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Need for Hospice and Palliative Care Services in Patients with End-Stage Heart Failure Treated with Intermittent Infusion of Inotropes

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Summary

Background: Hospice and palliative care programs to relieve suffering and optimize management of terminally ill patients have grown rapidly in the United States. However, there are no data on the need for these services among patients with end-stage heart failure receiving intermittent infusion of intravenous inotropes.

Hypothesis: The need for hospice and palliative care programs among patients in end-stage heart failure who receive intermittent infusion of inotropes is investigated.

Methods: The study included all stable patients with refractory heart failure symptoms treated with inotropes in our outpatient unit. A total of 73 patients (65 ± 12 years; left ventricular ejection fraction 22 ± 9%; New York Heart Association class 3.6 ± 0.4) were seen during a 49-month period. Of these, 35 patients (48%) met hospice or palliative care evaluation criteria upon referral but were offered, and accepted, the alternative of parenteral inotropes. In all, 1,737 individual outpatient treatment sessions were given, with a mean of 24 ± 19 sessions per patient (range 5 to 118 sessions), representing a minimum of 9,948 h of inotrope therapy.

Results: A total of 18 (25%) patients died, 6 (8%) patients were withdrawn from the program (3 by their primary physicians and 3 because of significant travel limitations); 4 (5%) patients required continuous intravenous home therapy; and 44 (61%) patients were discharged with significant improvement in their heart failure symptoms. Only 7 of the 18 patients who died had received hospice or palliative care intervention, mainly for the sake of comfort and to ease the transition among family members. The rest of the patients were comfortable and had accepted the natural evolution of their disease; they were not interested in or did not require hospice or palliative care intervention. Of the patients discharged from the outpatient cardiac infusion unit, the interval free of heart failure symptoms after the final infusion treatment ranged from 201 to 489 days, with no need for hospitalization or emergency room visits.

Conclusion: Our results demonstrate that intermittent infusion of intravenous inotropes can be safely administered and can improve symptoms in a significant number of patients, probably by slowing the natural progression of heart failure. Although the full clinical impact of inotrope therapy in an outpatient setting has not been fully defined, other nonhemodynamic-related benefits should be sought and investigated. Our results suggest that intermittent infusion of intravenous inotropes is one of the prominent variables that requires particular attention. In our experience, the institution of intermittent infusions of intravenous inotropes can, in fact, modify end-stage heart failure symptoms that, in most patients, are currently perceived to lead to a terminal event. Thus, appropriate use of intermittent infusion of intravenous inotropes may not only improve functional class and symptoms in a significant number of patients identified as terminal by their poor response to conventional therapy, but it may also facilitate better utilization of hospice and palliative care resources among patients with end-stage heart failure. Furthermore, the need for hospice and palliative care in patients with heart failure should be revisited in view of adjuvant treatment options such as intermittent infusion of intravenous inotropes.

Key words: functional class, hospice, inotrope therapy, heart failure, palliative care

Introduction

Hospice and palliative care programs have grown rapidly in the United States over the last two decades. Their primary goals include the relief of suffering while optimizing utiliza-

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tion of symptom control management as well as improving psychosocial health and providing spiritual care.[1] Establishment of these programs has proven invaluable in the treatment of numerous patients who otherwise would not receive proper terminal care. Hospice and palliative care programs have been responsive to the needs of the dying, particularly cancer patients, allowing them to retain control, providing adequate care giving and grief counseling, as well as appropriate coping mechanisms to accept their terminal illness with dignity. Similarly, they have helped health care professionals to understand critical personal issues, cultural values, unusual medical circumstances, as well as pressing health care issues.[2, 3] Hospice and palliative care programs have been critical in providing adequate pain management;[4] treatment for patients infected with the human immunodeficiency virus, particularly among the marginalized and minorities;[5] management of patients with dementia[6] and those with end-stage renal disease.[7]

Heart failure is a chronic debilitating cardiac illness that currently affects over 4 million Americans, and its incidence continues to increase, with 400,000 new cases expected each year.[8, 9] Patients afflicted with heart failure live an average of approximately 4 to 5 years, but nearly all suffer from fatigue and breathlessness that limit exercise capacity and compromise quality of life.[10] The 3-year mortality rate of heart failure is mainly related to severity of symptoms and ranges from 40% in asymptomatic patients in New York Heart Association (NYHA) class I to 82% in those patients with symptoms at rest or in NYHA class IV.[11, 12] Furthermore, hospital readmission rates for heart failure range from 16 to 47.5% at 1 year,[13] with half of the readmitted patients requiring costly and prolonged hospital stays.[14] A growing number of these patients will require hospice care; however, to be eligible, these patients generally must have a prognosis for survival of < 6 months.

Infusion of intravenous inotropes is currently considered by some as a therapeutic option not only for improving symptoms of decompensated heart failure, but also for reducing hospital readmissions and emergency room visits.[15–19] However, no data are currently available to address the need for hospice and palliative care programs among patients with end-stage heart failure who are treated with intermittent infusion of intravenous inotropes. Thus, we reviewed our experience with such patients at our outpatient unit at Buffalo General Hospital for the preceding 4 years to investigate the need for hospice and palliative care programs in these patients.

Methods

Intermittent Infusion of Inotropes in the Outpatient Setting

In all, 73 consecutive patients with end-stage heart failure were seen at the Buffalo General Hospital Outpatient Cardiac Infusion Unit between April 1997 and May 2001. Inclusion criteria for outpatient infusion of cardiac inotropes were (1) symptoms compatible with NYHA class III or IV heart failure; (2) administration of oral therapy with digitalis, diuretics, angiotensin-converting enzyme inhibitors, or hydralazine-isordil combination; (3) diagnosis of left ventricular systolic dysfunction confirmed by echocardiography prior to initiation of the infusion. Exclusion criteria were (1) acute myocardial infarction within 3 months, (2) unstable ventricular arrhythmias within 3 months, (3) aortic or mitral valve stenosis, (4) hypertrophic cardiomyopathy, (5) intracardiac masses or thrombus, (6) history of repeated noncompliance, (7) history of alcohol or drug abuse, (8) pregnancy (women in childbearing years must practice contraception). Once eligibility criteria were assessed, patients were assigned to either milrinone or dobutamine.

Each intravenous infusion was first started at a low dosage, with a subsequent increase to a medium dose if tolerated. The following doses were used for dobutamine and milrinone: (1) low dose 2.5 mg/kg/min and 0.375 mg/kg/min, respectively, and (2) medium dose 5.0 mg/kg/min and 0.50 mg/kg/min, respectively. Treatment was then continued until there was improvement in symptoms of heart failure, quality-of-life scores, and 6-min walk test results. Treatments were started on a schedule of two or three times a week for 4-h periods. Patients started on a three-times-a-week schedule were (1) decompensated class IV patients, (2) those recently discharged from hospitalization for decompensated congestive heart failure, (3) those whose quality-of-life score was < 10, and (4) those unable to ambulate or with a functional capacity score < 500 m. Patients initially started on a two-times-a-week schedule were (1) patients in NYHA class III–IV, (2) those with a quality-of-life score > 10, and (3) those with a functional capacity score > 500 m. Each treatment cycle was then given for a 4- to 8-week period, and symptoms, physical findings, and clinical response were reassessed. In case of improvement, the treatment cycle was then continued at the same interval or reduced accordingly. In the case of continuous symptomatic improvement, infusion therapy was then weaned over a period of four treatments, each one once a week. Upon discharge from the outpatient cardiac infusion unit, patients were followed at our outpatient congestive heart failure clinic weekly for two visits, biweekly for two visits, monthly for two visits, and then every 2 months thereafter.

Several variables were monitored in each patient on an hourly basis. The following are the clinical guidelines used to determine whether the infusion rate should be either reduced or discontinued: (1) systolic blood pressure > 90 but < 150 mmHg; (2) heart rates < 130 beats/min; (3) absence of new atrial or ventricular arrhythmias, including premature ventricular depolarizations, and absence of symptoms such as nervousness, palpitations, chest pain, nausea, vomiting, or worsening shortness of breath.

Assessment of the Impact of Inotrope Therapy

After giving signed consent, the last 29 patients enrolled in our Outpatient Cardiac Infusion Unit were randomly assigned to receive dobutamine, milrinone, or matching placebo consisting of half normal saline. This double-blind, placebo-controlled randomization protocol was approved by the Institution Board Review committee of the State University of New York at Buffalo. The primary endpoints of this study were improve-

ment on quality-of-life scores using the Minnesota Heart Failure questionnaire[20] and functional capacity evaluations using a standard 6-min walk test.[21] The secondary endpoints were need for hospice care, reduction in emergency room visits, and hospital readmissions due to heart failure.

The treatment protocol was broken when clear clinical deterioration was evident on repeated visits. Under these circumstances, patients who had been receiving placebo were then given an inotrope or inodilator at the physician's discretion in an open-label treatment format. Patients who continued to deteriorate while receiving dobutamine or milrinone were allowed to leave the study protocol and were treated according to the attending physician's preference until death.

All adverse events were recorded whether or not they were considered drug related. Side effects, injuries, toxic reactions, sensitivity reactions, and intercurrent illnesses were also counted as adverse events during these infusions.

Palliative Care and Hospice Services

At the Center for Hospice and Palliative Care at Buffalo General Hospital, Kaleida Health System is a certified program with a professional staff that includes a dedicated hospice physician, registered nurses, nurses' aids, social workers, nondenominational pastoral caregivers, and trained volunteers who provide compassionate care to those patients who, because of the advanced stage of their illness, want to remain in a familiar and supportive surrounding while receiving comfort-focused care. For patients with congestive heart failure requiring hospice or palliative care, entry criteria are (1) optimal medical therapy; (2) significant symptoms or recurrent congestive heart failure at rest, rendering a patient unable to carry out any physical activity without discomfort; and (3) presence of additional aggravating circumstances such as symptomatic arrhythmias resistant to therapy, history of cardiac arrest, syncope, or embolic cerebrovascular accident. In addition to vital signs, all medications and physical findings pertinent to heart failure are recorded. The team reviews all clinical records and evaluates previous treatments and current options; a thorough interview is then conducted with the patient and relatives, and a final disposition is discussed with the attending physician who requested the evaluation.

Statistics

Results are expressed as mean values ± standard deviation. The distributions of the continuous variables were examined, and all showed normal distribution. Analysis of observed differences were made using the Student's *t*-test. Participants with missing data were uniformly excluded from the analyses. A p value of < 0.05 was considered significant.

Results

Baseline characteristics of the study population with refractory end-stage heart failure referred to and treated in the cardiac outpatient inotrope infusion unit and receiving intermittent intravenous infusions of either dobutamine or milrinone are given in Table I; the standard heart failure oral medication regimen profile, expressed as a percentage of each individual drug used in this population, is shown in Figure 1.

TABLE I Characteristics of the study population that received intermittent infusions of parenteral inotropes (Group I)

Demographics	Group I
Age (mean ± SD)	65 ± 12 years
Males	58
Females	15
LVEF (%; mean ± SD)	22 ± 9
NYHA class (mean ± SD)	3.6 ± 0.4
Ischemic cardiomyopathy	51
Idiopathic dilated cardiomyopathy	22

Abbreviations: SD = standard deviation, LVEF = left ventricular ejection fraction, NYHA = New York Heart Assoication.

During a 49-month period, in which intravenous infusions of inotropes were offered to stable patients with refractory symptoms of heart failure, 18 (25%) patients died, 6 (8%) patients were withdrawn from the program (3 by their primary physicians and 3 because of significant travel limitations); 4 (5%) patients required continuous intravenous home therapy; and 44 (61%) patients were discharged from the outpatient cardiac infusion unit as a result of significant improvement in their heart failure symptoms. Therapy was well tolerated, except for the development of arrhythmias as described below. No other significant side effects were reported. In all, 1,737 individual outpatient treatment sessions with a mean of 24 ± 19 sessions per patient (range 5 to 118 sessions), representing a minimum of 9,948 h of inotrope therapy, were given. During

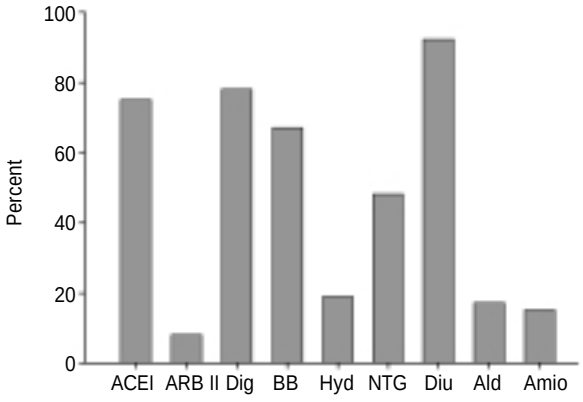

FIG. 1 Standard heart failure oral medication regimen expressed as a percentage of each individual drug used in this population of patients. ACEI = angiotensin-converting enzyme inhibitior, ARB = angiotensin II receptor blockers, Dig = digoxin, BB = beta blocker, Hyd = hydralazine, NTG = nitrates, Diu = diuretics, Ald = aldactone, Amio = amiodarone.

this time, five patients developed new-onset atrial fibrillation with controlled ventricular rate, two patients had nonsustained ventricular arrhythmias requiring elective hospitalization for treatment with amiodarone, and one patient had sustained ventricular fibrillation requiring immediate electrical defibrillation and subsequent implantation of an implantable cardiac defibrillator device. All these arrhythmias were noted within the first 6 to 8 treatment sessions. No patient developed subsequent supraventricular or ventricular arrhythmias during the infusion treatments, and there were no sudden cardiac deaths.

To assess the impact of inotrope therapy objectively, we evaluated the group of patients randomly assigned to receive dobutamine, milrinone, or matching placebo. Of 45 patients on standard heart failure therapy referred, 16 were not included (8 had been recently treated with inotropes, in 3 cases the primary physician refused participation in the study, 3 did not meet criteria, and 2 died before randomization). Thus, 29 patients met criteria and were enrolled while continuing with standard heart failure therapy. These patients were randomized to intermittent intravenous infusions of dobutamine, milrinone, or placebo. All 29 patients subsequently completed the study protocol with no adverse events. Of these patients, 11 received dobutamine, 10 received milrinone, and 8 received placebo. Only 4 of 21 (19%) patients assigned to inotropes needed crossover because of clinical deterioration or intolerance to therapy compared with 6 of the 8 (75%) patients assigned to placebo.

Baseline and end-of-study values for quality-of-life scores both in patients who received inotropes and in those who received placebo differed significantly (both $p < 0.001$) (Fig. 2). Baseline and end-of-study values for 6-min walk test results also differed significantly in the group receiving inotropes ($p < 0.01$), but not in the group that received placebo ($p < 0.4$) (Fig. 3).

Discussion

In this study, we review our experience with the use of intravenous inotropes given intermittently to patients with end-stage heart failure and intractable symptoms despite the use of standard heart failure therapy to assess the need for hospice and palliative care programs in the outpatient setting. In the population of patients who received outpatient inotrope therapy, 35 (48%) met hospice or palliative care criteria on their initial visit to our outpatient heart failure unit, but the alternative of infusion of intravenous inotropes was offered and accepted. Of the population studied, 7 patients quit the program and were lost to follow-up, 47 patients admitted with end-stage heart failure symptoms were eventually discharged from the outpatient infusion unit with almost complete resolution of symptoms on maintenance standard oral heart failure medications, and 19 patients died after starting infusion of intravenous inotropes. The patients who died had received intravenous inotropes for a mean of 20 ± 14 sessions. The causes of death were progressive heart failure in seven patients, sepsis in five, renal failure in three, and other causes in four patients. Only seven of these patients had required hospice or palliative care treatment, primarily for the sake of comfort and to ease the transition among family members. The other patients were comfortable; they had accepted the natural evolution of their disease and did not require hospice or palliative care services. In the patients discharged from the outpatient cardiac infusion unit, the interval free of heart failure symptoms after the final infusion treatment ranged from 201 to 489 days.

It has been already established by other investigators that disease management programs for the care of patients with heart failure involving specialized follow-up by multidisciplinary teams reduce hospitalizations and appear to reduce costs.[22] However, mortality rates for patients with heart failure

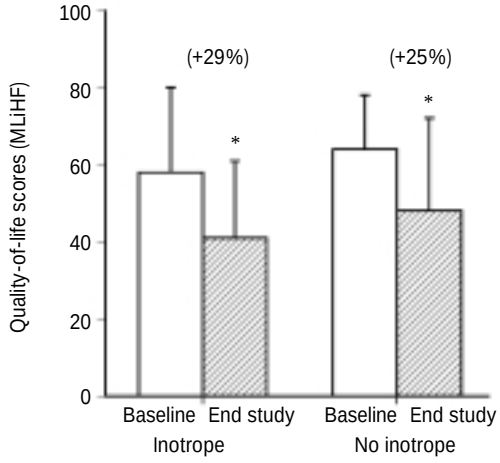

FIG. 2 Histogram demonstrating the impact of inotropes on quality-of-life scores. * = statistically significant difference between baseline and end-of-study values for quality-of-life scores for patients who received inotropes ($p < 0.001$) and those who received placebo ($p < 0.001$).

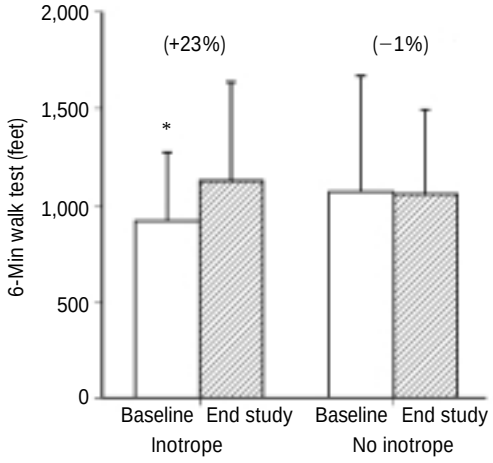

FIG. 3 Histogram demonstrating the impact of inotropes on 6-min walk test results. * = statistically significant difference between baseline and end-of-study values for inotrope 6-min walk test results ($p < 0.01$). No difference was found between these values in patients who received placebo.

remain high, and the number of patients afflicted with this chronic and debilitating cardiac illness continues to increase. A growing number will require hospice care; however, to be eligible, these patients generally must have a prognosis for survival of < 6 months. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) investigators evaluated a consecutive sample of 2,607 seriously ill patients hospitalized at five U.S. medical centers with chronic obstructive pulmonary disease, congestive heart failure, or end-stage liver disease, and who survived to hospital discharge. Based on National Hospice Organization guidelines aimed at providing thresholds for hospice eligibility, the use of descriptive and operating characteristics of five general and two disease-specific clinical criteria for identifying patients with a survival prognosis of ≤ 6 months were found not to be effective.[23]

In principle, our results are in agreement with the data from the SUPPORT Investigators,[23] particularly when we consider that the majority of our seriously ill patients with heart failure did survive more than 6 months, regardless of the initial clinical criteria used to ascertain their prognosis. However, in our case, we do not believe that faulty identification of patients with a poor survival based on clinical criteria explains the improvement in symptoms observed in a significant number of patients with longer than expected survival. Instead, we propose two potential mechanisms: first, a direct benefit, based on measured quality-of-life and functional capacity scores, of intermittent intravenous inotrope therapy to improve symptoms in these patients. We base this argument on the results seen in patients randomly assigned to receive either an intravenous inotrope or matching placebo following a double-blind, crossover randomization scheme. As mentioned above, 11 patients received dobutamine, 10 patients received milrinone, and 8 patients received placebo. Only 19% of patients assigned to inotropes needed crossover because of clinical deterioration or intolerance to therapy, compared with 75% of those assigned to placebo. Despite lack of hemodynamic data (since routine right heart catheterization was not part of the protocol in these terminally ill patients), it is quite evident that patients receiving inotropes had significantly better quality-of-life scores and 6-min walk test results than patients treated with placebo. Second, a potential and crucial variable is the presence of depressive symptoms among these patients. As reported by Vaccarino *et al.*, an increasing number of depressive symptoms has been found to be a negative prognostic factor in patients with heart failure, just as it is for patients with coronary heart disease.[24] We have seen similar improvements in patients with heart failure in our outpatient heart failure clinics.[25] In this study, we unfortunately were not able to assess the prevalence of depression, and thus cannot conclude that a reduction in depressive symptoms was in part responsible for some of the observed overall clinical benefit. However, we can only infer that routine and repetitive interaction with health care professionals and other patients with a similar condition could only improve the overall well-being of patients and reinforce a healthier lifestyle. Thus, further studies are needed to evaluate the impact of interventions such as inotrope therapy and others on depression, and how modification of this important, but almost forgotten variable influences overall clinical outcomes in patients with congestive heart failure.

Since depression was not assessed in patients randomized to receive inotropes or placebo, our analysis could risk criticism by the lack of evidence to support the overall benefit of inotropes in these severely ill patients. However, objective analysis of the quality-of-life scores, functional capacity, and need for crossover measured in these patients certainly emphasizes the fact that parenteral inotropes do confer substantial clinical benefit, particularly when more patients assigned to the placebo arm needed crossover because of worsening symptoms or treatment failure and experienced less improvement in either quality of life or functional capacity.

Based on our results, we infer that the overall improvement seen in patients assigned to intravenous inotropes can be probably explained by several factors: (1) hemodynamic improvement as result of the infusion of inotropes, (2) repetitive contact with fellow patients afflicted with the same disease, (3) multiple encounters with the same health care professionals at each visit providing patients with constant support and reinforcement regarding their condition. We assume that a combination of these interactions helped not only to improve heart failure clinically through treatment and optimization of compliance, but also to reduce depression, if present, by improving each individual's assertiveness of the disease process and thus cognitive recognition. A more objective measure of clinical benefit that can be attributed to inotropes is the fact that it was only in patients who received either dobutamine or milrinone that a statistically significant increase in functional capacity, as measured by the 6-min walk tests, was seen.

After reviewing our experience with patients with end-stage heart failure we can conclude the following. First, a small number of patients can be considered candidates for outpatient infusion of intravenous inotropes for refractory symptoms despite standard heart failure therapy that includes beta blockers and angiotensin-converting enzyme inhibitors. Second, for those requiring outpatient inotropes, the infusions are safe and reduce the need for hospital admissions, hospice, and palliative care. Third, the infusion of intravenous inotropes resulted in a significant clinical improvement for most patients. Although 19 patients died after starting infusion of intravenous inotropes (7 due to progressive heart failure, 5 from sepsis, 3 from worsening renal failure, and 4 from other causes), only 7 (6.8%) patients required hospice or palliative care treatment, primarily for the sake of comfort and to ease the transition among family members. More important, the interval free of heart failure symptoms after the final intravenous infusion treatment ranged from 201 to 489 days.

Conclusion

Our results suggest that intermittent infusions of intravenous inotropes is one of the prominent variables that requires particular attention in patients with end-stage heart failure. In our experience, these intermittent infusions of intravenous in-

otropes can modify end-stage heart failure symptoms that are currently perceived to lead to a terminal event in most patients. Thus, appropriate use of intermittent infusion of intravenous inotropes may not only improve functional class and symptoms in a good number of patients improperly identified as terminal by their poor response to conventional therapy, but it may also help minimize the inappropriate use of hospice and palliative care resources currently offered to many patients with end-stage heart failure. Furthermore, the need for hospice and palliative care in patients with heart failure should be revisited in view of adjuvant treatment options, such as intermittent infusion of intravenous inotropes that can modify the currently perceived end-stage heart failure symptoms.

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