ORIGINAL RESEARCH

Intermittent infusions of carperitide or inotoropes in out-patients with advanced heart failure

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Abstract

Background: The ambulatory treatment of advanced heart failure (HF) with intermittent infusions of inotropes or natriuretic peptide chosen immediately before each infusion has not been described.

Methods: Between May 2005 and July 2009, we treated 11 patients presenting with advanced HF, who received a total of 369 infusions of carperitide, olprinone, dopamine, or dobutamine, once or twice weekly. The pharmaceutical was selected before each infusion based on the systolic blood pressure (BP).

Results: Carperitide, olprinone, and catecholamines were administered to 8 (73 infusions of 0.030±0.004 μg/kg/min for 3.3±0.8 h), 4 (18 infusions of 0.070±0.017 μg/kg/min for 3.3±0.5 h), and 6 patients (278 infusions of 3.6±1.9 μg/kg/min for 2.8±1.0 h), respectively. No adverse effect requiring cessation of infusion was observed. Over a mean follow-up of 29.3±28.8 months (range: 2-104), 4 patients died, all from cardiac causes. The Kaplan-Meier cumulative survival rate was 69.3% at 20 months (median follow-up). Compared with the pre-infusion period, the duration and number of hospitalizations for management of HF were decreased by 73.9% (p=0.017), and 51.9% (p=0.007), respectively, during the treatment period, and the overall medical costs by 56.9% (p=0.021).

Conclusions: In this study population, intermittent drug infusions selected from inotropes or natriuretic peptide based on the baseline systolic BP significantly decreased the length and

number of hospitalizations and costs, without increasing mortality. These results indicate that the intermittent infusions might be one of therapeutic options of advanced HF.

Introduction

The rehospitalization of patients suffering from heart failure (HF) is associated with an increased risk of death **[1].** Therefore, besides alleviating symptoms and enhancing the quality of life, the prevention of acute cardiac decompensation and hospitalizations is an important therapeutic objective, which might lower the long-term morbidity and mortality. The remote monitoring of body weight (BW) **[2]** and of intrathoracic impedance **[3]** have been found to anticipate the development of acute cardiac decompensation, and transtelephonic interventions to lower the rate of hospitalization for management of HF **[4]**.

In spite of recent therapeutic progress, patients presenting with American College of Cardiology/American Heart Association (ACC/AHA) stage D HF remain at high risk of hospitalization and death **[5]**. In these patients, the only interventions known to improve outcomes, beyond standard management, are cardiac transplantation and left ventricular assist devices, which are limited by the availability of donor organs, or by hemorrhagic, thromboembolic, and infectious complications. Thus, the need persists to find other means of lowering the rates of hospitalization and death.

Multiple studies have been published on the use of intermittent drug infusions in patients presenting with advanced HF **[6-9]**. While symptomatic improvements **[6]** and an increase in exercise tolerance **[7]** have been observed with inotropes, a retrospective analysis of the ADHERE registry found a significantly higher in-hospital mortality associated with the

short-term administration of dobutamine or milrinone, than with vasodilator therapy with nitroglycerin or nesiritide **[10]**, suggesting that intermittent infusions of inotropes increase mortality **[8]**. On the other hand, in a randomized trial, infusions of a natriuretic peptide lowered neither mortality nor the rate of hospitalizations **[9]**.

We have studied the intermittent infusions of drugs in patients presenting with advanced HF since 1995 **[11]**. In contrast to several other studies of intermittent infusions, which administered a single inotrope or natriuretic peptide **[6-9]**, we choose among different drugs with each infusion, depending on the baseline systolic blood pressure (BP), a strategy which might represent a progress in intermittent infusion therapy.

Methods

Patient selection

We evaluated all patients who received intermittent drug infusions in our hospital between May 2005 and July 2009. To be included in this analysis, the patients had to fulfill all the following criteria before the beginning of intermittent infusion therapy: 1) ≥2 hospitalizations for management of HF within the previous 12 months, 2) symptoms consistent with New York Heart Association (NYHA) functional class III or IV, 3) optimally treated with oral and device therapy, 4) had granted a written informed consent to participate in the study. Patients were excluded from intermittent infusion therapy if they had suffered an acute myocardial

infarction within 3 months, or presented with a) unstable angina, b) an estimated glomerular filtration rate <15 ml/min/1.73 m^2 or long-term dialysis, or c) pure right ventricular failure (e.g. primary pulmonary hypertension).

Informed consent

Written informed consent was obtained from all the participants of this study, and all study procedures were in compliance with the Declaration of Helsinki and the institutional guidelines of Hyogo Prefectural Amagasaki Hospital.

Infusion therapy

The drugs were administered intravenously for 3 or 4 h, once or twice weekly. The choices of drugs included a) the A-type natriuretic peptide, carperitide, b) olprinone, and c) dopamine or dobutamine. The pharmaceutical and infusion schedule were chosen by each individual physician. Carperitide was avoided when the systolic BP was <90 mmHg, and dopamine and dobutamine when the systolic BP was ≥110 mmHg. Boluses of furosemide were administered during the infusions as needed. The patients were hospitalized if HF worsened in spite of the twice-weekly infusions.

To confirm the short-term safety and tolerance of therapy, the electrocardiogram, BP and urine output (UO) were monitored throughout the infusions. BW, systolic and diastolic

BP, heart rate (HR), and oxygen saturation were recorded at the beginning and end of each infusion. A patient was defined as a responder to therapy when the length and number of hospitalizations and costs were all decreased after, compared with before the intermittent infusions. To define pre-infusion period, we picked up all periods that patients were not hospitalized for >24 months, and the last one of those periods was defined as the start of pre-infusion period for each patient. In other words, pre-infusion period was defined so that each patient experienced ≥1 hospitalization within 24 months of previous hospitalization in the pre-infusion period. The end of the post-infusion period was July 2009 or death of the patient, whichever occurred earlier.

Left ventricular ejection fraction was measured echocardiographically, and calculated by the modified Simpson's method. Diabetes mellitus was defined as a) a ≥126-mg/dl fasting or >200-mg/dl non-fasting serum glucose, or b) use of an antidiabetic medication. Hypertension was defined as a) a ≥140-mmHg resting systolic or ≥90-mmHg diastolic BP, or b) use of an antihypertensive medication.

Statistical analysis

The data are reported as means ± standard deviation (SD). To evaluate the long-term safety, survival curves were constructed by Kaplan-Meier method. To ascertain the effects of the intermittent infusions on medical costs, and on length and numbers of hospitalizations, we

compared the measurements made during the pre-infusion period with those in the post-infusion period. Continuous variables were compared by factorial analysis of variance, and dichotomous variables by chi-square analysis. The Wilcoxon's signed-rank test was used to compare the monthly numbers and lengths of hospitalizations for management of HF, and the monthly costs incurred, before versus after the infusions. Student's *t*-test was used to compare other data. The relationship between UO and other factors was examined by single and multiple variables linear regression analysis. Survival curves were constructed by the Kaplan-Meier method. A p value <0.05 was considered significant.

Results

Short-term effects of the infusions

The baseline characteristics of the 11 patients enrolled in the study are shown in table 1. A total of 369 infusions were administered, and the short-term effects of each pharmaceutical infused are summarized in table 2. The infusion of carperitide decreased the systolic and diastolic BP significantly, while dopamine and dobutamine increased the systolic BP and HR significantly. Olprinone changed neither BP nor HR. BW was significantly lowered by all treatments. No adverse effect was observed, including arrhythmias or changes in blood pressure, requiring the cessation of drug infusion.

By multiple linear regression analysis, using the variables listed in table 2, BW and

dose of intravenous furosemide were independent predictors of UO during the infusions (Table 3).

Long-term survival of the study population

Over a mean follow-up of 29.3±28.8 months (median = 20; range 2-104), 4 patients died, all from cardiac causes. By Kaplan-Meier analysis, the cumulative survival rate was 69.3% at 20 months (median follow-up), and 55.4% at 22 months (Figure 1).

Effects of treatment on costs and hospitalizations

Comparing the mean pre-infusion period of 15.7±9.4 months with the post-infusion period of 29.3±28.8 months (Figure 2), the mean duration of hospitalizations for management of HF was shortened from 6.9±3.0 to 1.8±1.5 days/month (73.9%; p=0.017), the mean number of hospitalizations decreased from 0.36±0.14 to 0.17±0.18 (51.9%; p=0.007), and the mean cost was lowered from 216±86 to 93±68 10^3 yen (56.9%; p=0.021).

Among the 11 patients, 8 responded to the intermittent infusions treatment (Table 4). Compared with the non-responders, the patients who responded tended to have a greater baseline body mass index (p=0.12), slower HR (p=0.10), higher UO (p=0.15), and higher systolic BP (p=0.17).

Discussion

This is, to our knowledge, the first study of intermittent infusions for the management of HF, in which the pharmaceuticals administered, inotropes or natriuretic peptides, were chosen on the basis of the pre-treatment systolic BP. We found that this treatment strategy significantly decreased the length and numbers of hospitalizations, as well as overall medical costs.

Since our preliminary report **[11]**, we have overcome several limitations by developing a system dedicated to the administration of intermittent infusion therapy, including the unlimited availability of beds in our ambulatory department. Furthermore, the longer duration of follow-up allowed a more reliable evaluation of the long-term safety of the treatment.

Safety and efficacy of intermittent infusions

The evaluation of the safety and efficacy of intermittent infusion therapy has not been standardized. On the short term, the UO, BP, HR, oxygen saturation, electrocardiogram and changes in BW should be monitored with each infusion. While these observations do not predictably correlate with clinical outcomes **[12]**, they are essential in the evaluation of safety. On the long term, survival and length and number of hospitalizations for management of HF are the most important endpoints. Quality of life is another important endpoint, which was not measured in this retrospective study, as the pre-infusion data were not available.

As a consequence of an aging population and greater proportion of survivors of acute coronary syndromes and cardiac decompensation, the costs of care for patients suffering from HF are increasing. While the economic impact of intermittent infusions has not been published previously, lowering these costs is as important as decreasing the rates of hospitalization or lowering mortality.

Selection of pharmaceuticals

The effects of intermittent infusions of dopamine have not been examined in a randomized study. The randomized trials of dobutamine have been reviewed by Bayram et al., who found a trend toward a greater alleviation of symptoms and increase in exercise capacity conferred by dobutamine compared with placebo **[8]**. However, they recommended, when a safer option is available, avoiding the administration of intermittent dobutamine infusions, because of their potentially adverse effects on survival.

Sanada et al. reported cardioprotective effects conferred by phosphodiesterase inhibitors **[13]**, while Cesario et al. observed symptomatic improvements and decreased rates of hospitalization by the intermittent administration of low doses of milrinone **[6]**. However, the intermittent use of phosphodiesterase inhibitors has not been studied in a randomized trial.

Natriuretic peptides are antagonistic to the hyperactivity of

renin-angiotensin-aldosterone system and promote reverse remodeling **[14]**, therefore are expected to confer clinical benefits when used intermittently. However, intermittent infusions of nesiritide did not lower the risk of death or hospitalizations in a randomized trial **[9]**. Patients presenting with advanced HF are usually in a low-output, hypotensive state. The administration of vasodilators during this state might further promote hypotension and decrease the perfusion of central organs, which may explain the absence of effects conferred by the intermittent infusions of natriuretic peptide on survival or rate of hospitalizations.

In all previous studies of intermittent infusions, the treatment was limited to a single drug, whether an inotrope or a natriuretic peptide. However, intermittent infusions of natriuretic peptide should be avoided in presence of low output or hypotensive state. Phosphodiesterase inhibitors or a catecholamine should be chosen instead and, in presence of severe low output or hypotensive state, a catecholamine may be the only choice. Furthermore, since, in the same patient, the vital signs may vary, a choice of drug before each infusion is likely to be associated with better outcomes.

A simple, inexpensive and reliable indicator is needed to twice weekly optimize the drug selection for each infusion. Echocardiography or measurements of pulmonary capillary wedge pressure or bioimpedance **[15]** are very useful, though cannot be used because of their complexity and cost. At present, the easily measurable and nearly cost-free systolic BP is the only indicator that meets the requirements. Finally, the 2008 European Society of Cardiology

guidelines for the diagnosis and treatment of acute and chronic HF recommend a choice of pharmaceuticals guided by the systolic BP **[16]**.

The systolic BP below which natriuretic peptides should be avoided, or a catecholamine be used, has not been firmly established. Pending further studies, however, we believe that natriuretic peptides be avoided when the systolic BP is <90 mmHg, and dopamine or dobutamine when it is ≥110 mmHg, considering that we observed no adverse event in this study.

In this study, we chose not continuous but intermittent infusions because of concern about arrhythmia or changes in blood pressure. However, intermittent infusions may have weaker effect than continuous infusions, and should be compared with continuous infusions in the future.

Safety of intermittent infusions

The main immediate adverse effects of intermittent infusion therapy are hypotension and arrhythmias. In a randomized trial of intermittent infusions of nesiritide, a higher rate of symptomatic and asymptomatic hypotension was reported in the actively treated than in the placebo-treated group [9]. On the other hand, no increase in arrhythmias has been reported with intermittent infusions of inotropes **[8],** and we observed neither hypotension nor an increase in arrhythmias during the infusions in this study. This short-term safety was achieved

by avoiding the administration of a) natriuretic peptides to patients presenting with hypotension, b) catecholamine whenever possible, c) high doses of pharmaceuticals.

The cumulative survival of our study population was 55.4% at 22 months. The survival rate of patients presenting with HF varies with the severity of disease, the age and race of the patient, and other factors. In absence of a large Japanese registry such as ADHERE **[10]**, we found a study of Japanese patients suffering from advanced HF with similar clinical characteristics, including NYHA functional class III or IV, brain natriuretic peptide >170 pg/ml, 70% treated with an angiotensin-converting enzyme inhibitor, and 28% with a beta-adrenergic blocker **[17]**. Although these patients (63.6±1.5 years of age) were, on average, younger than ours (71.0±8.4 years), their survival rate was about 55% at approximately 600 days. Therefore, the intermittent infusions do not appear to have increased the mortality rate, which is acceptable, considering the severity of our patients' clinical presentation.

Response to therapy

Out of our 11 patients, 3, who did not respond to the intermittent infusions, tended to have a lower baseline body mass index, faster HR, lower UO, and lower systolic BP. However, we couldn't find any predictor of response to intermittent infusion therapy in this small study population, and larger studies are warranted to determine the predictor.

Systolic BP may be a predictor of the response because low systolic BP was a predictor of hospitalization within 1 month after the ambulatory administration of an intravenous diuretic **[18]**. Furthermore, a low systolic BP has been associated with adverse clinical events in acute **[19]** and in chronic **[20]** HF.

Body mass index may also be a predictor of response to intermittent infusion therapy. Cardiac cachexia is common in chronic HF and a predictor of poor outcome **[21]**. Although the definition of cardiac cachexia has not been standardized **[21]**, the prognosis of patients presenting with chronic HF and a low body mass index is poor **[22].**

HR is reported to the independent risk factor of poor cardiac function and in-hospital death after acute myocardial infarction **[23]**, and may be used as a marker of the autonomic nervous activity in patients with chronic heart failure **[24]**. However, the prognostic power of HR in HF remains undetermined. It was found to be an independent predictor of HF in one previous study **[25]**, however not in another **[20]**.

Diuretics activate the renin-angiotensin-aldosterone system in patients suffering from chronic HF, who are at risk of renal dysfunction and dehydration **[16]**. However, in that study, the UO of responders during the infusions tended to be greater, after adjustment for BW, and the dose of furosemide and BW were both independent predictors of UO during the infusions. In addition, the ambulatory administration of intravenous diuretics decreases the rate of hospitalizations for management of HF **[18]**. Therefore, the addition of intravenous

furosemide to the infusions may have increased the benefits conferred by the infusions of inotropes or natriuretic peptide. However, the optimal dose of furosemide remains to be determined.

Limitations of our study

In this study, which included a small patient population from a single institution, the effect of infusion therapy on hospitalizations and costs was assessed by comparison with pre-infusion periods of the same patients instead of control-group. Accordingly a larger, double-blind, multicenter trial is warranted. Moreover, because we didn't perform invasive hemodynamic measurement during infusions or at systematically planned timing, pulmonary capillary wedge pressure or cardiac output could not be assessed in this study. Further, because of concern about arrhythmia or changes in blood pressure, we chose not continuous but intermittent infusions, which might decrease the effect of infusions.

Conclusion

This is the first study of intermittent infusion therapy, in which inotropes or a natriuretic peptide were administered on the basis of the pre-treatment systolic BP. In 11 patients presenting with advanced HF, the infusions significantly decreased a) the length and rate of hospitalizations for management of HF and b) medical costs, without decreasing survival.

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Conflict of Interest: none declared.

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Figure legends

Figure 1. Cumulative survival rates of the 11 patients

Over a mean follow-up of 29.3±28.8 months (median = 20; range 2-104), 4 patients died. The cumulative survival rate was 69.3% at 20 months (median follow-up), and 55.4% at 22 months.

Figure 2. Effects of infusion therapy on the medical costs and length of hospitalizations

Comparing the pre-infusion period (15.7±9.4 months) with the post-infusion period (29.3±28.8 months), the infusions significantly decreased the length and number of hospitalizations and costs.

Figure1

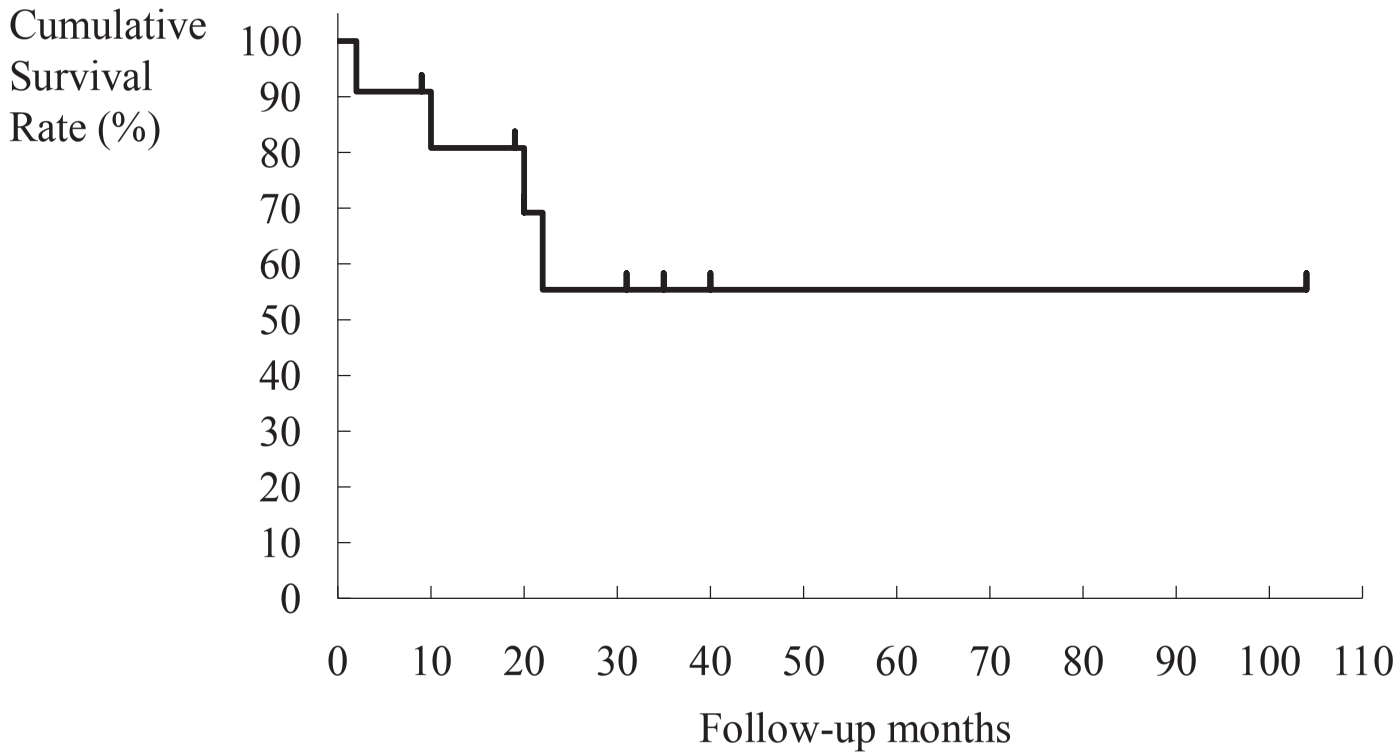
Cumulative
Survival
Rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
110
Follow-up months

Figure2

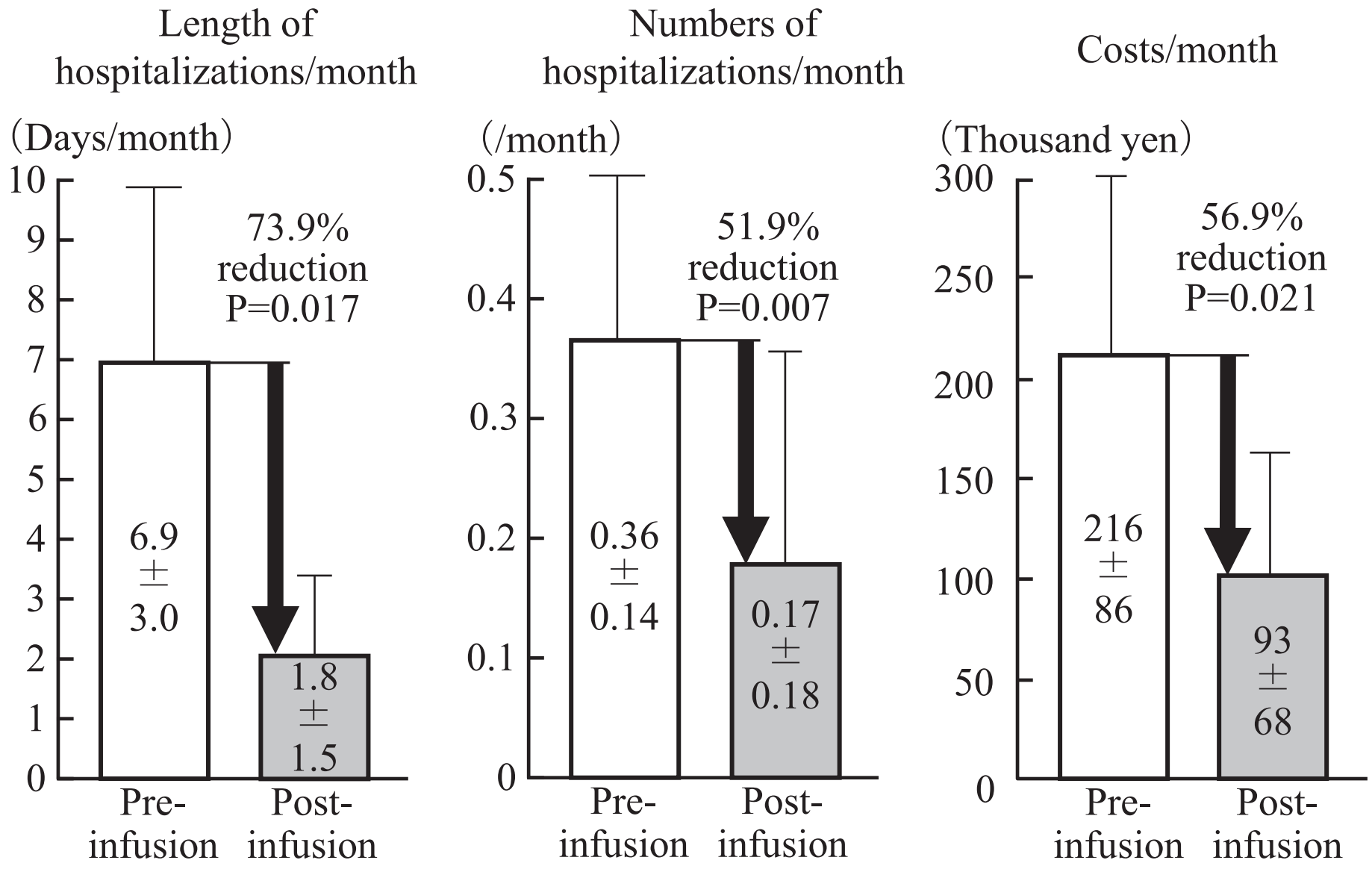
Length of hospitalizations/month
(Days/month)
10
9
8
7
6
5
4
3
2
1
0
73.9% reduction P=0.017
6.9 ± 3.0
1.8 ± 1.5
Pre-infusion
Post-infusion
Numbers of hospitalizations/month
(/month)
0.5
0.4
0.3
0.2
0.1
0
51.9% reduction P=0.007
0.36 ± 0.14
0.17 ± 0.18
Pre-infusion
Post-infusion
Costs/month
(Thousand yen)
300
250
200
150
100
50
0
56.9% reduction P=0.021
216 ± 86
93 ± 68
Pre-infusion
Post-infusion

Table 1 Baseline characteristics of the 11 study patients

Age, years	71±8
Men/women	7/4
Ischemic heart disease	2 (18)
Left ventricular ejection fraction, %	38.7±14.2
Body mass index, kg/m^2	20.7±4.8
History of:	
Hypertension	8 (73)
Diabetes	6 (55)
Atrial fibrillation or flutter	5 (46)
Serum creatinine, mg/dl	1.6±0.9
Estimated glomerular filtration rate, ml/min/1.73m^2	42±22
Blood urea nitrogen, mg/dl	40±22
Sodium, mmol/l	138±2
Systolic blood pressure, mmHg	103±16
Heart rate, bpm	71±10.
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	7 (64)
Beta-adrenergic blocker	7 (73)
Aldosterone antagonist	4 (36)
Days of hospitalizations* per month before infusions	6.9±3.0
Number of hospitalizations* per month before infusions	0.35±0.14
Costs per month before infusions, 10^3 yen/month	216±86

Values are means ± SD, or numbers (%) of patients

*for management of heart failure

Table 2 Characteristics and short-term effects of each infusion

	Carperitide (n=8 patients, 73 infusions)	Olprinone (n=4 patients, 18 infusions)	Catecholamine (n=6 patients, 278 infusions)
Duration, h	3.3±0.8	3.3±0.5	2.8±1.0
Dose, μg/kg/min	0.030±0.004	0.070±0.017	3.6±1.9
Furosemide, mg	13±13	48±16	53±38
Urinary output, ml	728±685	450±359	592±350
Body weight, kg			
Before infusion	55.8±11.8	53.8±6.1	55.7±7.8
After infusion	55.0±11.5*	53.3±5.4*	54.7±7.5*
Blood pressure, mmHg			
Systolic			
Before infusion	117.2±18.0	107.8±13.2	100.5±11.3
After infusion	104.4±17.7*	102.3±12.5	107.4±13.9*
Diastolic			
Before infusion	63.8±9.2	55.3±14.5	53.7±9.2
After infusion	57.2±8.3*	50.2±11.5	54.2±9.4
Heart rate, bpm			
Before infusion	72.7±9.4	62.9±9.5	69.0±10.2
After infusion	71.1±8.0	61.7±8.8	72.4±14.9*
Oxygen saturation, %			
Before infusion	96.5±3.6	98.7±1.6	96.8±4.6
After infusion	96.2±3.4	99.3±0.8	96.0±5.3

* $p<0.0001$ vs. before infusion.

Table 3 Correlates of urinary output during infusions

	Analysis			
	Single variable	***p***	**Multiple variable**	***p***
Body weight before infusion, kg	20.7 (14.5-26.9)	<0.0001	21.1 (15.0-27.2)	<0.0001
Blood pressure before infusion, mmHg				
Systolic	2.47 (-1.68-6.63)	0.24		
Diastolic	3.59 (-2.19-9.36)	0.22		
Heart rate before infusion, bpm	0.57 (-4.82-5.95)	0.84		
Intravenous furosemide, mg	80.1 (21-139)	0.0079	89.2 (34.4-144.0)	0.0015

Values are regression coefficients (95% confidence intervals).

Table 4

Table 4 Characteristics of 11 patients and of responders versus non-responders

	All patients (n=11)	Responders (n=8)	Non-responders (n=3)	*P**
Age, years	71.0±8.4	73.6±8.1	65.0±6.2	0.15
Men/women	7/4	5/3	2/1	0.77
Ischemic heart disease	2/11	2/8	0/3	0.49
Left ventricular ejection fraction, %	38.7±14.2	38.6±16.9	39.0±4.0	0.97
Body mass index, kg/m^2	20.7±4.8	22.3±4.4	17.1±4.3	0.12
Hypertension	8/11	7/8	1/3	0.10
Diabetes	6/11	4/8	2/3	0.49
Atrial fibrillation or flutter	5/11	4/8	1/3	0.78
Serum creatinine, mg/dl	1.60±0.93	1.63±0.96	1.53±1.04	0.89
Estimated glomerular filtration rate, ml/min/1.73 m^2	41.5±22.1	40.3±23.6	44.1±22.6	0.82
Blood urea nitrogen, mg/dl	39.8±21.8	38.7±25.3	42.3±14.0	0.83
Serum sodium, mmol/l	138±2	138±2	137±2	0.24
ACE inhibitors or ARB	7/11	5/8	2/3	0.88
Beta-adrenergic blocker	7/11	5/8	2/3	0.88

Aldosterone antagonist	4/11	2/8	2/3	0.26
Days of hospitalizations per month,**	6.9±3.0	6.6±2.2	7.5±5.0	0.69
Numbers of hospitalizations* per month	0.35±0.14	0.34±0.13	0.36±0.18	0.82
Costs/month, 10^3 yen/month	216±86	232±74	184±116	0.47
Pre-infusion				
Body weight, kg	54.4±12.8	56.1±12.2	50.2±16.0	0.53
Body mass index, kg/m^2	20.8±4.3	22.2±4.0	17.5±3.8	0.12
Systolic blood pressure, mmHg	107.4±19.0	113±20	95±10	0.17
Diastolic blood pressure, mmHg	58.3±8.2	59.8±8.0	54.6±8.9	0.38
Heart rate, bpm	70.4±3.9	69.1±4.0	73.5±0.8	0.10
Urinary output during infusion, ml	680±527	860±562	320±175	0.15
Pre-infusion urinary output/body weight, ml/kg	11.7±7.8	14.5±8.3	6.1±1.5	0.14
Intravenous furosemide, mg	27±16	23±1	29±17	0.62

Values are means ± SD, or numbers (%) of patients; *responders versus non-responders; **for management of heart failure
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.