The DOREMI Trial

Key Article

Mathew R, et al. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. N Engl J Med. 2021. 385:516-25.

Background

- Cardiogenic shock is defined as a state of low cardiac output that results in clinical and biochemical manifestations of end-organ hypoperfusion.
- Emergency revascularization is considered standard care for patients with cardiogenic shock due to an acute myocardial infarction.
- However, for patients with cardiogenic shock not due to an acute MI, there is very little data to guide optimal management. Current literature in this patient population is primarily limited to observational studies.
- Current management of patients with cardiogenic shock focuses on hemodynamic treatment with vasopressors, inotropes, and implantable devices (LVAD, impella, etc.).
- In regards to vasopressors, norepinephrine has emerged as the vasopressor of choice for many over epinephrine and dopamine.
- In regards to inotropes, both milrinone and dobutamine are used and primarily based on clinician preference.
- Milrinone is a phosphodiesterase 3 inhibitor that increases cardiac inotropy, lusitropy, and peripheral vasodilation.
- Dobutamine is a synthetic catecholamine that acts as a beta-1 and beta-2 agonist and increases cardiac output and peripheral vasodilation.
- With the exception of pulmonary hypertension, where milrinone is preferred, there is little comparative data on the use of milrinone and dobutamine in cardiogenic shock.

Objective

- To compare the efficacy and safety of milrinone and dobutamine in patients with cardiogenic shock in a pragmatic randomized clinical trial.

Study

- Randomized, double-blind clinical trial
- Single quaternary cardiac care unit at the University of Ottawa
- Patients
    - Included
        - 18 years of age or older
        - Admitted to the cardiac ICU
        - Had cardiogenic shock, as defined by the Society for Cardiovascular Angiography and Interventions definition
    - Excluded
        - OHCA

        - Pregnant
        - Clinician preference for a specific inotrope
- Trial Procedures
    - Patients stratified according to LV, RV, or both ventricles affected
    - Assigned in a 1:1 fashion to receive either milrinone or dobutamine
    - Once randomized, patients received the medication in a concealed bag at a dose from "stage 1 to stage 5".
        - For milrinone, this corresponded to a dose range of 0.125, 0.250, 0.375, 0.500 and > 0.500 mcg/kg/min
        - For dobutamine, this corresponded to a dose range of 2.5, 50., 7.5, 10.0, and > 10.0 mcg/kg/min
    - Adjustment of these doses was performed in a blinded fashion
    - PACs were permitted but not mandated
- Primary Outcome
    - Composite outcome of:
        - In-hospital death from any cause
        - Resuscitated cardiac arrest
        - Receipt of cardiac transplant or mechanical circulatory support
        - Nonfatal MI
        - TIA or CVA
        - Initiation of RRT
- Secondary Outcomes
    - LOS in the cardiac ICU
    - Arrhythmia requiring intervention
    - Total duration of inotropic duration
    - Total hospital LOS
- Statistical Analysis
    - Investigators hypothesized that milrinone would result in a 20% lower incidence of the primary outcome compared with dobutamine.
    - Power calculations indicated that 192 patients would been to be enrolled to have adequate power to detect this difference.

Results

- Total of 319 patients were screened and 192 were ultimately enrolled
- Baseline characteristics were similar in the milrinone group and the dobutamine group
    - Presence of coexisting conditions such as HTN, DM, and afib were similar
    - Medical therapy in the first 24 hours (including beta-blockers) was similar between the groups
    - Overall, 10 patients had an IABP and 23 patients had a PAC
    - Medium serum lactate was 2.9 mmol/L in the milrinone group and 2.9 mmol/L in the dobutamine group
- Primary Outcome
    - Dobutamine group: 54%
    - Milrinone group: 49%
    - RR 0.90
    - 95% CI 0.69 to 1.19; p=0.47

    - No effect on prespecified subgroups including affected ventricle or concomitant use of vasopressors
- Secondary Outcomes
    - No difference in the individual components of the composite primary outcome
    - No difference in total duration of inotropic support, hospital and ICU LOS
    - No difference in arrhythmias that required intervention
    - No differences in heart rate, MAP, serum lactate/creatinine, or urine output

Limitations

- Single center study – limiting generalizability
- Dose adjustments based on physician judgment and not a standard study protocol
- Only in-hospital outcomes were evaluated
- Time from ICU admission to randomization up to 24 hours in some patients (is this too long?)
- Power calculations based on a fairly large difference between milrinone and dobutamine (20% difference)

Take Home Points

- The DOREMI trial did not find a significant difference between milrinone and dobutamine for patients with cardiogenic shock.
- In addition, there was not an increase in arrhythmias or hypotension with one agent over the other.