Decompensated congestive heart failure - treatment with levosimendan

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Final version: *January 5th. 2019*

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http://dx.doi.org/10.1590/1806-9282.65.4.524

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

Levosimendan has been extensively evaluated for the treatment of acute heart failure (AHF) and in various other clinical situations characterized by impaired cardiac performance, including heart surgery and sepsis.[1] Among the drugs generally classified as inotropic, levosimendan was the agent most widely researched over the past 20 years.[2] It is a drug that belongs to the class of calcium sensitizers and has been commercially available in Brazil since 2002. Through sensitizing action of troponin C to calcium, levosimendan has the potential to improve the cardiac contractility during systole without harming the relaxation during the diastole. It could also have a vasodilating action, which would result in a significant, dose-dependent, improvement of cardiac output (CO) without increasing myocardial oxygen demand. Other hemodynamic effects of the drug on heart failure include increased systolic volume and reduced pulmonary wedge pressure (PWP) and pulmonary arterial pressure.[3-5] These effects are observed immediately after the beginning of the continued intravenous therapy (I.V.) for 24 hs with levosimendan and persist (up to ≈ 10 days) after the interruption of perfusion, through the action of the long-acting active metabolite OR-1896.[3-6]

OBJECTIVE

This review aims to assess the impact of the use of levosimendan on the total mortality outcome in patients with dilated cardiomyopathy and ejection fraction lower than 30% as a method of treatment in comparison with dobutamine.

METHOD

The method used followed the steps of a systematic review of the literature available to answer the clinical question: What is the impact on the outcome of total mortality of levosimendan in the treatment of

patients with dilated cardiomyopathy and an ejection fraction < 30% (heart failure post-intervention or not) when compared to dobutamine?

The question was structured as follows: Patients - Dilated cardiomyopathy and an ejection fraction < 30% (heart failure post-intervention or not); intervention - I.V. levosimendan; Comparison - dobutamine; Outcomes - Death due to all causes. The search strategies used were: (SIMENDAN OR LEVOSIMENDAN OR DEXTROSIMENDAN) AND DOBUTAMIN* AND (RANDOM* OR SYSTEMATIC[SB]) (MEDLINE / PubMed) and (SIMENDAN OR LEVOSIMENDAN OR DEXTROSIMENDAN) AND DOBUTAMIN (CENTRAL / Cochrane).

All evidence retrieved was evaluated with regards to their risk of biases. For RCTs, we considered: if the question was focal, the randomization appropriate, the allocation blind, double-blind, losses (>20%), prognostic characteristics, outcomes (time, adequacy, measurement), analysis per intention to treat (ITT), sample size calculation, JADAD scale.[7] After the search for evidence, 120 papers were retrieved, which then had their title and/or summary individually accessed, and of which 28 were selected for evaluation of the full texts. Finally, after evaluating the eligibility criteria, 7 studies were included. The studies included[9-15] were described in relation to the characteristics of their patients, intervention, comparison and outcome considered (death) to express benefit or harm. The outcome expressed in absolute numbers, absolute risks [absolute risk of the intervention (AR) and absolute risk in comparison (ARC), with differences in risk [reduction (ARR) or increase (ARI) of absolute risk], a confidence interval of 95% (95% CI) and number needed to treat (NNT) or to harm (NNH). When there was the presence of the outcome (death) shared by the studies included, the results were expressed through a meta-analysis of data extracted from the selected trials analyzed using the Cochrane software (RevMan 5.3).

RESULTS

In Table 1, the studies included are described, from which the data were extracted to calculate the meta-analysis (Table 2). The exclusion criteria are available in Figure 1. The studies excluded and the reasons therefor are available in ANNEXES (Table 4).

All evidence retrieved was evaluated according to their risk of biases (Table 3). The individual and global strength of the evidence is expressed in the Synthesis of the Results (Table 5 - ANNEXES)

TABLE 1. CHARACTERISTICS OF THE STUDIES INCLUDED

Study and year	Patients and number (N)	Intervention (N)	Comparison (N)	Outcomes	Follow-up time
Adamopoulos S, et al.[9] 2006	L. ventricular dysfunction EF < 30% (46)	Levosimendan 6 microg/kg attack 0.1 microg/kg/min continuously for 24h (23)	Dobutamine 5microg/kg/min 24h (23)	Death	4 months
Alvarez J, et al.[10] 2006	PO of heart surgery with low cardiac output (50)	Levosimendan 12 microg/kg attack 0.2 microg/kg/min continuously for 24h (25)	Dobutamine 7.5microg/kg/min 24h (25)	Death	24h
Bonios MJ, et al.[11] 2012	Chronic heart failure EF < 30 resistant to the standard treatment NYHA 4 (42)	Levosimendan 0.2 microg/kg/min weekly / 6 months (21)	Dobutamine 10 microg/kg/min weekly / 6 months (21)	Death	6 months
Domingues-Rodriguez A, et al.[12] 2008	Cardiogenic shock (AMI) after percutaneous intervention. EF < 30 (22)	Levosimendan – 24 microg/kg attack – 0.1 microg/kg/min continuously for 24h (11)	Dobutamine 5microg/kg/min 24h (11)	Death	24h
Follath F, et al.[13] 2002	Heart failure EF < 35 (203)	Levosimendan – 24 microg/kg attack – 0.1 microg/kg/min continuously for 24h (100)	Dobutamine 5microg/kg/min 24h (103)	Death	24h, 31d, 180d
Levin RL, et al.[14] 2008	PO of revasc. Syndr. Low Cardiac Output (137)	Levosimendan 10 microg/kg attack 0.1 microg/kg/min continuously for 24h (69)	Dobutamine 5microg/kg/min 24h (68)	Death	30 days
Mebazaa A, et al.[15] 2007	Acute heart failure EF < 30	Levosimendan 12 microg/kg attack 0.1 microg/kg/min continuously for 50min 0.2 microg/kg/min 23h (664)	Dobutamine 5microg/kg/min 24h (663)	Death	31 d; 180 d

NYHA = New York Heart Association functional class; EF = ejection fraction; AMI = acute myocardial infarction; PO = postoperative.

TABLE 2. RESULTS FOR THE DEATH OUTCOME OF THE SELECTED STUDIES

Study and year	Levosimendan		Dobutamine	
	Number of deaths	Total of patients	Number of deaths	Total of patients
Adamopoulos S, et al.[9] 2006	2 (120d)	23	5 (120d)	23
Alvarez J, et al.[10] 2006	1 (24h)	25	1 (24h)	25
Bonios MJ, et al.[11] 2012	4 (180d)	21	8 (180d)	21
Domingues-Rodriguez A, et al.[12] 2008	0 (24h)	11	0 (24h)	11
Follath F, et al.[13] 2002	0 (24h); 8 (31d); 27 (6m)	103	3 (24h); 17 (31d); 38 (6m)	100
Levin RL, et al.[14] 2008	0 (24h); 6 (30d)	69	0 (24h); 17 (30d)	68
Mebazaa A, et al.[15] 2007	79 (31d) 173 (6m)	664	91 (31d) 185 (6m)	663

TABLE 3. DESCRIPTION OF THE BIASES OF THE STUDIES

Study and year	Random	Blinded allocation	Double-blind	Losses	Prognostic characteristics	Outcomes	Analysis by ITT	Sample size calculation	JADAD
Adamopoulos S 2006									1
Alvarez J 2006									2
Bonios MJ 2012									1
Domingues-Rodriguez A 2008									1
Follath F 2002									3
Levin RL 2008									2
Mebazaa A 2007									5

AIT = analysis by intention to treat

absence of biases presence of biases no information

META-ANALYSIS

Seven RCTs reported the number of deaths in various moments comparing levosimendan versus dobutamine. These studies provided sufficient data for a meta-analysis, considering the results (number of deaths) in these various points or intervals of time of follow-up: 1. Mortality at 24 hours (Figure 2); 2. Mortality at 30 days (Figure 3) and 3. Mortality between 120 and 180 days (Figure 4)

Four of the primary trials analyzed death at 24 hours as their outcome. The incidence of death was 0.5% (1 in 208 patients) in the levosimendan group and 2% in the dobutamine group (4 in 204 patients). Levosimendan did not reduce the absolute risk of death at 24 hours; there was no statistical significance (ARR1.5%; 95% CI -0.6% to 3.6%; p = 0.28; I^2 = 0%, NNT = NS), Figure 2.

Three of the primary trials analyzed death at 30 days as their outcome. Levosimendan reduced the risk of death (ARR) in comparison with dobutamine with values ranging between 2% and 16% and an overall reduction of risk equal to 8%; however, there was no statistical significance (95% CI -0.01 to 0.16; p = 0.07; I^2 = 70%), Figure 3.

Four of the primary trials analyzed death between 120 and 180 days as their outcome. The incidence of death was 25.4% (206 in 811 patients) in the levosimendan group and 29.2% in the dobutamine group (236 in 807 patients). Levosimendan did not reduce the absolute risk of death between 120 and 180 days; there was no statistical significance (ARR 3.8%; 95% CI - 0.5% to 8.1%; p = 0.08; I^2 = 28%, NNT = NS), Figure 2.

FIGURE 2. MORTALITY AT 24 HOURS

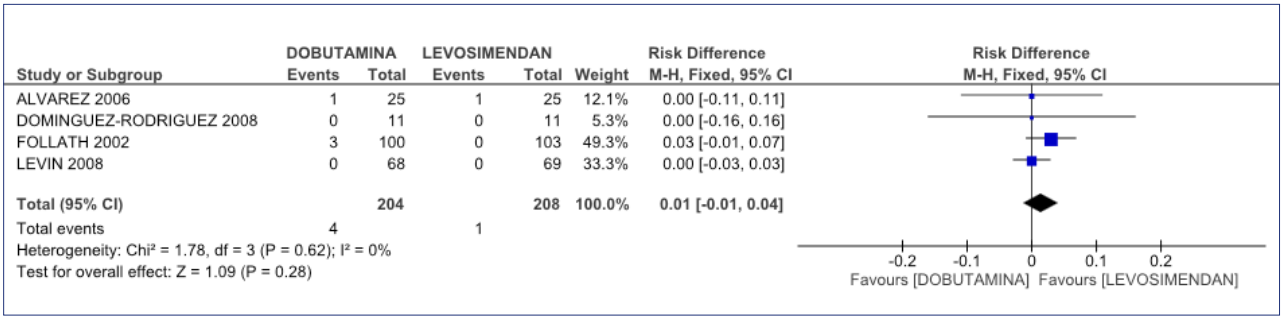


FIGURE 3. MORTALITY AT 30 DAYS

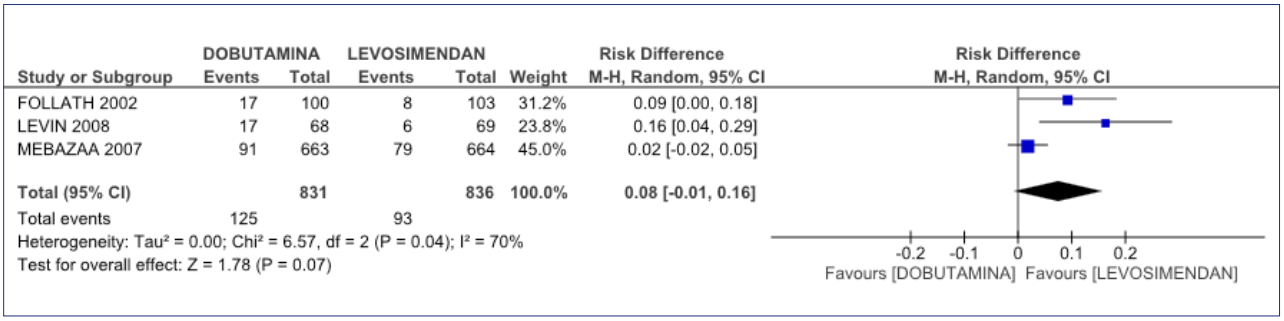
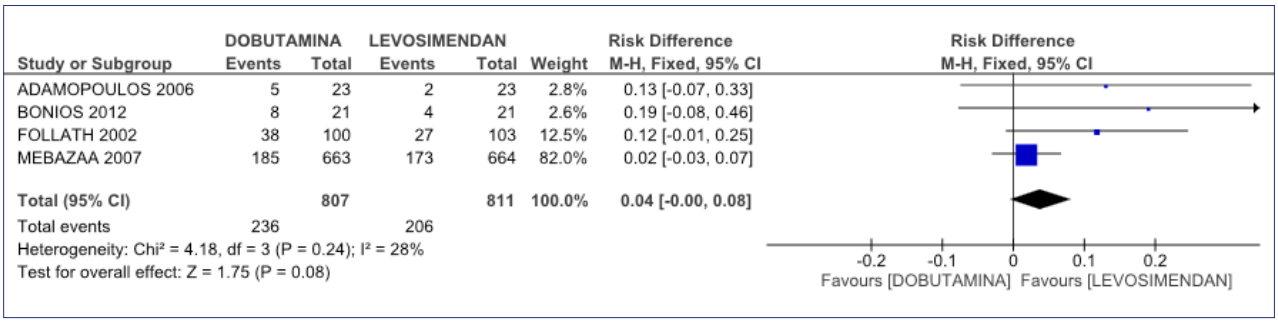


FIGURE 4. MORTALITY BETWEEN 120 AND 180 DAYS



QUALITY OF EVIDENCE (GRADE) PER OUTCOME - TABLE 4 (ANNEXES)

- Death, 24-hour follow-up (Figure 2) = MODERATE
- Death, 30-day follow-up (Figure 3) = LOW
- Death, 120/180-day follow-up (Figure 4) = LOW

RECOMMENDATION

In patients with dilated cardiomyopathy and ejection fraction < 30% (heart failure post-intervention or not), levosimendan does not reduce the risk of death. **STRENGTH OF EVIDENCE MODERATE/LOW**

ANNEXES

TABLE 4. STUDIES EXCLUDED AND REASON

Study and year	Reason for exclusion
1- Schumann J 2018	Systematic review
2- Shang G 2017	Systematic review
3- Kandasamy A 2017	Does not answer PICO
4- Ishihara S 2016	Systematic review
5- Kivikko M 2016	Subgroup analysis of a study included
6- Gong B 2015	Systematic review
7- Yi GY 2015	Systematic review
8- Chivite D 2014	Narrative review
9- Alvarez J 2013	Intermediary outcome
10- Huang X 2013	Systematic review
11- Yontar OC 2010	Intermediary outcome
12- Bergh CH 2010	Subgroup analysis
13- Duman D 2009	Intermediary outcome
14- Duygu H 2009	Intermediary outcome
15- Yilmaz MB 2009	Intermediary outcome
16- Duygu H 2008 (a)	Intermediary outcome
17- De Hert SG 2008	Oral formulation
18- Samimi-Fard S 2007	Does not answer PICO
19- Duygu H 2008 (c)	Intermediary outcome
20- GarcÃa-GonzÃ¡lez MJ 2006	Intermediary outcome
21- Cleland JG 2003	Economical evaluation

TABLE 5. QUALITY OF EVIDENCE (GRADE)

Certainty assessment							# of patients		Effect		Certainty	Importance
# of studies	Design of the study	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Levosimendan	Dobutamine	Relative (95% CI)	Absolute (95% CI)		
Mortality at 24 hours (assessed with: Number of deaths in 24 hours)												
4	randomized clinical trials	severe a	not severe	not severe	not severe b	None	1/208 (0.5%)	4/204 (2.0%)	RR 3.05 (0.49 to 18.90)	40 more per 1,000 (from minus 10 to 351 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Mortality at 30 days (assessed with: Number of deaths up to 30 days)												
3	randomized clinical trials	not severe	severe c	not severe	severe d	None	93/836 (11.1%)	125/831 (15.0%)	RR 1.74 (0.94 to 3.19)	111 more per 1,000 (from minus 9 to 329 more)	⨁⨁◯◯ LOW	IMPORTANT
Mortality between 120 and 180 days (follow-up: variation 120 days to 180 days; assessed with: Number of deaths in this period)												
4	randomized clinical trials	severe e	not severe	not severe	severe f	None	206/811 (25.4%)	236/807 (29.2%)	RR 1.15 (0.98 to 1.35)	44 more per 1,000 (from minus 6 to 102 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio – Explanations: **a.** 50% with randomization inadequate or not described; only one with blinded allocation, 3 studies without blinding; only with sample size calculation; b. The overall result does not exclude the benefit or harm; c. Test for inconsistency I2 equal to 70%; small overlap of confidence intervals; **d.** The result does not exclude great harm or benefit; **e.** 2 studies with JADAD = 1 and 2 studies with JADAD >= 3; **f.** The result does not exclude great harm or benefit

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