REVIEW ARTICLE

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Efficacy of milrinone and dobutamine in low cardiac output states: Systematic review and meta-analysis

Abstract

Purpose: Patients in cardiac intensive care units (ICU) are admitted with increasingly higher disease acuity and a larger burden of non-cardiac critical illness. Accordingly, positive inotropes are being used with increased frequency and little comparative data to support drug selection. We compared the effectiveness and safety of dobutamine and milrinone in low cardiac output states (LCOS) and/or cardiogenic shock (CS).

Methods: We performed a systematic review comparing dobutamine to milrinone on all-cause mortality, length of stay in the ICU (LOS-ICU), length of stay in hospital (LOS-H) and significant arrhythmias in hospitalized patients with LCOS and/or CS.

Results: We identified 11 studies that meet eligibility requirements and which were published between 2001 and 2016 and included 23,056 patients. Only one randomized clinical trial was identified, with the remaining studies comprising observational cohort studies. The primary outcome, all-cause mortality, trended towards a benefit with milrinone but did not meet pre-specified significance (OR 1.13, 95% CI 1.00-1.29, $p=0.06$). While LOS-ICU (mean difference -0.72, 95% CI -1.10- -0.34, $p=0.0002$) was shorter with dobutamine, there was no difference in LOS-H (mean difference -1.22, 95% CI -4.68 – 2.24, $p=0.49$). Significant arrhythmias, specifically symptomatic and/or requiring anti-arrhythmic therapy, were no different between the groups (OR 1.78, 95% CI 0.85-3.76, $p=0.13$).

Conclusions: Currently available data comparing milrinone to dobutamine in patients requiring inotropic support is limited. Dobutamine may be associated with a shorter LOS in the ICU, with a worrisome signal of increased risk of all-cause mortality. Randomized data are needed to guide inotrope selection in patients with LCOS and/or CS.

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As the modern concept of a cardiac intensive care unit (ICU) continues to evolve, clinicians are faced with increasingly complex patients with greater co-morbid illness burden. This non-cardiac critical illness has been well-documented—particularly respiratory failure, acute kidney injury, and sepsis along with the increasing profile of respiratory, renal and circulatory intervention [1,2]. Critically ill patients are increasingly treated with inotropes for cardiogenic shock (CS) [3] or low cardiac output states (LCOS) [4] secondary to acute coronary syndromes (ACS), decompensated valvular disease, left ventricular dysfunction (myocarditis, Takotsubo's cardiomyopathy, etc.) and secondary ventricular failure (sepsis-mediated myocardial dysfunction, pulmonary embolism with right ventricular dysfunction, type II NSTEMI, etc.).

In Canada, the two approved inotropic agents are milrinone and dobutamine. Milrinone is a phosphodiesterase III inhibitor, which increases intra-cellular cyclic AMP levels resulting in improved cardiac contractility, inotropy and lusitropy with subsequent vasodilation of both systemic and pulmonary circulations [5]. Dobutamine is a synthetic catecholamine with affinity for both beta-1 and beta-2 receptors; binding to cardiomyocytes results in improved myocardial inotropy, weak chronotropy and mild systemic vasodilation. Inferences from their mechanisms of action and data from small retrospective studies suggest that both inotropes cause systemic and pulmonary circulation vasodilation, clinically significant hypotension [3] and both atrial and ventricular arrhythmias [6,7].

The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines [8] include the use of inotropes in the management of acute heart failure with reduction in cardiac output. The ACC/AHA guidelines also recommend cautious use of inotropes in patients with ST-elevation myocardial infarction complicated by CS [9]. These recommendations are based on predominantly expert consensus, with poor evidence to support selection of one inotrope over another. We set out to evaluate the comparative efficacy and safety of dobutamine compared to milrinone in hospitalized patients with CS or LCOS.

Methods

Systematic review

The population of interest was hospitalized patients with evidence of LCOS or CS in whom the intervention was

inotropic therapy with the goal of comparing dobutamine to milrinone. The primary outcome of interest was all-cause in-hospital mortality. Secondary efficacy end points included all-cause mortality in long-term follow up (at one year following discharge from initial hospitalization), length of stay in the ICU (LOS-ICU) and in-hospital length of stay (LOS-H). Secondary safety end points included atrial and ventricular tachyarrhythmias that were associated with symptoms and/or required anti-arrhythmic therapy.

Search strategy, study selection and data collection

The systematic review search strategy was created by a medical librarian (SV) in consultation with the research team (RM, GMS and BH) and peer-reviewed by a second medical librarian. The search was created in MEDLINE using a combination of index terms and keywords related to milrinone and dobutamine. Once the search was finalized, it was translated to the other bibliographic databases (Full MEDLINE search strategy available upon request from the authors as Supplemental Appendix 1). Searches were conducted to December 14, 2016 in Medline (1946-present), the Cochrane Central Register of Controlled Trials (CENTRAL) (November 2016) and Embase (1974-) in Ovid. Search results were exported to EndNote X7 and

FIGURE 1. PRISMA flow diagram of literature search

duplicates were removed through manual inspection using the EndNote duplicate identification function (see Figure 1).

For reports that were suspected of reporting outcomes of the same patients, the most recent source or the source with the largest sample size with outcome data available was selected for inclusion (primary author was also contacted to confirm same cohort of patients). Articles were independently screened by two authors (RM and GMS) using Covidence software. Disagreements were resolved by consensus or adjudication (BH). Details of study design, inotrope administration strategy (route of administration, dosing, duration, etc.) as well as baseline patient characteristics were collected, when reported. For abstracts and full publications where no baseline characteristics were published, the primary author was contacted by email to request permission to access the raw data.

Risk of bias

The methodological quality of studies was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [10,11].

Analysis and synthesis of results

The results of included studies with complete data are summarized individually and evaluated collectively. Random-effects meta-analysis was completed for efficacy and statistical heterogeneity evaluated using the I² statistic. Risk ratios and mean differences were used as the primary effect measures. All analyses were completed using RevMan v.5.3 (Cochrane Collaboration, Copenhagen, Denmark) with two-tailed significance level of 0.05. For outcomes identified in only one included report, descriptive summaries are provided instead of results from a meta-analysis.

Results

Study selection and characteristics

Of 2,608 non-duplicate citations identified, 11 reports from 12 studies met inclusion criteria. Studies were published between 2001 and 2017 (Figure 1). Two thirds (64%) of the studies constituted full published manuscripts (seven studies) but only one of the studies was a randomized controlled trial (comprising 36 patients); the remaining reports were retrospective cohort studies and one prospective cohort study. In total, 23,056 patients are reported: 6,452 on milrinone therapy and 16,604 on dobutamine therapy. Details of study characteristics, risk of bias and quality

assessments are available upon request from the authors (Supplemental Table 1; alphabetically, by abstract and full publication status). Patient characteristics, where provided, are available upon request from the authors (Supplemental Table 2).

All-cause mortality: in-hospital and long-term

Six studies reported in-hospital mortality by use of inotrope and were included in the primary efficacy analysis [12-17]. Comparatively, there was no observed difference between dobutamine (14,627 patients) and milrinone (4,507 patients) on in-hospital mortality (OR 1.13, 95% CI 1.00-1.29, $p=0.06$, Figure 2A) although a trend towards reduction in mortality was observed. Long-term follow-up was available in three studies: King et al. at 180-days following discharge and in two studies at 1-year following discharge [18-20]. In follow-up, there was lower long-term mortality at one year with milrinone ($n=1,077$ patients) compared with dobutamine ($n=1,187$) (OR 1.95, 95% CI 1.27-2.97, $p=0.002$, Figure 2B).

Length of stay: ICU and in-hospital

Total hospital length of stay was reported in seven studies [12-16,19,20] and LOS-ICU was reported in three studies [14,16,21]. There was no difference in LOS-H between milrinone ($n=2,665$ patients) and dobutamine ($n=5,906$ patients) (mean difference -1.22 , 95% CI $-4.68 - 2.24$, $p=0.49$, Figure 3A). In the three studies reporting the outcome, LOS-ICU was shorter with dobutamine ($n=5,577$ patients) compared with milrinone ($n=2,481$ patients) by nearly one day (mean difference -0.72 , 95% CI $-1.10 - -0.34$, $p=0.0002$, Figure 3B).

Comparative safety: incidence of clinically significant arrhythmia

The most commonly reported adverse event with inotrope utilization is arrhythmia. Our search strategy identified three studies [13,17,22] that reported the incidence of arrhythmias associated with the use of inotropes. The definition of clinically significant arrhythmia reported in the studies is available upon request from the authors (summarized in Supplemental Table 3). No differences in clinically significant arrhythmia was noted between dobutamine (338 patients) and milrinone (127 patients) in the identified studies (OR 1.78, 95% CI 0.85-3.76, $p=0.13$, Figure 4) with an increase frequency of arrhythmia numerically reported with dobutamine.

FIGURE 2A.

Forest plot of in-hospital mortality with dobutamine versus milrinone inotropic therapy.

FIGURE 2B.

Forest plot of long-term mortality (at 1-year following hospital discharge) with dobutamine versus milrinone inotropic therapy.

Discussion

With augmenting complexity of patients being cared for in cardiac ICUs, clinicians are increasingly faced with choosing between inotropic therapies without a sizeable body of evidence upon which to make a selection. Herein, we report the summary of all studies evaluating the efficacy and safety of dobutamine compared to milrinone in hospitalized patients in critical care settings. Our review showed that the available data are of poor methodological quality and mostly retrospective in nature, with only a single randomized controlled trial performed, with 36 patients. Our primary end-point of all-cause in-hospital mortality was not different between the therapies, although a trend favoring milrinone was observed. Nonetheless, long-term mortality was significantly reduced in studies reporting the outcome. In contrast, dobutamine was associated with significantly shorter LOS-ICU, although the data were inadequate to

assess the impact of mortality on this observed difference. Finally, with regards to safety we observed no differences in clinically significant arrhythmias between the therapeutic regimens. Thus, based on the currently available data, no strong recommendation can be made preferring one agent over another when deciding between inotropic therapies in managing hospitalized patients.

The lack of difference between the therapeutic agents on short-term mortality is not surprising given the existing body of evidence. Available studies have failed to show meaningful differences when inotropic therapy is compared to another active therapy—with some observational data suggesting an increased risk of harm [23]. A retrospective analysis of the ADHERE national registry suggested short-term vasodilator therapy (nitroglycerin or nesiritide) was associated with a significantly lower in-hospital mortality compared with the use of inotropic therapy (milrinone or dobutamine) [12]. In a small randomized study of

FIGURE 3A.

Forest plot of in-hospital LOS with dobutamine versus milrinone inotrope therapy.

FIGURE 3B.

Forest plot of ICU LOS with dobutamine versus milrinone inotrope therapy. ICU = intensive care unit; LOS = length of stay.

FIGURE 4.

Forest plot of arrhythmias (symptomatic, sustained arrhythmias and non-sustained arrhythmias requiring AAT) with dobutamine versus milrinone inotrope therapy. AAT = anti-arrhythmia therapy.

hospitalized patients awaiting cardiac transplant, patients randomized to milrinone or dobutamine had no significant between-group differences in in-hospital death. Moreover, they reported similar rates of symptomatic sustained or non-sustained arrhythmias requiring anti-arrhythmic therapy [13]. Finally, a comparative analysis of chronic dobutamine or

milrinone infusions for heart failure patients showed no difference in all-cause mortality after adjustment for baseline characteristics (in the full cohort) or in the propensity-matched cohort [24]. Thus, comparative studies have failed to show differences in hard outcomes between agents—a finding echoed in our analysis.

The most surprising finding of our study was the shorter LOS-ICU in patients treated with dobutamine compared with those treated with milrinone. First, there may be the possibility of increased mortality—and resultantly shorter LOS—in dobutamine-treated patients. Second, given the primarily observational nature of the data, selection bias may have resulted in patients with specific hemodynamic profiles being selected for treatment with dobutamine. Finally, it is plausible that dobutamine is more efficacious in providing more rapid stabilization of hemodynamics and, subsequently, a shorter LOS-ICU. While an interesting and conspicuous observation, further studies are needed to validate the observed effect.

Limitations and future directions

Our study has several limitations that must be considered. First, there was very little robust data comparing milrinone with dobutamine, with the analysis including only one randomized controlled trial contributing 36 patients. Accordingly, numerous confounders undoubtedly exist and preclude us from drawing firm conclusions despite the large sample size. Second, there was significant heterogeneity in the study populations—including patients with CS, ADHF, awaiting cardiac transplant, post cardio-pulmonary bypass, etc. While this is reflective of current cardiac ICUs, studies often excluded the most unstable patients, making application of these data to all patients needing inotrope therapy difficult. Finally, for the safety analysis of arrhythmias, details of the specific types of supraventricular and ventricular arrhythmias were not provided—limiting the interpretation the data. Hence, while our analysis represents the totality of comparative data, there remains a significant need for additional high quality studies in this field.

Conclusion

Our study found no difference in in-hospital mortality or arrhythmias among hospitalized patients treated with either dobutamine or milrinone. Currently available data are primarily observational and of poor methodological quality. Prospective randomized studies are needed to better inform clinical decision making in hospitalized patients requiring inotrope therapy.

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