Influence of myocardial contractility therapy for advanced heart failure

Arun S[1], Dinesh Chiriki[2]

From [1]Assistant Professor, Department of General Medicine, Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry, [2]Assistant Professor, Department of General Medicine, Sri Venkateshwaraa Medical College Hospital and Research Institute, Chennai, Tamil Nadu, India

Correspondence to: Dr. Dinesh Chiriki, Department of General Medicine, Sri Venkateshwaraa Medical College Hospital and Research Institute, Redhills, Chennai, Tamil Nadu, India. E-mail: sehejan@gmail.com

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ABSTRACT

With more than 5 million patients' diagnosed with heart failure (HF) and more than 1 million hospitalizations each year, HF continues to have a significant impact on health-care resources. Despite treatment, a significant number of patients continue to have progressive HF symptoms, classified as Class III or IV. The aim of this study was to compare different inotropic therapy for patients of End-Stage Heart Failure. When persistent intravenous access was used and acute hemodynamic improvement was established, the durable medical equipment (DME) benefit category reimbursed 80% of outpatient inotropic medication and supplies for HF. Acute hemodynamic improvement was defined as a 20% reduction in pulmonary capillary wedge pressure and/or a 20% increase in cardiac index, both of which were related to a decrease in dyspnea. The Centers for Medicaid and Medicare Services contracted with regional carriers to run the program. The amounts reimbursed per beneficiary for inotrope and supplies (not adjusted for differential follow-up) were essentially representative of the inotrope cost. Dobutamine, milrinone, and supplies had mean (and median) amounts of 5025 (1168), 87781 (31440), and 7284 (3131), respectively. We found that patients who received this medication had a relatively high death rate, however not as high as people who received chemotherapy. Milrinone-treated patients were compensated more for hospitalizations both before and after starting the inotrope. In addition, the milrinone group had a higher level of digoxin use in the background. Nonetheless, there is an early decrease in overall expenditures following inotrope initiation, which can be attributed to a decrease in hospitalization. Considering the lack of double-blind trials comparing inotropes to placebo or dobutamine to milrinone, decisions regarding the use of inotropes, the type of inotrope used, and the duration of treatment should take into account the impact on resources.

Key words: *Dobutamine, Heart failure, Inotropes, Milrinone*

With more than 5 million patients diagnosed with heart failure (HF) and more than 1 million hospitalizations each year, HF continues to have a significant impact on health-care resources. Despite treatment, a significant number of patients continue to have progressive HF symptoms, classified as Class III or IV [1]. Significant progress has been made in the therapy of individuals with HF and impaired systolic function over the past two decades. Medical treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, blockers, aldosterone antagonists, and diuretics, as well as device therapy with implantable cardioverter–defibrillators and cardiac resynchronization therapy, has resulted in significant improvements in symptoms and survival. By enhancing myocardial contractility, most often by raising intracellular calcium concentrations, inotropes can ameliorate the symptoms associated with low cardiac output. Although inotropes are critical in the treatment of patients with acute decompensated heart failure (ADHF) who have a low cardiac output and poor organ perfusion, as well as in the transition of some patients to cardiac transplantation, their usefulness in the treatment of advanced HF patients is debatable [2]. The majority of studies have looked at the risks and benefits of inotropic drugs in ADHF patients. Numerous inotropes, including oral and intravenous (IV), have been tested in ambulatory individuals with chronic severe HF. Dobutamine and the phosphodiesterase inhibitors (PDEIs) milrinone and enoximone are the two most commonly investigated types of inotropes in the treatment of ADHF.

Milrinone and enoximone, two phosphodiesterase inhibitor (PDEIs), have also been tested in advanced HF patients. Milrinone used orally has been found to produce an increase in mortality. The parenteral formulation is also linked to side effects that limit its application [3]. When given twice-daily to ambulatory HF patients, enoximone, which is accessible in anoral formulation, showed some early promise. However, reports of increased mortality in individuals taking enoximone compared to placebo have dampened initial enthusiasm linked with enhanced exercise capacity and patient complaints. This medicine was found to have a neutral impact in a recent large randomized experiment. Calcium sensitizers are a new class of inotropes that work by causing cardiac contractile filaments to become more sensitive to calcium. Levosimendan has been investigated mostly in acute HF patients and has been linked to increased cardiac output and decreased capillary wedge pressure [4]. However, it has demonstrated no substantial advantages in chronic advanced HF [5,6]. Pimobendan is an oral supplement that has been found to improve exercise capacity

and overall quality of life. However, one study found that its use is linked to an increased risk of death [7].

There have not been any randomized controlled trials on the use of IV inotropes in palliative care. Patients with chronic HF who are not candidates for advanced therapy have been proven to have a bad prognosis when given palliative inotropes [8,9]. Despite the lower survival rate, many patients prefer a higher quality of life, even if it means a shorter life span [10,11].

The aim of the present study was to compare various inotropic therapies for the patients at End-Stage Heart Failure.

METHODOLOGY

From 1995 to 2002, administrative and limited chart data were collected from a randomly selected cohort of Medicare beneficiaries from territories served by the estimated number of Medicare participants in each of the four Durable Medical Equipment (DME) Regional Carriers region (DMERC) regions. In comparison to regions A, B, and C, the absolute annual number of unique beneficiaries on chronic intravenous inotropic therapy is smaller in region D. Despite the fact that there was no Medicare medication benefit throughout the study period, several intravenous pharmacologic therapies were covered under the DME benefit category when administered through a chronic intravenous line with an external infusion pump. When persistent intravenous access was used and acute hemodynamic improvement was established, the DME benefit category reimbursed 80% of outpatient inotropic medication and supplies for HF[11]. Acute hemodynamic improvement was defined as a 20% reduction in pulmonary capillary wedge pressure and/or a 20% increase in cardiac index, both of which were related with a decrease in dyspnea. The Centers for Medicaid and Medicare Services (CMS) was contracted with regional carriers to run the program; CIGNA Healthcare Medicare Administration was the contracted carrier for region D. Data were gathered from five different sources: (1) The Health Insurance Claim Form (HCFA-1500), which contains information on the beneficiary's demographics, secondary insurance, and the prescribing physician's unique physician identifier number; (2) the Certificate of Medical Necessity (CMN) form, which contains information on the type, duration, and initiation date of inotropic therapy; and (3) the data collection form, which contains clinical data on the beneficiary's hemodynamic profile and the extent of acute improvement.

We measured healthcare use by describing costs and hospitalizations in dollars and days, respectively, for each beneficiary, and controlling for follow-up time by censoring on the date of death or last contact. For both inotropic therapy and hospitalizations before and after the date of therapy beginning, average accumulated costs were determined. If an inotrope was switched or a second inotrope was introduced, the initial medicine was regarded to be the primary treatment using intention-to-treat approach. Two patients were treated with milrinone and dobutamine at the same time, but because the former was used for a longer amount of time, these instances were assigned to the milrinone cohort. We did not include dopamine data, because it was only used by two patients for a total of 125. Furthermore, we compared patients on dobutamine and milrinone before starting inotropes in terms of demographics, medications, and hospitalizations. The asymptotic distribution for cost curves, as derived by us, was yet to be determined. As a result, analytic contraindications (CIs) are unavailable. Instead, we employed bootstrapping to calculate standard errors and confidence intervals.

Statistical Analysis

Statistical analysis was done using SPSS v28.0. The results were analyzed using three-way ANOVA followed by *post hoc* Turkey test. The level of significance was set at $p<0.05$.

RESULTS

The amounts reimbursed at 30 and 60 days before and after inotrope began favoring pharmacological therapy in terms of health care usage (excluding professional and nursing fees). However, after inotrope beginning, the amounts reimbursed after 180 days were higher among patients who lived for 6 months on a per-beneficiary-per-day basis. We observed similar trends, though the amounts were lower the longer the beneficiary which was on inotrope. Milrinone's cost drove the higher reimbursements at 180 days; the average accumulated drug cost curve for inotrope shows a substantial difference between dobutamine and milrinone as shown in Table 1.

DISCUSSION

The aging population, rising rates of chronic congestive HF in the elderly, and rising health-care costs have all prompted efforts to evaluate the care given to individuals with advanced heart failure. Chronic intravenous inotropic medication infusions, for example, have not been subjected to major double-blind, randomized clinical studies, and there is no published data to demonstrate that this therapy enhances survival in any age group. In fact, prolonged inotrope infusions have been linked to an increase in mortality rate. Because epidemiologic studies show that the prevalence of HF is rising in the Medicare population, it is likely that the number of individuals who could benefit from his treatment is growing as well. Furthermore, if implantable cardio defibrillators become more widely used, the number of patients who develop refractory symptoms and die through progressive pump malfunction rather than sudden death may continue to rise. In severe heart failure, every strategy that relieves symptoms and reduces hospital readmission rates is critical. In this respect, our research aimed to describe Medicare patients receiving chronic outpatient inotropic therapy (either continuous or intermittent) as well as drug and supply reimbursement.

We found that patients who received this medication had a relatively high death rate, however not as high as people who received chemotherapy. Milrinone-treated patients were compensated more for hospitalizations both before and after starting the inotrope. In addition, the milrinone group had a higher level of digoxin use

Table 1: Comparison of pre- and post-certificate of medical necessity

Drugs	Other Inotropes		Dobutamine	
Certificate of Medical Necessity (CMN)	Pre CMN	Post CMN	Pre CMN	Post CMN
30 Days	n=320	n=331	n=246	n=255
Person days	9,226	9,214	7,090	7,041
Hospital cost	5,453,726	2,033,818	3,900,394	1,337,708
INO cost	0	11,176,681	0	202,160
Supply cost	725	309,262	276	225,302
Total	5,454,447	3,519,761	3,900,771	1,765,169
60 days	n=297	n=287	n=218	n=69
Persons days	17941	17,164	13,789	13,139
Hospital cost	7419824	3,754,822	5,548,636	2,305,657
Inotropic therapy cost	0	1,967,432	0	365,317
Supply cost	4,020	529,136	916	388,592
Total	7,423,846	6,251,390	5,549,552	3,059,566
180 Days	n=283	n=262	n=217	n=202
Persons day	50,462	41,766	38,789	32,325
Hospital cost	10,159,767	704,561	7,689,627	4,263,679
Inotropic therapy cost	0	4,179,268	0	813,734
Supply cost	5,618	1,096,567	1,466	817,794
Total	10,165,385	12,321,447	7,691,092	5,895,207

in the background. These retrospective data cannot tell if these patients were more unwell; however, survival following inotrope commencement was not different between the groups. Background therapy was significant for apparent underuse of both angiotensin-converting enzyme inhibitors and b-blockers; however, given the severity of the illness and the likelihood that many of the patients were intolerant of the drugs due to low cardiac output syndrome, hypotension, or other comorbidity, no conclusions can be drawn about the appropriateness of this treatment.

CONCLUSION

In a Medicare cohort, the use of chronic intravenous inotropic therapy is associated with high mortality, which likely reflects the severity of the underlying disease. The costs of managing HF in both inpatient and outpatient settings are significant, with the latter being driven by the cost of milrinone. Nonetheless, there is an early decrease in overall expenditures following inotrope initiation, which can be attributed to a decrease in hospitalization. Given the lack of double-blind trials comparing inotrope infusion to placebo or dobutamine to milrinone, the decision to use inotropes, the type of inotrope used, and the duration of treatment should all take into account the impact on resource use.

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