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Preliminary results of the Multicenter Observational Study with Enoximone in Cardiac surgery (MOSEC)☆

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ABSTRACT

Background: Perioperative administration of Enoximone has been shown to improve hemodynamics, organ function, and inflammatory response. Aim of the present study was to evaluate the effects of Enoximone after on-pump cardiac surgery.
Methods: A protocol for a multicenter observational study was reviewed and approved by local ethic committee. This preliminary report involves the first 29 patients enrolled, in whom Enoximone was perioperatively administered in the context of on-pump cardiac surgery. All patients enrolled were propensity-matched 1:1 with controls not receiving Enoximone, renal function was evaluated in terms of estimated glomerular filtration rate (eGFR) with the CKD-EPI equation.
Results: After propensity matching, the two cohorts of patients receiving Enoximone or not did not show any significant differences among baseline characteristics. Patients receiving Enoximone showed a progressive improvement of eGFR at each time-point of follow-up: roughly +4.3, +10.0, and +12.3 mL/min/1.73 m^2 on postoperative days 2, 7, and 30; respectively. Consistently, maximum difference versus baseline was +12.6 mL/min/1.73 m^2 (or +19.3%) among Enoximone patients vs +3.3 mL/min/1.73 m^2 (or +4.4%) among controls ($p = 0.02$). Multivariable regression analysis (R^2-adjusted 0.47) showed only age (β −0.53; $p = 0.01$), preoperative eGFR (β −0.39; $p = 0.02$), diabetes (β 2.1; $p = 0.01$), cardio-pulmonary bypass duration (β 0.08; $p = 0.05$), and Enoximone administration (β −0.74; $p = 0.05$) to be independently correlated with delta eGFR variation on day 30.
Conclusion: These preliminary results show that perioperative Enoximone administration improved renal function in patients undergoing on-pump cardiac surgery. Further studies are needed to confirm these findings.

1. Introduction

Recent life expectancy models in "high-income" countries show an increase of at least 65% in women and 85% in men by year 2030 which translates into a careful planning for health and social services [1].

In this scenario, patients undergoing cardiac surgery are increasingly older with multiple risk factors. Cardio-pulmonary bypass (CPB), which is commonly used in the setting of cardiac surgery, may increase morbidity and mortality in such a higher risk population.

Indeed, the well-known systemic inflammatory response due to CPB, with its possible sequelae, may play a role in determining postoperative outcomes. Specifically, the non-physiological perfusion along with blood contact with non-endothelial surfaces both activate coagulation, promote endothelial layer modifications, and trigger the expression of leukocyte adhesion molecules, which may lead to post-CPB target-organ damage [2].

In particular, postoperative renal failure (RF) is a major issue affecting outcomes of cardiac surgery, and it has been clearly demonstrated to be strongly correlated with the use and length of CPB [3]. As a result, RF is an established significant cause of morbidity and mortality after cardiac surgery; thus it has been found to increase short- and long-term mortality, the incidence of post-operative complications such as

☆ Each of the above authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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respiratory infections, sepsis, and gastrointestinal bleeding, and intensive care unit and hospital lengths of stay [3,4].

Because of the latter, in the last decades many efforts have been made to avoid CPB (e.g. off-pump techniques, percutaneous valve procedures) or to manipulate the inflammatory process associated with CPB; including the introduction of miniaturized CPB, and the use of corticosteroids or other specific inhibitors of inflammatory mediators [5–8].

Enoximone is a selective inhibitor of Phosphodiesterase (PDE) III, known to modulate hemodynamics and phlogosis [9]; indeed, recent studies have shown that perioperative administration of Enoximone results in beneficial effects on hemodynamic status, organ function, inflammatory response, and endothelial integrity [9–11].

In order to evaluate the effects of Enoximone in patients undergoing cardiac surgery, we designed a multicenter prospective observational study.

2. Materials and methods

2.1. Patients and variables

The MOSEC is a Multicenter Observational Study of Enoximone in Cardiac surgery involving 2 Italian centers, with other 4 awaiting for ethic committee approval. The study was initially approved by the Ethics Committee of "Sapienza" University of Rome (EC Ref. no. 4116_2016, MOSEC Protocol no. 110SA_2016, authorized June 09th 2016). Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

We prospectively enrolled patients scheduled for on-pump cardiac surgery for whom anticipated prolonged CPB and/or comorbidities preoperatively suggested the use of Enoximone. Exclusion criteria were: off-pump interventions, non-hypothermic CPB, preoperative severe renal failure, preoperative liver disease, preoperative infection, and history of pathological alcohol consumption. The decision to include the individual was shared by the anaesthesiologist and the surgeon in charge for the case, and every patient, after being provided with full information about the study, gave his written informed consent.

Renal function was evaluated by means of glomerular filtration rate (GFR) estimated with the CKD-EPI equation [12]. Diagnosis of severe preoperative renal disease was made [13,14] because of previous renal replacement therapy (RRT) or because of eGFR < 15 mL/min/1.73 m^2 (CKD-EPI class V). Subsequently, postoperative RF was defined as a decline of ≥50% in GFR relative to baseline or need for renal replacement therapy. The rationale for the latter was the strong association shown by such defined values and operative mortality in previously published studies dealing with cardiac surgery cohorts [13,14].

In those patients included, Enoximone was administered from the weaning from CPB to 48–72 h postoperatively; the administration was performed with a starting bolus of 0.5 mg/kg followed by continuous infusion at 3 μg/kg/min.

Other drugs used perioperatively in the whole study population included epinephrine, norepinephrine, dopamine, dobutamine, and levosimendan; aprotinin and vasopressin have been used in no patient.

Primary end-point was renal function, assessed as described above. Secondary endpoints were operative mortality, length of stay, blood drainage in the first 24 h, and need for transfusions. For the latter two, too few data were available in order to make a statistical comparison in this preliminary report.

End-points were assessed at baseline, postoperatively at the arrival in the intensive care unit (ICU), and on day 2, 7, and 30 postoperatively. Thirty-day follow-up data were collected at the time of outpatient visits at each Institution.

2.2. Statistical analysis

For the purpose of the study, patients receiving Enoximone were compared with similar patients operated in the same period (June 2016–December 2017) without the use of Enoximone and to control for selection bias, a propensity score [15] was calculated.

To obtain a semi-saturated model, continuous and binary variables were used for a total of 32 preoperative and intraoperative variables, including: age, gender, body mass index, diabetes mellitus, hypertension, smoking history, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, previous cerebro-vascular accident, preoperative left ventricular ejection fraction (LVEF), preoperative systolic pulmonary artery pressure, preoperative New York Heart Association (NYHA) functional class, preoperative eGFR, preoperative C-reactive protein level, preoperative hemoglobin level, preoperative myocardial infarction, preoperative medications, elective surgery, re-interventional surgery, type of surgical procedure, miniaturized extra-corporeal circulation devices usage, aortic cross-clamp time, CPB time and post-operative transfusions. After a perfect 1:1 propensity-matching process, two balanced cohorts of 29 patients each were obtained. The final propensity model showed a satisfactory goodness of fit (*c*-statistic 0.81; $p < 0.0001$).

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 11.0 (SPSS, Chicago, IL). Variables were checked for normality by means of the Kolmogorov-Smirnov test for normal distribution and normality was accepted when $p \leq 0.05$. Continuous variables are shown as mean with standard deviation. All categorical data were displayed as percentages. Differences in baseline characteristics and postoperative data were compared using the *chi*-square test for categorical variables and *t*-test for continuous variables.

In order to control the efficacy of Enoximone for other important, clinically well-known factors associated with postoperative RF after cardiac surgery [16], a multivariable logistic regression analysis (significance level $p = 0.05$) was manually performed forcing clinically relevant variables into the model (age, preoperative eGFR, diabetes, recent myocardial infarction, preoperative chronic obstructive pulmonary disease, preoperative NYHA functional class, preoperative cardiogenic shock, previous cardiac surgery, and type of surgical intervention).

A second multivariable logistic model (significance level $p = 0.05$) was used to correct for other inotropic drugs administered during the perioperative period.

Goodness-of-fit of the logistic models was checked with the Coefficient of determination R^2 adjusted for entered variables.

3. Results

3.1. Overall data

Finally, the study population consisted of 58 patients (mean age 65.6 ± 8.4; with 39 or 78% being male) with a mean EuroSCORE II of 6.6 ± 2.5%, which reflects the increased-risk profile of those patients. There were no hospital deaths, whilst cumulative incidence of postoperative RF was 8.6% (5/58), with no patient requiring RRT.

After propensity matching, the two cohorts of patients receiving Enoximone (Group A, n = 29) or not (Group B, n = 29) did not show any significant differences among baseline characteristics (Table 1).

3.2. Comparison of groups

The fair comparison of propensity-matched groups showed that patients who received perioperative Enoximone had a lower incidence of postoperative RF: 0% (0/29) versus 17.2% (6/29) in those who did not ($p < 0.0001$). Furthermore, patients receiving Enoximone showed a progressive improvement of eGFR at each time-point of follow-up: roughly +4.3, +10.0, and +12.3 mL/min/1.73 m^2 on postoperative days 2, 7, and 30; respectively (Table 2). That slight amelioration of renal function was not seen among controls; with significant differences favoring patients treated with Enoximone on postoperative days 2 and 30 (Table 2). Consistently, maximum difference versus first value was +12.6 (95% CI: +7.9 to +17.3 mL/min/1.73 m^2) among Enoximone patients versus +3.3 (95% CI: −5.1 to +11.7 mL/min/1.73 m^2) among controls ($p = 0.04$). Given that, best proportional amelioration of

Table 1
Baseline characteristics stratified for treatment groups.

Variables	Group A Enoxinone (n = 29)	Group B No Enoximone (n = 29)	p value
Age, years	70.3 ± 8.1	69.2 ± 11.4	0.35
Gender male	18 (62.1)	18 (62.1)	0.99
BMI, kg/m^2	25.7 ± 4.5	25.3 ± 3.7	0.70
CAD	20 (69.0)	19 (65.5)	0.92
Hgb, g/dL	12.5 ± 3.7	12.7 ± 4.3	0.83
WBC, 10^3/mm^3	5337.6 ± 3133.5	5919.1 ± 3874.9	0.51
HR, bpm	72.2 ± 8.8	71.6 ± 15.1	0.54
SBP, mm Hg	119.5 ± 20.5	118.6 ± 22.7	0.41
DBP, mm Hg	61.9 ± 14.9	64.6 ± 14.9	0.37
eGFR, mL/min/1.73 m^2	74.1 ± 16.2	75.0 ± 15.2	0.61
CKD-EPI class	2.1 ± 0.7	2.0 ± 0.6	0.76
CPB duration, mins	134.4 ± 41.1	133.4 ± 31.5	0.39
Type of intervention			
Aortic (arch/ascending) ± CABG	11 (38.0)	11 (38.0)	0.66
Multiple valve procedure	6 (21.0)	8 (27.6)	0.36
CABG + valve procedure	12 (41.0)	10 (34.4)	0.29

BMI, body mass index; CAD, coronary artery disease; Hgb, hemoglobin; WBC, white blood cells; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting. Continuous variables are shown as mean ± standard deviation, categorical variables as absolute number (percentage).

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