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High-risk PCI facilitated by levosimendan infusion and Impella CP support in ACS cohort-pilot study

Short title: Levosimendan and Impella PCI

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INTRODUCTION

Despite the controversial nature [1] of percutaneous coronary intervention in patients with chronic coronary syndrome with significant impairment of left ventricular ejection fraction (LVEF), percutaneous coronary intervention (PCI) is emerging as a life-saving procedure for individuals with acute coronary syndrome (ACS). Although there have been undeniable improvements in PCI, coronary artery disease (CAD) remains one of the leading causes of death worldwide, with a particularly high mortality in the ACS. As PCI devices and techniques continue to advance, the number of patients eligible for PCI continues to grow.

The greatest improvements in treatment have occurred in subpopulations with the most advanced CAD, historically considered high-risk or ineligible for PCI. Since this subset of patients is often inoperable, it is imperative to establish appropriate treatment protocols for this group. Although randomized trials are missing and observational studies present conflicting results [2–4], the experts' consensus, supports the use of mechanical circulatory support [5].

Levosimendan was initially approved for therapy of patients with acutely decompensated chronic heart failure (HF). This novel drug is an inodilator that increases cardiac contractility through calcium sensitization and promotes vasodilation by opening adenosine triphosphate-dependent potassium channels. The unique mechanism of action allowed for significant expansion of clinical applications including cardiogenic shock, various types of cardiomyopathy, pulmonary hypertension, cardiac surgery, and emergency care [6]. Limited data suggest a beneficial effect of levosimendan in acute HF or cardiogenic shock following primary PCI [7,8] still, data regarding pre-PCI use are missing.

In this pilot study, we evaluated a novel therapeutic approach (preprocedural levosimendan infusion and periprocedural support of Impella CP) in patients undergoing high-risk ACS-PCI.

METHODS

The study population consisted of 20 consecutive ACS patients with severely reduced LVEF (<35% or less) undergoing high-risk PCI supported by preprocedural infusion of levosimendan and periprocedural support of Impella CP. All PCI procedures were performed at the Department of Cardiology, Copper Health Center (Lubin, Poland) between January 2021 and December 2023. The term high-risk PCI in our study was complementary to the generally accepted consensus [9] referring to a procedure in patients with one or more of the following characteristics: unprotected left main disease, intervention of the last patent vessel, or complex 3-vessel disease.

Exclusion criteria were identical to the contraindications for levosimendan administration, either the use of Impella CP, and included persistent cardiogenic shock requiring immediate revascularization or cardiac arrest on presentation to the hospital. Patients with concomitant mechanical complications of ACS (e.g., ventricular septal defect, left ventricular thrombus) or high-grade aortic valve stenosis were also excluded. No exclusion criteria for CAD severity or lesion morphology existed. The decision to perform high-risk PCI with Impella CP support was based on the judgment of the local Heart Team.

All patients undergoing PCI received a 24-hour intravenous infusion of levosimendan (0.1 ug/kg/min-cumulative dose 12.5 mg) at least 24 hours before PCI.

All patients provided written informed consent for all medical procedures and standard clinical follow-up. The study was approved by the local ethics committee (Lower Silesian Medical Chamber, ref. 7/BODB/2021 date of approval — 09.06.2021). First, a follow-up visit (outpatient or telephone contact) was performed 30 days after the discharged by trained medical staff.

The primary endpoint was 30-day mortality. The secondary endpoint was 1-month major adverse cardiovascular and cerebrovascular events (MACCE), including mortality, acute myocardial infarction, repeat revascularization, and stroke. All study endpoints were evaluated following the Academic Research Consortium Definitions [10]. In addition, we collected data on descriptive endpoints, including left ventricular assist device and PCI characteristics, acute kidney injury (AKI), and bleeding events.

Statistical analysis was performed with the R language. Depending on the normality of distribution(assessed by the Shapiro–Wilk test) the data is presented as the mean with the standard deviation or the median with the interquartile range(Q1–Q3).

RESULTS AND DISCUSSION

The vast majority of patients were male (85%) with a mean age of 71 (7.9) years. All patients were at high risk with a mean Syntax score of 35.4 (9.8) points. The average hospital stay was 16.7 (9.2) days. The vast majority of PCIs (60%) were performed via radial access. In 40% of cases, we used the single access technique. One patient developed AKI during in-hospital observation. At 1 month, the mortality rate was 10%-all deaths were related to in-hospital mortality (5 and 9 days after admission). We observed a MACCE rate of 10%. In the study cohort, we observed 4 (20%) major bleeding events, all related to the Impella access site, requiring blood transfusion. At 1-month follow-up, 35% of the study population had undergone implantable cardioverter-defibrillator/cardiac resynchronization therapy with defibrillator implantation. All study data were pooled in Table 1.

Patients with complex multivessel CAD or unprotected left main disease and ischemic cardiomyopathy represent a challenging subset with a poor prognosis and limited treatment options. While current revascularization guidelines recommend surgical revascularization, the high burden of comorbidities and advanced age resulting in unacceptable perioperative risk push these patients into either conservative treatment or PCI. In those high-risk populations despite the lack of strong evidence, experts’ consensus supports the use of mechanical

circulatory support [5]. Recommendations are based mainly on evidence coming from observational studies [2–4]. In our study, we investigated a novel approach regarding high-risk PCI subpopulation in which the procedure is facilitated with the pharmacological agent (levosimendan) along with classical Impella CP support. The short-term rates of life-threatening vascular complications, as well as mortality and MACCE rates in our registry were comparable to previous reports from high-volume expert centers [4, 11, 12]. It is important to note that the population in our study had a much higher incidence of reduced LVEF. In these studies, similarly impaired patients represented 30%–70% of all subjects. Nevertheless, this fact, combined with the well-documented association of LV dysfunction with increased short- and long-term mortality in patients undergoing high-risk PCI [13] may suggest that our treatment protocol may have a positive impact on the outcomes. Notably, compared to other inotropes, levosimendan may reduce not only the symptoms of HF, but also mortality [14].

In our study, despite access site-related complications, we did not observe any significant adverse events related to the applied therapeutic approach. Interestingly, despite the high risk of potential renal dysfunction (advanced HF, multivessel PCI, ACS subset), we observe only one case of AKI.

Particularly in patients with ACS treated with PCI, renal function is a two-sided coin: on the one hand, contrast media impair renal function, but their use is an indispensable part of life-saving therapy; on the other hand, as renal function deteriorates, the risk of death in long-term follow-up increases. The low number of AKIs in our cohort may be partly related to initial pretreatment with levosimendan, which has been shown to protect renal function [15] but future studies are necessary to evaluate this matter.

Our study has several limitations: a relatively small study population with a wide variety of initial diagnoses. The study protocol didn’t specify a maximum period between levosimendan infusion and PCI, the control group is missing, and the observation period is short.

The results of our pilot study suggest that initial intensive pharmacotherapy with levosimendan combined with Impella CP support appears to be a safe and may be a valuable adjunct to PCI in high-risk ACS patients. However, future large-scale studies are needed to fully evaluate the efficacy of this therapeutic protocol.

Article information

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Table 1. Clinical, procedural, and postprocedural characteristics of the study population

Age, mean (SD)	**71 (7.9)**
Sex (male), n (%)	17 (85)
Diagnosis:	
— unstable angina, n (%)	7 (35)
— NSTEMI, n (%)	12 (60)
— STEMI, n (%)	1 (5)
NYHA functional classification at admission, n (%)	
— I	0 (0)
— II	9 (45)
— III	7 (35)
— IV	4 (20)
Killip–Kimball classification at admission, n (%)	
— I	10 (50)
— II	8 (40)
— III	2 (10)
— IV	0 (0)
Kidney failure, n (%)	3 (15)
History of stroke, n (%)	2 (10)
COPD, n (%)	3 (15)
Post PCI status, n (%)	8 (40)
Post CABG status, n (%)	1 (5)
Primary diagnosis MI, n (%)	10 (50)
Syntax score, mean (SD)	35.4 (9.8)
PCI Syntax II score, median (Q1–Q3)	52.9 (44.6–56.7)
PCI Syntax II score 4-year mortality, median (Q1–Q3)	40.3 (21.3–48.4)

LVEF (%), mean (SD)	25.9 (9.1)
Treated vessel: **— LM, n (%)** **— LAD n (%)** **— Cx, n (%)** **— RCA n (%)**	 14 (70) 17 (85) 9 (45) 6 (30)
Initial hemoglobin level (g/dl), median (Q1–Q3)	13.9 (13.1–15.1)
Lowest hemoglobin level (g/dl), median (Q1-Q3)	11 (9.3–12.6)
Discharge hemoglobin level (g/dl), median (Q1–Q3)	11.9 (10.2–13.3)
Initial creatine level (umol/l), mean (SD)	90 (22.1)
Maximum creatine level (umol/l), mean (SD)	109.6 (28.2)
Discharge creatine level, (umol/l), mean (SD)	94.1 (22.2)
Time from levosimendan infusion to PCI (days), median (Q1–Q3)	2.3 (1.3–4)
Time of LV support (min), mean (SD)	128 (35.8)
Maximum Impella CP outflow (l/min), median (Q1–Q3)	3.4 (3.3–3.5)
Prolonged post-procedural Impella support, n (%)	1 (5)
Use of atherectomy device, n (%)	8 (40)
Use of S-IVL support, n (%)	4 (20)
Use of catecholamines, n (%)	4 (20)
Number of DES per procedure, mean (SD)	3.3 (1.2)
Total DES length per procedure (mm), mean (SD)	94.2 (32.7)
OCT/IVUS guided PCI, n (%)	16 (80)
Radial access, n (%)	12 (60)
Femoral access, n (%)	8 (40)

Impella single access point	8 (40)
6F guide catheter, n (%)	6 (30)
7F guide catheter, n (%)	14 (70)
Radiation doses (mGy), median (Q1–Q3)	2026.9 (966–2634.5)
Contrast amount (ml), median (Q1–Q3)	318.5 (182.3–218.5)
Acute kidney injury, n (%)	1 (5)
Any bleeding complication	6 (30)
Access point bleeding	6 (30)
Severe bleeding	4 (20)
Bleeding requiring blood transfusion	4 (20)
Length of hospitalization (days), mean (SD)	16.7 (9.2)
In-hospital MACCE, n (%)	2 (10)
30-days after procedure MACCE, n (%)	2 (10)
In-hospital mortality, n (%)	2 (10)
30-days mortality, n (%)	2 (10)

Abbreviations: CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; Cx, circumflex artery; DES, drug-eluting stent; IVUS, intravascular ultrasound; LAD, left anterior descending; LM, left main; LV, left ventricular; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infraction; NSTEMI, non-ST-elevation myocardial infraction; NYHA, New York Heart Association; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RCA, right coronary artery; S-IVL, shockwave intravascular lithotripsy; STEMI, ST-elevation myocardial infraction