Original Article

Cost Analysis of the Treatment of Acute Decompensated Heart Failure. Levosimendan versus Dobutamine

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Objective

To assess whether the treatment with levosimendan is more expensive than the usual one with dobutamine, since price of medications does not usually represent the greatest expense in the treatment of cardiac decompensation.

Methods

The cost of treatment of 18 inpatients with cardiac decompensation, 9 of which treated with dobutamine (dobuta group) and 9 with levosimendan (levo group), was compared. Groups were similar concerning age, sex, functional class and cardiac function.

Results

Treatment costs were similar for both groups. In the levo group, the costs with the drug were higher than in the dobuta group, but those related to the length of stay in intensive care unit and to the material used during admission were lower. **Levo** - drug: R$ 5,414.00; material: R$ 399.90; hospital daily rates: R$ 5,061.20; professional honorarium: R$ 3,241.80; total costs: R$ 14,117.00. **Dobuta -** drug: R$ 2,320.10; materials: R$ 1,665.70; hospital daily rates: R$ 6,261.90; professional honorarium: R$ 3,894.30; total costs: R$ 14,142.00.

Conclusion

Despite the higher price of levosimendan, the global cost of the treatment was similar for patients who were treated either with dobutamine or levosimendan. Patients who were treated with levosimendan had a shorter length of stay in intensive care unit.

Key words

decompensated heart failure, inotropics, levosimendan, dobutamine, pharmacoeconomics

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Heart failure is a prevalent disease and one of public health problems in the modern world, and it is advancing[1,2].

In Brazil, according to SUS (Unified Health System – *Serviço Único de Saúde*), which is responsible for approximately 75% of hospital admissions in the country, cardiovascular diseases are the fourth cause of hospitalizations, and heart failure is the disease responsible for the greatest number of hospitalizations among the cardiovascular causes[3,4]. In 2001, heart failure was the cause of 385,758 admissions[3]. The government spent R$ 201,939,410.42 with heart failure treatment, an amount that corresponded to 3.96% of the total expense of SUS with hospitalizations and 22.48% of the expenses resulting from cardiovascular diseases[3].

Cardiac decompensation treatment often consists of optimization of treatment with an increase in the dose of diuretics and vasodilators. However, in an expressive number of patients, there is the need for hospitalization due to disabling symptoms and, in many times, also due to low output[5,6]. In Brazil, dobutamine is the most used drug for cardiac compensation in those circumstances. However, its safety has been currently questioned[7-12]. Along with the lack of studies showing its safety, patients who receive dobutamine, due to its pharmacological profile, usually need to stay in an intensive care unit, where they stay for several days, with a slow drug withdrawal.

Another point to be highlighted is the change of treatment of patients with heart failure, with the growing prescription of beta-blockers for the control of the disease. Dobutamine, a sympathomimetic drug, in the presence of beta-blockers, might have a decreased effect. In this situation, dobutamine might not be the ideal choice for the treatment of patients with heart failure[5,7,11-13].

Currently, we have on the market, a new, efficacious and safe drug that is, however, regarded as expensive. Levosimendan can be prescribed for patients taking beta-blockers, its length of infusion time is only 24 hours, and its active metabolite has a long half-life, which makes the clinical effects last for 5 to 7 days. That pharmacokinetic profile brought about a discussion: is the treatment with levosimendan really more expensive than the usual one, made with the prescription of dobutamine[9,12]?

By using our database, we assessed the cost of treatment of patients with heart failure treated with dobutamine and levosimendan, and assessed whether the treatment with levosimendan is truly more expensive than the usually done with dobutamine.

Methods

Eighteen patients with congestive heart failure, with a functional class IV, who needed hospitalization for acute heart failure

decompensation, from the Heart Institute of Medicine School of São Paulo University (*Instituto do Coração da Faculdade de Medicina da Universidade de São Paulo - InCor*), were studied The patient's mean age was 58.61 years old (SD 15.58), 13 patients were men and 5 were women, 9 were treated according to the standard protocol of InCor (dobuta group), and 9 patients were treated according to the protocol used in the BELIEF study, with levosimendan (levo group).

Inclusion criteria included: meeting CHF diagnosis criteria without other complications; systolic ventricular dysfunction with LV ejection fraction <0,40; length of hospital stay not longer than a month; and exclusion of cases of mixed use of standard treatment and levosimendan.

Data from patient hospitalization in the two groups were analyzed, particularly length of hospital stay, length of intensive care unit stay, material used for treatment and hospital costs.

For comparison of the average cost of the different groups, data survey took the following factors into consideration, all of them taken on during the hospital admission period: price of drugs and materials that were used; prices of hospital resources that were consumed (hospital admission daily rates both in ward and ICU, radiologic and laboratorial tests and professional honorarium).

For such comparison, patients' charts were reviewed and analyzed regarding length of hospitalization, days spent in intensive care unit, type of treatment, required material and equipment, such as infusion pumps, circuitry, and nurse and support care teams. Prescribed drugs and tests performed during hospitalization were also taken into account. The data sheet that allowed for the comparison between both groups consisted of all those variables.

Prices used in this study were collected from the following sources: medications = Brasíndice Pharmaceutical Guide (*Guia Farmacêutico Brasíndice*) – Year XL – April 8, 2004; materials = Brasíndice Pharmaceutical Guide (*Guia Farmacêutico Brasíndice*) – Year XL – April 8, 2004 / InCor Health Insurance Reimbursement Formulary. Support Services to Diagnosis = InCor Health Insurance Reimbursement Formulary / Brazilian Medical Association *(Associação Médica Brasileira – AMB)* Reimbursement Formulary, 1990. Hospital Daily Rates = InCor Health Insurance Reimbursement Formulary. Professionals = InCor Health Insurance Reimbursement Formulary / AMB Reimbursement Formulary. Price Chart of SUS.

The calculation used to obtain the unitary values was: tablets and capsules = division of the total package value by the number of single tablets; ampoules = division of total package value by the number of single ampoules; drops = the quantities included in the tables refer to the quantities of applications. We considered the proportion of 20 drops for 1 ml, following the guidelines from Brazilian Pharmacopoeia (*Farmacopéia Brasileira)*, 3rd Edition.

Comparison of hospital bills was performed with the simulation of two different scenarios. In the first scenario, admissions to hospital covered by private health care providers were studied, and the InCor Health Insurance Reimbursement Formulary was used for the calculation of hospital daily rates and expenses. In the second scenario, admissions covered by the Unified Health System *(Sistema Único de Saúde – SUS)* were studied. SUS has its own system of hospitalization refunding, paying by package and distinctively for some procedures, high cost medications and days of stay in intensive care unit.

In the usual InCor treatment (dobuta group), patients received dobutamine in doses and time regarded as suitable to obtain hemodynamic benefit. This time ranged from 4 to 18 days. In the levo group, levosimendan was administrated in the dose of 0.1μg/kg/min, both groups without attack dose and continuously for 24 hours.

Patients in both dobuta and levo groups were treated with intravenous furosemide, in the required doses to reduce systemic and peripheral congestion. After cardiac compensation, these patients started to receive diuretics p.o., monitored by weight and signs of congestion or hypovolemia.

From the moment of hospital admission and the beginning of the infusion of inotropics, angiotensin converter enzyme inhibitors were reintroduced, titrated from a dose of 12.5 mg of captopril t.i.d, up to 50 mg t.i.d. Dose increases were done whenever the systolic blood pressure was higher than 100 mmHg.

In order to compare groups, the paired t-test was employed, considering differences as significant when p value was less than 0.05.

Results

Socio-demographic data is shown Table I. There were no differences between groups regarding age, sex and magnitude of ventricular dysfunction.

Comparing length of hospital stay, the number of days from admission until discharge was similar in both groups, but the length of stay in intensive care unit was shorter in the levo group (Table II).

Comparing hospital bill values, differences regarding total costs of hospitalization (p=0.991), costs of days in the ward (p=0.318) and values of professional honorarium (p=0.318) were not observed.

The price of the drugs was significantly more expensive in the levo group (R$ 5,413.99 vs. R$ 2,320.09; p=0.009).

Comparing the use of dischargeable materials, dobuta group was more expensive (R$ 399.94 vs. R$ 1,665.66; p<0.001)

Table I – Socio-demographic data (mean and standard deviation)

Variable	Levo group	Dobuta group	p
N	9	9	
Age (years old)	63+17.88	54.22+11.27	0.180
Male gender	6 (66.6%)	7 (77.7%)	ns
Ejection fraction	0.33+0.17	0.35+0.06	0.824
LVDD (mm)	69.88+7.65	66.33+7.31	0.421

LVDD - left ventricle diastolic diameter.

Table II – Length of hospital stay according to the treatment employed

	Levo group n=9	Dobuta group n=9	Teste t
Total length of hospital stay (days)			
Mean (sd)	17.0 (8.8)	17.6 (5.5)	p=0.874
Minimum – maximum	7-34	12-30	
Length of hospitalization			
Mean (SD)	3.6 (2.0)	7.9 (4.8)	p=0.029
Minimum – maximum	1-8	4-18	
Length of hospitalization in ward or apartment (days)			
Mean (SD)	13.4 (9.5)	9.7 (5.6)	p=0.318
Minimum – maximum	1-32	0-18	

and the cost of ICU daily rates was significantly lower in levo group (R$ 1,748.84 vs. R$ 3,880.23; p=0.029) (Table. III).

In the simulation made based upon hospital admissions covered by SUS, the mean cost was similar in the two groups (p=0.541), but the mean and the exceeding cost of ICU daily rates was significantly lower in levo group (R$ 759.86 vs. R$ 1,685.93; p=0.029).

Table IV shows the expenses with the treatment of 18 patients (average value per patient), according to the treatment group to which they were assigned. These data indicates that there is no difference in the global cost between the two therapeutic schemes (dobutamine or levosimendan).

Discussion

Heart failure (HF) is a frequent and, in most cases, a well-tolerated disease, but in its most advanced forms, it is a disabling disease that significantly reduces quality of life, and it presents a high mortality[1,2].

The current treatment has been modifying the natural history of the disease, improving the quality of life and reducing the mortality[5,6,14-20]. Current evidence shows that treatment must be done with the prescription of beta-blockers, converter enzyme inhibitors and spironolactone and, in the presence of the symptoms, digoxin and diuretics[5,6,14-20] must be associated.

Cardiac decompensation is part of the natural history of HF and most of decompensations result from incorrect treatment, either by improper intake of prescribed medications or by the prescription of medications in inappropriate doses.[21] There are many demonstrations that the treatment with appropriate doses promotes a better evolution, by reducing the number of decompensations, besides inducing reversion of the clinical features in an expressive percentage of patients, a non-observed fact when low dose of medications are prescribed[22,23].

In acute decompensation of chronic HF or in recent onset HF, depending on the intensity of the symptoms, patients may need to be admitted to hospital and some may need treatment with intravenous drugs[7].

Cardiac decompensation as cause of hospitalization has been increasing and it already represents one of the greatest expenses in public and private health systems.[3,4] Both in Brazil and in the United States, expenses with hospitalizations for HF treatment correspond to approximately 4% of total expenses with healthcare. Therefore, our best efforts for their reduction are very necessary[1,3].

In the presence of cardiac decompensation, our objective is patient stabilization, hemodynamic function restoration and symptom relief (control), without increasing death risk[5,7]. As long-term additional objectives, reduction of disease progression, reduction of rates of re-hospitalization and survival improvement[5,7] must be taken into consideration.

In order to achieve such objectives, at the stage of cardiac decompensation, we have diuretics, vasodilators and inotropic agents[5,7] as options. It is important to remember that diuretics and vasodilators are very useful to acutely control the symptoms, but as they do not change the intrinsic causes of the disease, their benefits cannot be kept for a long time and they do not prevent the progression of ventricular dysfunction.[7] Inotropic agents are very useful at hemodynamic stabilization and acute symptom improvement[7].

In most cases of cardiac decompensation, diuretics prescription or the increase of their dosage controls the symptoms, but in hypotensive patients, in those with important congestion and in those with low output signs, hospital admission is imposed and inotropic drug prescription is frequently necessary in order to obtain symptom reduction, acute control of the clinical features and preservation of renal and cerebral functions[5,7].

Treatment with inotropics, by improving the contractile power, is an important mechanism by which the cardiac output can be

Table III - Descriptive measurements of the expense parameters, through Brasíndice price, per study group

	Levo group n=9	Dobuta group n=9	t-Test
Total price (R$)			
Mean	14,117.0	14,142.0	p=0.991
(SD)	(4,232.4)	(4,870.9)	
Minimum – Maximum	7,694.9 – 19,971.8	8,510.4 – 22,925.7	
Price of medications (R$)			
Mean	5,414.0	2,320.1	p=0.009
(SD)	(2,739.1)	(1,545.1)	
Minimum – maximum	3,990.3 – 12,637.2	954.4 – 4,748.0	
Price of materials (R$)			
Mean	399.9	1,665.7	p<0.001
(SD)	(342.6)	(650.7)	
Minimum – Maximum	84.7 – 1,095.5	921.2 – 2,563.6	
Price of hospital daily rates in ICU (R$)			
Mean	1,748.8	3,880.2	p=0.029
(SD)	(987.1)	(2,338.9)	
Minimum – maximum	491.9 – 3,934.9	1,967.4 – 8,853.5	
Price of daily rates in ward or apartment (R$)			
Mean	3,312.4	2,381.7	p=0.318
(SD)	(3,894.3)		
Minimum – maximum	246.4 – 7,884.2	0 – 4,434.8	
Price of professional services (R$)			
Mean	3,241.8		
(SD)	(1,397.6)	(1,286.7)	
Minimum – maximum	1,404.3 – 5,821.3	2,481.5 – 6,462.9	

Table IV – Average price of the treatment per patient in the study (n=18), according to the therapeutic scheme employed

	Levo	Dobuta
Drugs	R$ 5,414.00	R$ 2,320.10
Materials	R$ 399.90	R$ 1,665.70
Hospital daily rates	R$ 5,061.20	R$ 6,261.90
Professional honorarium	R$ 3,241.80	R$ 3,894.30
Total	R$ 14,117.00	R$ 14,142,00

increased in the management of cardiac decompensation, being one of the most used therapeutic strategies, due to its easiness of administration[7].

In Brazil, for patients who keep symptoms despite many days of attempts of compensation or in those who have low output, the inotropic usually chosen is dobutamine, which achieves symptom control in most cases. Despite the fact that dobutamine is efficacious, some studies have demonstrated that it may increase mortality rates[7-11,24]. An important matter in the current treatment of heart failure is that dobutamine should not be any longer the drug of choice for the treatment of cardiac decompensation of patients using beta-blockers, that may be more and more used in the treatment of heart failure[7,13]. Another non-clarified question is wheter there is a treatment with an inotropic agent with a better cost-benefit ratio.

Levosimendan is an inotropic that had its efficacy proven and that can be prescribed for patients who take beta-blockers.[12] However, it has not been widely used in our environment, mainly because it is regarded as expensive and it is not refunded by SUS, or by some private health care providers.

The choice of a certain therapeutic scheme is based on many variables, as the experience of the physician with the drug, its cost and availability in the service. Change in prescription behaviors is not easy and frequent , and it depends on proofs of superiority and safety of the new treatment in relation to the usual one.

In this study, we assessed the price of treatment of patients treated with dobutamine or levosimendan, in order to assess whether the treatment with levosimendan is really the most expensive.

The treatment with dobutamine and levosimendan shows some important singularities, which can have an economic impact, along with the intrinsic cost of the medication.

Levosimendan must be administrated for 24 hours and then suspended, whereas dobutamine is kept for 3 to 5 days, and then the dose is progressively reduced[7-12,24]. The time of infusion of dobutamine may vary from one to more than 30 days, depending on the severity of the case. In the routine of our Unit, whenever the patient shows a consistent and stable clinical improvement for more than 48 hours and is euvolemic, we reduce the drug progressively until its suspension. Our experience in the treatment of patients with advanced heart failure shows that it is not always possible to suspend dobutamine quickly. In fact, 2/3 of patients with advanced heart failure need more than 7 days to achieve compensation and thus be able to be withdrawn from dobutamine. The need for a long period of drug infusion has, undoubtedly, an economic impact.

Levosimendan is the newest inotropic agent approved for clinical use in Brazil. The drug has already been marketed in many countries in Europe since 2000, and the growing experience with the product has shown that it is a safe and very potent drug, with distinctively features from the drugs that were available until Levosimendan's introduction[25]. Levosimendan represents an additional choice for the treatment of cardiac decompensation and it is indicated for episodes of acute decompensation of heart failure, when inotropic therapy is needed.

Levosimendan has many mechanisms of action. The most important is the myofibril sensitization to calcium, with consequent increase in contractility. Therefore, levosimendan is classified as a calcium sensitizer drug[25]. Its action is also mediated by phosphodiesterase inhibition, autonomous nervous system tonus modulation and endothelin release suppression by the vasculature, although those mechanisms seem to be stimulated only in high doses, higher than those usually employed[11,25].

Levosimendan increases ventricular contractility and promotes systemic vasodilatation, including coronary dilatation, reduces the systemic vascular resistance and the ventricular filling pressure and increases cardiac performance, by increasing the ejected volume and the cardiac output[11,25]. An increase of contractility takes place with a lower energetic loss and without increasing the occurrence of arrhythmias, since there is no important increase in the calcium cellular inflow, but a sensitization of troponin to calcium[11]. Although other drugs can be categorized as calcium sensitizers, levosimendan has been shown superior in many concluded studies[25].

Levosimendan half-life is of approximately 1 hour, which makes its use easy in clinical practice[25]. We used levosimendan in infusion, without attack dose, in a dosage range from 0.1 to 0.2 μg/kg/min. A great advantage of the levosimendan is that it must be infused within 24 hours, with no requirement of maintenance for longer periods. Levosimendan´s effect is sustained for up to 7 days, as one of its metabolites is also a positive inotropic and keeps the effect for more than 72 hours.

Levosimendan is contraindicated in cases of hypersensitivity to the drug or to any of its excipients; in severe renal failure (creatinine clearance <30 ml/min) severe hepatic failure, severe hypotension and shock from any etiology. Three great recent studies have assessed levosimendan's safety in patients who recently had a myocardial infarction and in those with heart failure. In both groups of patients, levosimendan showed to be safe and efficacious for the treatment of cardiac decompensation.

RUSSLAN study observed patients with acute HF following myocardial infarction, assessing the safety of levosimendan, observing particularly the occurrence of hypotension and ischemia[26]. The incidence of hypotension was similar to that observed with placebo (10.8% vs. 13.4%).

Patients who received levosimendan showed less dyspnea. An important finding was the reduction of the risk of death combined with worsening of CHF in the 24 hours after randomization, which was significantly lower (p=0.025) with levosimendan than with placebo. Such mortality reduction remained significant on the 14th post-infarction day (11.4% vs. 19.6%; p=0.029). In conclusion, the study showed that the prescription of levosimendan was associated to the reduction of HF symptoms, risk of death and worsening of HF, without causing hypotension or myocardial ischemia[26].

In the LIDO study, HF and low output patients were treated and the effect of levosimendan was compared to that of dobutamine[12,27].

The LIDO study showed that in patients with HF and low output, levosimendan improved hemodynamic performance in a better and more efficacious way than dobutamine. That benefit came with a lower mortality in 30 days (reduction of 50%) and in 6 months of follow-up.

The CASINO study, designed to compare the safety and efficacy of levosimendan, dobutamine and placebo in patients with decompensated heart failure,[24] should include 600 patients, but it was early terminated due to the clear benefit on the mortality observed favoring levosimendan. The mortality observed in 6 months was 24.7%, 39.6% and 15.3% with placebo, dobutamine, and levosimendan, respectively.

Therefore, current evidences show that the treatment with levosimendan is safe and it can promote a long-term mortality reduction, when compared with dobutamine[12,24-26].

Our results showed that patients treated with levosimendan needed a shorter length of stay in intensive care unit, with fewer expenses concerning the equipment required to intravenous infusion of drugs, specially infusion pumps, and concerning the total costs of care inherent to ICU stay.

The lesser need of hospitalization in intensive care unit and the reduction of costs related to such shorter stay made the global treatment costs with levosimendan similar, and not more expensive than dobutamine as it was usually thought, despite of the fact that the unit dose of levosimendan is more expensive than dobutamine's. Actually, the cost of the drugs was not the most important in the assessment of the final cost of a treatment.

Specially in the case of levosimendan, costs were similar, but if we consider that patients treated with levosimendan needed a shorter time under both intensive care and general care, and taking into account the deficit of this type of bed in Brazil, this reduction in the length of stay in ICU allows that a greater number of patients can take advantage of such important therapeutic resource. We must also take into consideration that a shorter time of intravenous infusion leads to a lower necessity of central venous catheter implantation. This is associated to a lower possibility of occurrence of phlebitis, venous thrombosis and infection in puncture places.

In the analysis of the cost-benefit ratio, we must not only consider the price of drugs, but understand the cost-benefit ratio as the sum of economic values consumed from resources, along with the assistance rendered to a patient.

In pharmacoeconomics studies in Brazil, we must also consider the ways of refunding of hospitalizations, which differ in public and private medicine. In the treatment of SUS patients, the refunded value is defined, being a fixed amount per disease. In the cases of private health providers, the value of hospital bill is refunded.

The Unified Health System *(Sistema Único de Saúde – SUS)* pays a fixed value of R$ 700.00 per patient with CHF, to which the value of R$ 213.71 per day of hospitalization in Intensive Care Unit (ICU) is added. All unit costs related to tests, materials, drugs, and professionals must be covered by such values, as not a single additional cent is refunded. However, the refunded value does not necessarily represent the real expenses, which are often much higher than the refunded values. It is interesting that institutions knows the real costs related to the global treatment of HF. This study aims to obtain the value of this real cost.

Private health providers pay the bills in a detailed way, as soon as unit values of each item correspond to standards values provided by them (Brasindice, AMB Reimbursement Formulary, etc).

By the sum of the values of the treatment for each patient, in each studied group, we reached the aforementioned values, showing that in the two scenarios (levo and dobuta group), the global cost of treatment is similar. Therefore, the treatment with levosimendan is not more costly than the usually done with dobutamine. However, patients treated with levosimendan needed to stay under intensive care for a shorter time. We must also consider the results from literature that showed hat levosimendan showed a lower mortality in the long-term follow up[12,24-27].

The results from this study were similar to the ones obtained by Cleland *et al*., that carried out a cost estimate based on the data from the LIDO study[28]. Our study, despite being also retrospective, analyzed the hospital bills from 18 patients and showed real data (not a simple expense simulation) and documented similar values in the bills of patients treated with levosimendan and dobutamine.

However, we highlight some limitations: this was a retrospective study, with a small and very specific sample, the follow-up was short and did not take into consideration the best rate of saved lives. In fact, this study analyzed a small number of patients, but allowed to show that the hypothesis that the treatment with a higher cost medication does not obligatorily results in a more expensive treatment at the endpoint. Those results allowed a design of a prospective study that will assess the question if the treatment with levosimendan is cost-effective, adding the advantage of not increasing the risk of death. This study began in December 2004.

In this study we were able to show that the cost of the treatment of patients with decompensated advanced heart failure with levosimendan is not more costly than the one carried out with the prescription of dobutamine. Patients treated with dobutamine needed to stay longer under intensive care and this was associated to a greater expenditure of materials during hospitalization. Our data confirm that not always the more expensive medication necessarily results in greater expenses.

Considering the easiness of administration and its safety, levosimendan is an excellent option of treatment for patients with decompensated heart failure, specially considering that it does not represent an increase of expenses when compared with the usual treatment.

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