Prognosis on Chronic Dobutamine or Milrinone Infusions for Stage D Heart Failure

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Background—There are no published clinical trials comparing dobutamine with milrinone in outpatients with stage D heart failure on continuous inotropes.

Methods and Results—In a retrospective analysis of 112 inotrope-dependent patients with stage D heart failure who were not transplant candidates at enrollment, we investigated the relationship between choice of dobutamine or milrinone and mortality. Half the patients were on dobutamine (mean dose, 5.4±2.5 μg/kg per minute) and half on milrinone (mean dose, 0.4±0.2 μg/kg per minute). Those on dobutamine tended to be older (63 years old versus 54 years old), male (86% versus 79%), and fewer had implantable cardioverter-defibrillators (57% versus 74%). During a median follow-up time of 130 days (range, 2 to 2345 days), there were 85 deaths (76% of cohort) and 55 rehospitalizations. Use of dobutamine compared with milrinone was associated with higher all-cause mortality in an unadjusted analysis (hazard ratio [HR], 1.63; 95% CI, 1.06 to 2.52; P<0.03). However, this association was not significant after adjustment for baseline characteristics in the full cohort (N=112; HR, 0.99; 95% CI 0.5 to 1.97; P=0.98) or propensity-matched cohort (N=70; HR, 0.94; 95% CI 0.48 to 1.85; P=0.86).

Conclusions—In this single-center retrospective study, there were no mortality differences between chronic intravenous dobutamine or milrinone in patients with stage D heart failure being discharged from the hospital. The high mortality in this group selected for inotrope dependence warrants careful consideration of all options and priorities for further care. (Circ Heart Fail. 2009;2:320-324.)

Key Words: heart failure ■ inotropic agents ■ mortality

Latest treatment guidelines1 assign continuous intravenous infusion of a positive inotrope agent for palliation in patients with refractory end-stage heart failure (HF), a class IIb indication. However, data regarding the choice of inotrope for these patients are lacking.2 Dobutamine and milrinone are the 2 most commonly used intravenous inotropes in the United States. These medications have significantly differing pharmacological properties,3 cost,2 and short-term clinical response,4 though it is unknown if they have differing mortality outcomes. Therefore, we sought to examine the rate of all-cause mortality among patients with stage D HF who were discharged on intravenous dobutamine versus milrinone infusion, while adjusting for demographic, clinical, and laboratory measures.

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Methods

Study Population
The study participants were identified retrospectively by use of case management and pharmacy records. We included all 18 years and older patients, discharged on continuous intravenous dobutamine or milrinone infusion from a specialty HF cardiology service at our institution between 2002 and 2007. All patients had stage D HF and were deemed inotrope dependent after failing to wean from inotropes in an intensive care unit. Inotrope dependence was defined by a combination of clinical and hemodynamic factors. Clinical factors included limited functional capacity, worsening congestive symptoms, symptomatic hypotension, or deteriorating renal function without inotrope infusion. Hemodynamic factors included a failure to maintain an adequate cardiac index >2.0 L/min per m² or wedge pressure ≤20 mm Hg without inotrope infusion, on maximum doses of loop diuretics and oral vasodilators.

At our institution, patients listed for heart transplantation who are inotrope dependent remain hospitalized until they either receive a ventricular assist device (VAD) or a transplant. Decisions regarding VAD and heart transplantation are made by our advanced HF therapeutics committee, which meets once a week. Members of the team include the following: HF/transplant cardiologists and surgeons, fellows, nurses, a pharmacist, a social worker, a pathologist, a bioethicist, and a staff member from the transplant immunology laboratory. When a patient is reviewed, all options are considered including medical, surgical, and device therapy, as well as mechanical VADs, and heart transplantation. The patients in the present cohort were not heart transplant or VAD candidates at the time of discharge.
entry into the cohort (ie, initial hospital discharge) because of the patient characteristics, medical contraindications, or patient choice. Of these, some ultimately went on to become heart transplant candidates after weight loss, demonstrating medical compliance, stopping tobacco use, or completing a chemical dependency program.

Patients discharged on >1 inotrope were excluded. For patients with multiple hospitalizations, only the first hospital discharge on inotropes was examined. Implantable cardioverter-defibrillators were not turned off before discharge. Demographic, clinical, medication, and laboratory values were collected through electronic and paper chart review. Laboratory values were those obtained within 1 to 2 weeks before discharge. Institutional review board approved this study.

Outcomes
The primary end point was all-cause mortality as ascertained both by the hospital records and the Social Security Death Index. Patients were followed until a common closing date of August 1, 2008. Data on clinical outcomes including rehospitalizations, left ventricular assist device implantation, and heart transplantation were also recorded.

Statistical Analysis
Continuous variables are presented as mean±SD. Differences in baseline characteristics were compared using the Wilcoxon Rank Sum test for continuous variables and the χ² test for categorical variables. We used Kaplan–Meier curves and Cox proportional hazards modeling to examine the association between inotrope choice and all-cause mortality in (1) an unadjusted model, (2) adjusting for age and gender, and (3) adjusting for age, gender, type of cardiomyopathy, race, blood urea nitrogen, angiotensin converting enzyme inhibitor use, aldosterone blocker use, and a propensity score (described later). Adjusting variables were partially selected using variable importance as assessed by out-of-bagging, a more detailed explanation is found in the Appendix. The proportional hazards assumption was confirmed by testing the weighted Schoenfeld residuals and by plotting hazard ratio against time plots for selected variables. All Cox models were constructed from, and validated in, 1000 bootstrap samples of the data.

Because milrinone and dobutamine were not randomly assigned in this patient population, potential confounding and selection biases were accounted for by developing a propensity score. The propensity for milrinone or dobutamine use was determined without regard to the outcome, using a multivariable logistic regression model. For this model, we chose variables that we thought may have increased the propensity for dobutamine over milrinone use, including age, gender, device status, and β-blocker use. This model yielded a concordance statistic of 0.76 indicating good discrimination. A propensity score was then calculated from the logistic equation for each patient, in effect representing the probability that a patient would be using dobutamine over milrinone.

Subsequently, using a publicly available macro, we used the propensity scores to match milrinone users to dobutamine users (Supplemental Figure). We were able to match 35 milrinone users with 35 dobutamine users.

Statistical analyses were performed with R version 2.7.2 (http://cran.r-project.org) and SAS version 9.1 (SAS Institute, Cary, NC). Kaplan–Meier plots, Cox modeling, and model assessment were performed in R version with Harrell’s Design and Hmisc libraries. Propensity analysis was performed in SAS using Lori Parson’s Greedy Match Macro (http://www2.sas.com/proceedings/sugi26/p214-26.pdf).

Results
Baseline Characteristics
We identified 115 patients who were discharged on continuous intravenous inotropes from a specialty HF cardiology service at our institution between January 2002 and December 2007. All were originally admitted for management of decompensated HF. Three of these patients were discharged on both dobutamine and milrinone and were excluded from the analysis. Of the 112 remaining patients, 56 were discharged on dobutamine (mean dose, 5.4±2.5 μg/kg per minute) and 56 on milrinone (mean dose, 0.4±0.2 μg/kg per minute). Patients discharged on dobutamine tended to be older, male, and fewer had implantable cardioverter-defibrillators (Table 1). There were no significant differences in the use of dobutamine versus milrinone during the calendar time span of the study.

Outcome for Overall Cohort
During a median follow-up of 130 days (range, 2 to 2345 days), 85 patients died. The rate of death was significantly higher in the dobutamine group compared with that in the milrinone group (47 patients [84%] versus 35 patients [62%], P<0.01) (Figure, A). Seven (6%) patients went on to receive left ventricular assist device support, and 12 (11%) patients receive heart transplantation. Among the patients on dobuta-
mine, there was a trend toward less left ventricular assist device implantations (1 patient [2%] versus 6 patients [11%], P=0.051) and less heart transplantations (3 patients [5%] versus 9 patients [16%], P=0.07). There were no significant differences in the rates of rehospitalizations (1 or more rehospitalization over the study period: 28 patients [50%] versus 27 patients [48%], P=0.85).

To examine the impact of inotrope dose on outcome, the cohort was stratified by low and high doses of dobutamine (7.5 g/kg per minute versus ≥7.5 g/kg per minute) and milrinone (<0.5 and ≥0.5 μg/kg per minute) by the United Network for Organ Sharing transplant listing criteria. There were no survival differences in either the dobutamine (log-rank P=0.68) or the milrinone (log-rank P=0.68) groups.

Propensity Analyses
To account for multiple confounding factors that were associated with dobutamine use, such as increased age and decreased usage of implantable cardioverter-defibrillators, we generated a propensity-matched cohort. We were able to match 35 patients on dobutamine with 35 on milrinone. In general, both the groups were well matched for all baseline variables (Table 2).

During a median follow-up of 95 days (range, 2 to 1765 days), 53 patients died. In this propensity-matched cohort, the associations between dobutamine or milrinone and mortality (27 patients [77%] versus 26 patients [74%], P=0.78) (Figure, B), left ventricular assist device implantation (1 patient [3%] versus 2 patients [6%], P=0.55), and cardiac transplantation (2 patients [6%] versus 6 patients [17%], P=0.13) were not statistically significant.
Predictors of All-Cause Mortality

In the full cohort, we tested the association between inotrope type and mortality in multiple models. In an unadjusted model, there was a significant association between dobutamine and mortality (HR, 1.63; 95% CI, 1.03 to 2.59; P=0.04). After adjustment for age and gender, the association was no longer significant (HR, 1.09; 95% CI, 0.64 to 1.85; P=0.75). Finally, we constructed a multivariable Cox proportional hazards model adjusting for inotrope type, age, gender, type of cardiomyopathy, race, blood urea nitrogen, angiotensin converting enzyme inhibitor use, aldosterone receptor blocker use, and the propensity score. The association between inotrope type and mortality was not significant (HR, 0.99; 95% CI, 0.5 to 1.97; P=0.98). The only significant predictors of all-cause mortality were age (66 years [75th percentile] versus 44 years [25th percentile]; HR, 2.53; 95% CI, 1.35 to 4.74; P<0.01) and blood urea nitrogen (44 [75th percentile] versus 23.5 [25th percentile]; HR, 1.49; 95% CI, 1.05 to 2.11; P=0.02). No interaction was statistically significant including that between the propensity score and the adjusting covariates. In the propensity-matched cohort, there was no significant association between inotrope type and mortality (0.94; 95% CI, 0.48 to 1.85; P=0.86).

Discussion

In patients with stage D HF who were discharged on continuous intravenous inotrope infusion, the choice between dobutamine and milrinone did not have a mortality impact in our cohort. Although the mortality with dobutamine versus milrinone in an unadjusted analysis seemed to be higher, this association was no longer significant after multivariable adjustment and propensity-matched analyses.

Both milrinone and dobutamine increase contractility via elevation of cAMP, and are arrhythmogenic, and both are associated with higher rates of mortality compared with placebo, but it is unknown whether the pharmacological differences between these inotropes leads to differences in the rate of mortality. Several previous studies examined inotrope use in patients with end-stage HF, but none compared the rate of death with the inotrope choice. Their focus was mainly on clinical feasibility, safety, cost-effectiveness and resource utilization, and as a bridge to transplantation or for palliation. We present new information on a common clinical dilemma: the prognostic implications of choosing between dobutamine and milrinone for patients with stage D HF being discharged from the hospital.

The pharmacological differences between dobutamine and milrinone influence their choice in clinical practice. Dobutamine is a racemic mixture consisting of “+” isomers that stimulate β1 receptors and “−” isomers that stimulate α1 receptors. In low doses, it can cause vasodilation but at higher doses it raises blood pressure. It increases heart rate, and myocardial oxygen demand more than milrinone and is short acting with a half-life of 2 minutes compared with milrinone that has a half-life of 2.3 hours. The inotropic and chronotropic effects of dobutamine are due to stimulation of β1 adrenergic receptors, which are often downregulated in patients with end-stage HF and therefore the effect of the drug may change with time. Prolonged continuous intravenous administration of dobutamine has also been reported to be associated with eosinophilic myocarditis and peripheral eosinophilia. Milrinone, conversely, is a phosphodiesterase inhibitor that increases cAMP by preventing further metabolism. It is frequently given to patients with HF with concomitant pulmonary hypertension because it causes greater vasodilatation than dobutamine via phosphodiesterase inhibition in vascular smooth muscle cells. However, as an inodilator, milrinone also confers a higher risk of systemic hypotension that can be difficult to treat because of its long half-life. Despite these pharmacological differences, we did not find a difference in rates of death among the patients with stage D HF treated at our medical center with either dobutamine or milrinone.

Our findings have important implications. We cannot conclude from this experience whether chronic inotropic therapy prolonged life or hastened death, though consistent with previous reports, we can conclude that patients requiring inotropic therapy have a poor short-term prognosis.

The poor prognosis of inotrope-dependent patients who are not candidates for VAD or heart transplantation makes it important that clinicians review all options and preferences including hospice, implantable cardioverter-defibrillator deactivation, and requests for resuscitation including intubation with the patient and family. The patient and family should be made aware of the short-life expectancy before consideration of inotrope usage, and the most important goals of the patient should be thoughtfully elicited and honored. Additionally, we feel that the high rate of mortality and rehospitalization with either dobutamine or milrinone suggests that neither should be considered an appropriate control arm for a randomized trial for the outcome of death, except possibly in comparison with a completely new strategy.

The strengths of our study include a relatively large cohort for a single-center study and the use of propensity matching to compare only patients with similar baseline characteristics. Although our analysis is retrospective, this is the only study to date, which primarily focuses on inotrope choice and mortality in patients with stage D HF in a contemporary “real world” practice population.

Study Limitations

This study has several limitations. It is a retrospective study from a single tertiary-care institution and is prone to biases related to unmeasured factors. However, we used multivariable methods and propensity analysis methods to carefully match patients in an effort to eliminate bias as best as possible. Although we found an effect in our main cohort, our propensity-matched cohort was small and the finding of no effect may represent a type II error.

Our analysis also did not address issues of cost and quality-of-life. Another limitation was our lack of data on cause of death, specifically arrhythmic versus pump failure. However, for patients, families, and clinicians, all-cause mortality is likely the most clinically relevant outcome.

Conclusions

There were no mortality differences between chronic intravenous dobutamine or milrinone in patients with stage D HF
being discharged from the hospital. The high mortality in both the inotrope groups warrants clinicians to carefully consider all options and priorities for further care.

Sources of Funding
This work was supported by the National Heart, Lung, and Blood Institute CAN No. 8324207 (E.Z.G.), Case Western Reserve University/Cleveland Clinic CTSU (1KL2RR024990) (M.H.S.), The American Heart Association National Scientist Development Grant No. 0730307N (E.H.), and The National Institute of Allergy and Infectious Diseases U01 AI063594-04 (R.C.S.).

Disclosures
None.

References

CLINICAL PERSPECTIVE

Treatment guidelines for patients with stage D heart failure advise the use of inotropic therapy in the outpatient setting strictly for palliative care, but do not contain recommendations regarding choice of inotrope. In this retrospective single-center study, we primarily examined whether the choice between continuous infusion of dobutamine versus milrinone for patients with stage D heart failure who were not heart transplant candidates had an impact on all-cause mortality. Although there appeared to be higher mortality with dobutamine versus milrinone in an unadjusted analysis, this association was no longer significant after multivariable adjustment. Our findings are consistent with previous reports of <50% 6-month survival in this patient population, but further suggest no difference in outcome with inotrope choice. Clinicians should choose an inotrope based on clinical response and cost-effectiveness because there is no impact on prognosis.
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Circ Heart Fail. 2009;2:320-324; originally published online May 14, 2009;
doi: 10.1161/CIRCHEARTFAILURE.108.839076

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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SUPPLEMENTAL MATERIAL.
**Supplemental Figure.** Distribution of propensity scores (i.e., probability of a patient being on dobutamine)

- **Full Cohort**
- **Propensity Matched Cohort**

Graphs showing the distribution of propensity scores for different treatments.
Approach to variable selection

We pre-specified the use of age, gender, type of cardiomyopathy, and the propensity score in our multivariable Cox model. We used variable importance as assessed by out-of-bagging to help select the other adjusting variables. Our approach was as follows. We created a set of 5000 models incorporating all the variables in Table 1. Each model was constructed from a bootstrap sample of the original cohort. Each bootstrap sample left out, on average, ~37% of patients, which was referred to as the “out-of-bag” (OOB) sample. Each model was applied to its corresponding OOB sample to calculate a measure of prediction error (e.g., c-index). In order to identify the most important variables we evaluated the change in prediction error (i.e., variable importance) attributed to each variable by recalculating the prediction error after random permutation of each variable in the OOB sample (effectively converting the variable’s value into completely uninformative noise); an important variable would be expected to yield a greater degradation in the OOB prediction error. The process was repeated 5000 times for each variable, and aided in identifying the adjusting variables mentioned in the methods section.