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LETTER TO THE EDITOR

Levosimendan improves the acute course of takotsubo syndrome: a pooled analysis

Takotsubo syndrome (TTS) is a stress-induced acute cardiac syndrome characterized by transient, reversible left ventricular (LV) systolic dysfunction in the absence of coronary artery obstruction.[1] TTS represents approximately 1–3% of all and 5–6% of female patients presenting with the suspected acute coronary syndrome.[2,3] About 60% of patients with TTS present with LV ejection fraction (LVEF) ≤40%, and up to 20% experience severe complications in the acute phase, including acute heart failure and cardiogenic shock.[4,5] The in-hospital mortality varies between 1% and 5%, similar to patients with acute myocardial infarction due to obstructive coronary artery disease.[6] The mechanisms underlying the onset of TTS are not fully established; therefore, therapeutic management remains merely empirical. Circulating levels of plasma catecholamines can cause acute myocardial stunning in TTS; however, the exogenous use of catecholamines (i.e. adrenaline, dobutamine, and dopamine), particularly in patients with LV outflow tract obstruction, is contraindicated.[7] Thus, a better therapeutic option seems to be a non-catecholamine inotrope, the calcium-sensitizing inodilator levosimendan, which is the inotrope of choice in acutely decompensated severe congestive heart failure where conventional therapy is insufficient and conditions where inotropic support is considered appropriate.[8] In this context, TTS may represent an ideal target for this non-catecholamine inotrope; however, this statement also relies on expert opinion.[9] Herein, we performed a pooled analysis of studies evaluating the efficacy and safety of levosimendan in TTS.

Two authors (L. S. and M. J. J.) searched the electronic resources (MEDLINE, MEDLINE In-Process, Embase, Cochrane Library for clinical trials, PubMed, Web of Science, and Scopus) from database inception to 15 November 2020. Subsequently, the relevant article bibliographies and searched articles were analysed and reviewed for relevance to title and abstract. The key search words were 'levosimendan' AND 'takotsubo cardiomyopathy' OR 'stress cardiomyopathy' OR 'apical ballooning syndrome' OR 'broken heart syndrome'. All results are presented as mean difference (MD) or odds ratio with their 95% confidence interval (CI). When the continuous outcome was reported in a study as median, range, and inter-quartile range, we estimated means and standard deviations using the formula described by Hozo *et al*. $P < 0.05$ two-tailed statistical testing was considered statistically significant. The analyses were performed using RevMan5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark). The full list of publications included in the pooled analysis is presented in the Supporting Information.

Eight studies including 272 patients were selected for quantitative analysis. All studies reported the use of levosimendan in TTS patients who required inotropic support (Supporting Information, *Table S1*), compared to standard treatment: one randomized double-blind study, three observational studies (including one conference paper), and four cases studies. In the pooled analysis (*Table 1*), the baseline characteristics were comparable between the levosimendan and control groups. At admission, NT-proBNP, serum creatinine, and LV ejection fraction were lower on levosimendan therapy ($P = 0.006$, $P < 0.001$, and $P = 0.002$, respectively). At discharge or after 30 days, LVEF was higher in the levosimendan group compared to the control group (MD = 1.4; 95% CI: 0.32, 2.48; $P = 0.01$), whereas NT-proBNP was lower on levosimendan therapy (MD = −98.30; 95% CI: −122.21, −74.39; $P < 0.001$). The hospital stay duration (MD = −4.90; 95% CI: −5.90, −3.90; $P < 0.001$), time to recover to the baseline troponin values (MD = −3.10; 95% CI: −4.31, −1.89; $P < 0.001$), and time to rise in LVED above 50% (MD = −2.50; 95% CI: −4.01, −0.99; $P = 0.001$) were shorter in the levosimendan group compared to the control group. There was a trend towards lower mortality in the levosimendan group (OR 0.29; 95% CI 0.07, 1.12; $P = 0.07$). There were 13/135 adverse events related to levosimendan during hospitalizations (9.8%).

Our pooled analysis demonstrates that the use of levosimendan might be associated with a reduced length of hospital stay and a rapid recovery time in patients with TTS who required inotropic support, although the bias due to the differences in baseline characteristics cannot be excluded. The major limitation of this analysis is the lack of statistical power to detect differences in mortality. Although the lack of early LVEF recovery is an independent predictor of

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Table 1 Pooled analysis of the studies reporting levosimendan use in patients with takotsubo syndrome who required inotropic support

Parameter	Levosimendan group	Control group	MD or OR (95% CI)	*P* value
Participant characteristics at admission				
Age (years)	70.4 ± 6.5 (*n* = 135)	70.1 ± 4.7 (*n* = 125)	0.30 [−1.07, 1.67]	0.67
Sex (female)	97/135 (71.9%)	89/125 (71.2%)	1.03 [0.60, 1.77]	0.91
Hypertension	27/118 (22.9%)	27/126 (21.4%)	1.09 [0.59, 1.99]	0.78
Diabetes mellitus	21/130 (16.2%)	18/138 (13.0%)	1.28 [0.65, 2.54]	0.47
SBP	131.7 ± 16.8 (*n* = 119)	127.6 ± 12.3 (*n* = 125)	4.10 [0.39, 7.81]	0.03
DBP	70 ± 8.5 (*n* = 119)	69.6 ± 5 (*n* = 125)	0.40 [−1.36, 2.16]	0.66
Heart rate	93.6 ± 9.8 (*n* = 118)	94.4 ± 12.7 (*n* = 125)	−0.80 [−3.64, 2.04]	0.58
NYHA Class IV	100/100 (100%)	100/100 (100%)	NE	NA
NT-proBNP (pg/mL)	2370.23 ± 385.48 (*n* = 100)	2504.3 ± 296.43 (*n* = 100)	−134.07 [−229.38, −38.76]	0.006
Serum creatinine (μmol/L)	81.88 ± 4.58 (*n* = 100)	84.9 ± 2.77 (*n* = 100)	−3.02 [−4.07, −1.97]	<0.001
ACEI/ARB, *n* (%)	46/117 (39.3%)	47/125 (37.6%)	1.08 [0.64, 1.81]	0.78
Beta-blockers, *n* (%)	15/117 (12.8%)	21/125 (16.8%)	0.73 [0.36, 1.49]	0.39
Diuretics, *n* (%)	85/117 (72.6%)	90/125 (72.0%)	1.03 [0.59, 1.81]	0.91
LVEF at admission (%)	29.3 ± 2.3 (*n* = 123)	30.2 ± 2.2 (*n* = 125)	−0.9 [−1.46, −0.34]	0.002
Outcomes at discharge or 30 days				
LVEF (%)	49.6 ± 4.6 (*n* = 136)	48.2 ± 4.3 (*n* = 125)	1.4 [0.32, 2.48]	0.01
NYHA class (%)	(*n* = 117)	(*n* = 125)	1.32 [0.81, 2.15]	0.27
I	—	—		
II	68.7%	52.2%		
III	29.3%	41.3%		
IV	2.0%	6.5%		
NT-proBNP (pg/mL)	795.25 ± 95.23 (*n* = 100)	893.55 ± 76.23 (*n* = 100)	−98.30 [−122.21, −74.39]	<0.001
Serum creatinine (μmol/L)	85.95 ± 4.9 (*n* = 100)	86.68 ± 4.65 (*n* = 100)	−0.73 [−2.05, 0.59]	0.28
Mortality, *n* (%)	3/122 (2.5%)	8/100 (8.0%)	0.29 [0.07, 1.12]	0.07
Hospital stay (days)	9.4 ± 1.7 (*n* = 17)	14.3 ± 1.5 (*n* = 25)	−4.90 [−5.90, −3.90]	<0.001
TRTV (days)	5.1 ± 1.6 (*n* = 17)	8.2 ± 2.4 (*n* = 25)	−3.10 [−4.31, −1.89]	<0.001
TRLVEF (days)	8.3 ± 1.9 (*n* = 17)	10.8 ± 3.1 (*n* = 25)	−2.50 [−4.01, −0.99]	0.001
Adverse events during hospitalization				
Recurrent TTC	1/13 (7.7%)	—	NE	NA
Pulmonary oedema	1/13 (7.7%)	—	NE	NA
Torsades de pointes	1/13 (7.7%)	—	NE	NA
Sinus tachycardia	1/13 (7.7%)	—	NE	NA
Dyspnoea	1/13 (7.7%)	—	NE	NA

CI, confidence interval; LVEF, left ventricular ejection fraction; MD, mean difference; NA, not applicable; NE, not estimable; OR, odds ratio; TRLVEF, time to rise in left ventricular ejection fraction above 50%; TRTV, time to recover to the baseline troponin values; TTC, takotsubo cardiomyopathy.

adverse long-term outcomes, including mortality,[10] the significant difference in LVEF remains clinically less relevant than the mortality endpoint. Moreover, the length of hospital stay and time to recover to the baseline troponin values were assessed based on 17 vs. 25 patients only, making the results hypothesis generating rather than ultimately demonstrating the benefits of levosimendan in TTS. Finally, the low rate of adverse effects such as pulmonary oedema and dyspnoea should also be interpreted with caution, considering that all patients were initially in NYHA Class IV. Altogether, further randomized studies are warranted to confirm these preliminary results.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Main characteristics of the studies reporting levosimendan use in patients with takotsubo syndrome who required inotropic support.

Milosz J. Jaguszewski
1st Department of Cardiology, Medical University of Gdańsk, Gdańsk, Poland

Aleksandra Gasecka
1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

Dagmara Hering
1st Department of Cardiology, Medical University of Gdańsk, Gdańsk, Poland

Krzysztof J. Filipiak
1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

Lukasz Szarpak
Maria Sklodowska-Curie Medical Academy in Warsaw, Warsaw, Poland
Maria Sklodowska-Curie Białystok Oncology Center, Białystok, Poland

Marcin Fijałkowski
1st Department of Cardiology, Medical University of Gdańsk, Gdańsk, Poland

Marcin Gruchała
1st Department of Cardiology, Medical University of Gdańsk, Gdańsk, Poland

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