7 (7%) in the milrinone group
    - 9 (9%) in the dobutamine group
- Cardiac transplant or mechanical circulatory support
    - 11 (12%) in the milrinone group
    - 14 (15%) in the dobutamine group
- Arrhythmia leading to medical team intervention
    - 48 (50%) in milrinone group
    - 44 (46%) in dobutamine group
- Initiation of RRT
    - 21 (22%) in the milrinone group
    - 16 (17%) in dobutamine group

Strengths:

- Randomized controlled trial
- Double-blind study: Patients and providers were both blinded. Dosing was based on a standardized protocol ranging from stage 1 to 5 of increasing doses.
    - Dobutamine doses were 2.5 (1), 5.0 (2), 7.5 (3), 10 (4), and >10 (5) mcg/kg/min
    - Milrinone doses were 0.125 (1), 0.250 (2), 0.375 (3), 0.5 (4), and >0.5 (5) mcg/kg/min
- Used an intention-to-treat analysis
- Demographic and baseline data were predominately balanced between the two groups
- Mean duration of exposure to the study drug was similar between groups (36 hours in milrinone group, 39 hours in dobutamine group).
- Included severe patients (predominately SCAI classes C and D)

Limitations:

- Underpowered to detect small differences in the primary outcome
- Single-center – external generalizability is limited
- Possible selection bias as treating team inotrope preference may have limited enrollment of certain patients
- Standard dosing protocol was only used for initiation, adjustments were left to the discretion of provider without any adjustment protocol.
- MAP $\leq$ 65 mmHG at initiation of inotrope was 11 (12%) in the milrinone group and 24 (26%) in the dobutamine group - difference between groups may have confounded results
- Hemodynamic monitoring using pulmonary-artery catheters (as guidelines suggest) was only used in patients not responding to therapy. Thus, no comparisons between pulmonary wedge pressures or cardiac index were reported.

Discussion:

- Author's Conclusion: "In patients with cardiogenic shock, no significant advantage of milrinone over dobutamine was found with respect to the primary composite outcome or important secondary outcomes."
- Clinical take home point: In this study, no statistical difference in efficacy or safety between milrinone and dobutamine in patients with cardiogenic shock requiring positive inotrope therapy was found. An increased use of dobutamine over milrinone, with no treatment consequence, could be a cost-saving measure.

References:

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