Effects of intravenous home dobutamine in palliative end-stage heart failure on quality of life, heart failure hospitalization, and cost expenditure

Pieter Martens1,2, Jan Vercammen1, Wendy Ceyssens1, Linda Jacobs1, Evert Luwel1, Herwig Van Aerde3, Peter Potargent3, Monique Renaers4, Matthias Dupont1 and Wilfried Mullens1,5*

1Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 63600, Genk, Belgium; 2Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; 3Primary care physician region Genk, Genk, Belgium; 4Clinic Care Pathway Home-Dobutamine, Wit-Geel Kruis, Limburg, Belgium; 5Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

Abstract

Aims In patients with palliative end-stage heart failure, interventions that could provide symptomatic relief and prevent hospital admissions are important. Ambulatory continuous intravenous inotropes have been advocated by guidelines for such a purpose. We sought to determine the effect of intravenous dobutamine on symptomatic status, hospital stay, mortality, and cost expenditure.

Methods and results All consecutive end-stage heart failure patients not amenable for advanced therapies and discharged with continuous intravenous home dobutamine from a single tertiary centre between April 2011 and January 2017 were retrospectively analysed. Dobutamine (fixed dose) was infused through a single-lumen central venous catheter with a small pump that was refilled by a nurse on a daily basis. Symptomatic status was longitudinally assessed as the change in New York Heart Association class and patient global assessment scale. Antecedent and incident heart failure hospitalizations were determined in a paired fashion, and cost impact was assessed. A total of 21 patients (age 77 ± 9 years) were followed up for 869 ± 647 days. At first follow-up (6 ± 1 weeks) after the initiation of dobutamine, patients had a significant improvement in New York Heart Association class (−1.29 ± 0.64; P < 0.001), global assessment scale (<0.001), and N-terminal pro-brain natriuretic peptide (6247 vs. 2543 pg/mL; P = 0.033). Incident heart failure hospitalizations assessed at 3, 6, and 12 months were significantly reduced (P < 0.001 for all) in comparison with antecedent heart failure hospitalizations over the same time period. Cost expenditure was significantly lower at 3 (P < 0.001), 6 (P = 0.005), and 12 months (P = 0.001) after initiation of dobutamine. Mortality rate at 1 year was 48% with 9/12 (75%) patients dying at home, most often from progressive pump failure.

Conclusions Continuous intravenous home dobutamine in patients with palliative end-stage heart failure is feasible and associated with improved symptomatic status, heart failure hospitalizations, and health-care-related costs. Nevertheless, results should be interpreted in the context of the small and retrospective design. Larger studies are necessary to evaluate the effect of dobutamine in palliative end-stage heart failure.

Keywords End-stage heart failure; Dobutamine; Mortality and morbidity; Cost

Introduction

Despite advances in the therapies for heart failure, a proportion of patients ultimately progress towards end-stage heart failure. In these patients, the decision to alter the focus of care from modifying disease progression towards improvement of quality of life is often welcomed.1 Inotropic agents can improve the haemodynamic status in patients with low cardiac output leading to improved quality of life, yet they are associated with increased mortality.2 However, patients
with severe heart failure symptoms often opt for quality instead of quantity of life, and informing the patient about the potential benefits and harm of inotropic agents allows to make a joint decision on its use for improving quality of life.\(^1\) Nevertheless, practical issues with the infusion of inotropic agents through a central venous catheter, different types of infusions strategies (continuous vs. intermittent), and organization of home-based care with fear of increased cost might prevent its widespread implementation in the palliative setting. The goal of this analysis is to report on the subjective and objective impact of continuous intravenous low-dose dobutamine infusion on an ambulatory basis. Additionally, we analysed the impact on heart failure hospitalization and the costs (reduction) incurred with this therapy.

**Methods**

**Study population and selection**

Eligible patients for home dobutamine were end-stage heart failure patients with reduced ejection fraction and severe and recurrent symptomatology secondary to low cardiac output for which advanced therapies (heart transplant of assist device) were not an option. All patients underwent a similar protocol to determine whether intravenous therapy with dobutamine relieved symptoms. Briefly, patients were electively admitted for right heart catheterization with placement of a Swan–Ganz catheter. The presence of low cardiac output was determined (defined as a cardiac index \(< 2.0 \text{ L/min/m}^2\)). Afterwards, patients were admitted for 24 h to the cardiac critical care unit to determine the responsiveness to intravenous dobutamine. After initiation of dobutamine, beta-blockers were discontinued in all patients, and amiodarone 200 mg was initiated in all patients. Intravenous dobutamine was started at an infusion rate of 1.0 \(\mu\text{g/kg/min}\) and always up-titrated to 4.0 \(\mu\text{g/kg/min}\). Afterwards, haemodynamic success was determined as the presence of (i) an absolute increase of cardiac index to \(> 2.4 \text{ L/min/m}^2\) and/or 25% increase of cardiac index; and/or (ii) a drop in pulmonary wedge pressure \(< 18 \text{ mmHg}\) and/or a drop of 25% of wedge pressure (if previously elevated \(> 18 \text{ mmHg}\) ) both paralleled with a subjective improvement in generalized well-being; and/or (iii) an increase in hourly diuresis rate by \(> 25\%\). If haemodynamic response was present, patients received a single-lumen Hickman catheter, and preparations for discharge and home therapy were made. This analysis is a retrospective analysis of all consecutive patients discharged with home-dobutamine infusion for end-stage heart failure. The electronic medical record was used to construct the baseline characteristics of the patient population at the time of the index hospitalization on which dobutamine was started.

**Ambulatory treatment protocol**

For convenient home administration of dobutamine, patients received an automated continuous infusion pump (Caesarea Medical Electronics, T34L-PCA, see Supporting Information, Figure S1). This pump is designed to fit a 60 mL syringe. For home administration, a home nurse uncouples and refills the syringe and rinses the Hickman catheter, with aseptic draping of the bandages afterwards once daily. The ambulatory dosing of dobutamine is fixed for all patients and is determined by the volume of the pump but closely approximates the \(4 \mu\text{g/kg/min}\) administered in the hospital. Two 20 mL vials of 250 mg dobutamine (250 mg/20 mL) are added with 10 mL of glucose 5% in the syringe, to form a 50 mL volume containing 500 mg of dobutamine. This 50 mL volume is administered at 1.9 mL/h equating to \(4 \mu\text{g/kg/min}\) for a patient weighing 80 kg. Therefore, patients with a weight \(> 80 \text{ kg}\) receive a dose in microgram per kilogram per minute slightly lower or slightly higher than for patients with a weight \(< 80 \text{ kg}\).

**Follow-up and study endpoints**

After initiation of the therapy, patients remained in regular follow-up at the outpatient clinic. The follow-up intensity was left at the discretion of the treating physician and ranged between once every 4–12 weeks with intermittent checks as indicated by their treating general practitioner. Laboratory follow-up was performed at the first follow-up visit. Hospital records were used to construct the antecedent frequencies of heart failure admissions before initiation of intravenous dobutamine. These antecedent hospitalizations were evaluated at \(- 3, - 6, \) and \(- 12 \text{ months}\). Incident heart failure hospitalizations were registered at similar intervals (+3, +6, and +12 months). Vital status was checked in the electronic medical record, which is automatically updated. Time to death was calculated, and the location of death (home or hospital) was determined. In patients with an implantable electronic device who died at home, the final tele-monitoring transmission was used to determine the mode of death (presence of ventricular arrhythmias).

**Cost analysis**

The cost reduction potential of intravenous dobutamine was analysed by plotting the antecedent heart failure hospitalizations costs at \(- 3, - 6, \) and \(- 12 \text{ months}\) vs. the incident costs following the initiation of home dobutamine. Incident costs included the following: heart failure hospitalization, placement of the Hickman catheter, cost related to Hickman replacement or infusion of thrombolysis to solve clotting, daily medication cost (dobutamine), and home-nursing costs. Patients were assessed
in a paired method with the duration of incident and antecedent follow-up set to match each other. This to prevent that patients who died before 3, 6, and 12 months of follow-up inflated the antecedent cost and reduced the incident costs. Patients were seen by their treating general practitioner as indicated, which corresponded with two visits monthly before and after the start of dobutamine.

Statistics

Continuous variables are expressed as mean ± standard deviation if normally distributed or median (interquartile range) if not normally distributed. Normality was checked by the Shapiro–Wilks statistic. Categorical data were expressed as numbers and percentages and compared with the Pearson χ² test or Fisher exact test, when appropriate. Continuous variables were compared with the Student t-test or Mann–Whitney U-test, as appropriate. Paired measurements before and after intravenous dobutamine were analysed using the paired t-test. Statistical significance was always set at a two-tailed probability level of <0.05. Statistics were performed using SPSS version 22 (IBM, Chicago, IL). Event-free survival was analysed using Kaplan–Meier curves with the log-rank test used to compare different groups.

Results

Study population and baseline characteristics

A total of 21 consecutive patients were included between April 2011 and January 2017. Baseline characteristics are available in Table 1. All patients had end-stage heart failure as evident by the advanced age, poor left ventricular ejection fraction, high symptomatic baseline status (New York Heart Association [NYHA] class), low blood pressures, and ubiquitous loop diuretic use. All patients used beta-blockers at baseline, which were stopped after start of dobutamine. Therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers was continued in two of the 12 patients taking ACE-inhibitors or angiotensin receptor blockers at baseline. In the remaining 10 patients, this was discontinued owing to the persisting presence of hypotension after the initiation of dobutamine, which improved after discontinuation of the ACE-inhibitors or angiotensin receptor blockers. Mineralocorticoid receptor antagonists were continued in 16 of the 17 patients taking mineralocorticoid receptor antagonists and discontinued in one patient owing to persisting mild hyperkalaemia (>5.5 meq/L). Loop diuretics were continued in all patients. Of the 16 patients with an implantable cardioverter–defibrillator (ICD), only five (31%) patients decided to have their antitachycardia programming deactivated. The remaining 11 patients decided to keep their device activated after being thoroughly informed about the risk of receiving appropriate or inappropriate therapy after initiation of dobutamine.

Symptom and laboratory changes

The impact on symptomatic status was analysed as the difference between the index hospitalization and follow-up. Only patients who had paired measurements available were included in the analysis. Table 2 illustrates the longitudinal impact on the NYHA class reported by the patient. Figure 1 illustrates the difference in patient global assessment (PGA)
in comparison with baseline. Both the NYHA class and PGA indicate sustained improvement in functional status after the initiation of dobutamine. Table 3 illustrates the impact on biomarkers, measured as the difference between baseline and first follow-up. Parallel to the subjective functional improvement, a significant drop in N-terminal pro-brain natriuretic peptide (NT-proBNP) was found. No statistical significant changes were seen on creatinine and urea values.

Heart failure hospitalization and death

Figure 2 illustrates the mean number of heart failure hospitalization before and after initiation of dobutamine, indicating a clear drop in the number of heart failure hospitalizations after initiation of dobutamine. During a mean follow-up period of 869 ± 647 days, a total of 12 patients (57%) died. At 3 months, mortality rate was 24% (n = 5), at 6 months 43% (n = 9), and at 1 year 48% (n = 10). Patients who did not have an ICD or had the ICD switched off (n = 10; 48%) had a similar mortality rate as patients with their ICD function on (log-rank P-value = 0.849). Of the 12 patients who died, three patients (25%) died in the hospital, while nine patients (75%) died at home. Home tele-monitoring detected ventricular arrhythmias in two patients with an implantable device. In nine remaining patients, progressive pump failure was the cause of death, and one additional patient died in the hospital owing to a respiratory infection with sepsis.

Cost analysis

Figure 3 illustrates the average incurred cost per patient before the initiation vs. after the initiation of dobutamine. The grey line represents the antecedent cost, which was completely driven by heart failure hospitalizations. The black line represents the incident cost. The distribution of the
incident cost following initiation of dobutamine is reflected in Figure 4. Following the initiation of dobutamine, incident cost vs. antecedent cost was significantly reduced in patients with paired measurements at 3, 6, and 12 months. This was due to a significant drop in heart failure hospitalizations. During the entire follow-up, a total of eight Hickman replacements occurred for the entire population, and an additional three patients had successful administration of thrombolysis for an occlusion of the Hickman catheter. Of the eight Hickman catheters replacements, one removal was for infection, and the remaining replacements were for Hickman malfunctioning (rupture of the i.v. line or occlusions not responsive to thrombolysis).

**Discussion**

With aging of the population and a progressive increase in the prevalence of patients living with heart failure, the burden of end-stage heart failure is expected to increase. Although advanced therapies such as left ventricular assist device and heart transplantation remain valuable treatment options for some patients, others often fail to meet selection criteria owing to advanced age, device-related reimbursements, or co-morbidity burden. Therefore, often, the decision is made to change the goal of therapy, opting for quality of life instead of lengthening of life in the patient with palliative end-stage heart failure. For these patients, chronic...
infusion of intravenous inotropic agents remains a potential option. Despite absence of randomized controlled trials and the well-established increase in mortality rates using chronic oral inotropes, the American Heart Association/American College of Cardiology guidelines acknowledge the potential of such therapy in patients in a palliative end-stage heart failure setting (IIB recommendation).2,5 Several small-sized and medium-sized cohort studies have looked at the impact of intravenous home inotropic support.6–9 However, the indication for the use of inotropic support was often very diverse including end-stage heart failure awaiting transplantation or left ventricular assist device placement.9 Furthermore, the mode of inotropic delivery varied between intermittent home administration, continuous home administration, and intermittent inpatient administration.6–8 Additionally, the intravenous drug reported varied between milrinone, dobutamine, and dopamine.8 In contrast, we report on a very homogenous population undergoing a simplified treatment regimen. All patients had palliative end-stage heart failure and were treated with a fixed-dose continuous infusion. The dose we use allows for convenient once-daily syringe replacement by a home nurse not requiring calculation of individual doses. Furthermore, the dose administered closely approximates the 4 μg/kg/min often reported to generate beneficial haemodynamic improvements without leading to subjective side effects (tachycardia, dizziness, etc.).10–12

Importantly, continuous intravenous administration of dobutamine resulted in a significant functional improvement as reflected by the changes in the NYHA class and PGA. Our results are similar to an older report using dobutamine home administration indicating a drop in NYHA class by 1.2 points.6 Additionally, our results indicate that this symptomatic response is maintained over time and achieved at albeit low doses (previous reports used dobutamine up to 15 μg/kg/min).6 Furthermore, continuous home administration of dobutamine significantly reduced the number of heart failure hospitalization. Our results are in line with a previous large cohort study indicating a significant drop in the number of heart failure hospitalization following continuous or intermittent administration of milrinone or dobutamine.8 Aside from the inotropic effect of dobutamine with clear haemodynamic improvement and outpatient improvement in functional status and NT-proBNP, the fact that patients might also become less willing to come to the hospital might also contribute to the reduction in heart failure hospitalization.1 Furthermore, our protocol necessitates a daily visit from a home nurse, which might reduce heart failure hospitalizations owing to non-compliance or other related factors. In the Belgian health-economic setting, intravenous home dobutamine was associated with a reduced cost expenditure that was directly related to a reduction in heart failure hospitalizations. Previous reports have shown a significant reduction of health-care-related costs secondary to a reduced heart failure hospitalization burden following the initiation of an intravenous inotropic drug.8,13 However, most studies report on the drug milrinone, which is associated with a significant higher drug cost, as the drug-related cost–price of milrinone far exceeds that of dobutamine in the USA.8 As a result, continuous home administration of milrinone for >6 months resulted in an absence of cost reduction due to the high cumulative drugs-cost expenditure. In contrast, dobutamine remained associated with cost reductions even after 6 months of infusion. Therefore, our simple protocol might be cost-efficient in any health-care system, on the premise that affordable and convenient access to a home nurse

Figure 4 Overview of distribution of incident incurred costs. Cost represents the breakdown of costs for a patient living with dobutamine infusion for 6 months. The cumulative costs for 6 months is higher than those in Figure 3, as those of Figure 3 at 6 months also included the incurred costs for patients not living up to 6 months.
is available. In Belgium, the weekly cost for a home nurse was 287 euros, which formed the largest proportion of the incident cost expenditure (Figure 4).

Finally, the 1 year mortality rate was almost 50%. Nevertheless, this is somewhat lower than that of other large contemporary series. For instance, Hashim et al. reported a 1 year mortality rate of 52.4%, and Hauptman et al. 56.8%. The medical control arm in the REMATCH study even had a 1 year mortality rate of 75%. Given our small sample size, we were not able to analyse why our 1 year mortality rate is slightly lower than that of previous studies. Several factors might have played a role including the use of relative low doses of dobutamine, systematic prescription of amiodarone once beta-blockers were down-titrated, and a low number of device deactivations. Importantly, we noticed that patients in 75% of cases died at home. No patients were urgently admitted by ambulance with pulmonary oedema, perhaps indicating some effect of dobutamine or reconciliation with the end-stage heart failure once dobutamine is initiated.

Study limitations

Several limitations need to be addressed to fully interpret the results. Firstly, this is a small, single-centre study and, therefore, also reflective of local practices in our hospital and community. Secondly, this study is a non-randomized study, so the impact of dobutamine on symptomatic status is also influenced by a placebo effect. Nevertheless, more objective findings such as a reduction in NT-pro-BNP and heart failure hospitalization rate also point to more objective improvement. Thirdly, our study showed a reduction of cost; however, our protocol might not be cost reductive in applicable countries where dobutamine or home nursing is not readily available or at a higher cost.

Conclusions

In patients with palliative end-stage heart failure who opt for quality of life instead of length of life, continuous intravenous home administration of a fixed dose of dobutamine was associated with an improvement of functional status, reduced heart failure hospitalizations, and a beneficial cost expenditure.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1. Ambulatory pump with syringe coupled to single-lumen catheter. Additionally note the typical frail body morphology (muscle wasting), history of coronary artery bypass grafting (scar) and left subcutaneous CRT-defibrillator.

Figure S2. Ambulatory pump stored in a bag once patient is fully clothed.

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