EXPERIMENTAL PROTOCOL

Correlation between circulating biomarkers of organs damage and intraoperative hypotension management

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ABSTRACT

Intraoperative hypotension (defined as mean arterial pressure below 65 mmHg) is associated with increased organs dysfunction and mortality. Even short durations of reduced arterial blood pressure episodes significantly increased the risk of myocardial injury, neurological deficits, renal failure, and mortality (1-4). Hypotension rate during surgery is quite common and recent studies showed an incidence up to 60% of patients endured hypotension during anesthesia for an average of 10% of surgical time (5, 6).

Nowadays hypotension seems to be preventable even if current management of the hypotensive episodes is predominantly reactive and rather occurs with some delay. We hypothesize that the prevention of hypotension by means Edwards Lifescience new technology (HPI software) can improve patients outcome after surgery.

The present pilot randomized clinical trial is aimed at investigating various biomarkers involved in organ dysfunction and how they correlate with different intraoperative hypotension management strategies (Invasive blood pressure monitored by a normal arterial line vs Invasive blood pressure monitored by Edwards FloTracIQ system with HPI software).

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In the study will be enrolled forty adult patients requiring an arterial line (at discretion of treating physician) undergoing non-cardiac non-day surgery (with an expected duration of more than 2 hours and an aimed MAP of 65 mmHg) at the "Policlinico Universitario" of Catania.

Inclusion criteria:

• Aged 18 years or older;

• Planned for elective non-cardiac non-day surgery with an expected duration of more than 2 hours;

• Planned to receive general anesthesia;

• Planned to receive an arterial line during surgery;

• Aim for MAP of 65 mmHg during surgery;

• Being able to give written informed consent prior to surgery.

Exclusion criteria

• Age less than 18 years;

• Aim for MAP other than 65 mmHg at discretion treating physician;

• Significant hypotension before surgery defined as a MAP <65;

• Right- or left sided cardiac failure (e.g. LVEF<35%);

• Known cardiac shunts (significant);

• Known aortic stenosis (severe);

• Severe cardiac arrhythmias including atrial fibrillation;

• Chronic kidney disease (as chronic kidney disease may affect the interpretation and prognostic significance of changes in urinary biomarkers);

• Liver surgery;

• Vascular surgery with clamping of the aorta;

• Diabetes.

The patients will be randomly (1:1) assigned to one of the subsequent two groups: a group monitored with FloTracIQ with HPI software (Treatment Group) and a group with standard invasive blood pressure monitoring (Control Group).

All hypotensive episodes during surgery will be treated according to the following flowcharts (Fig. 1 and Fig. 2):

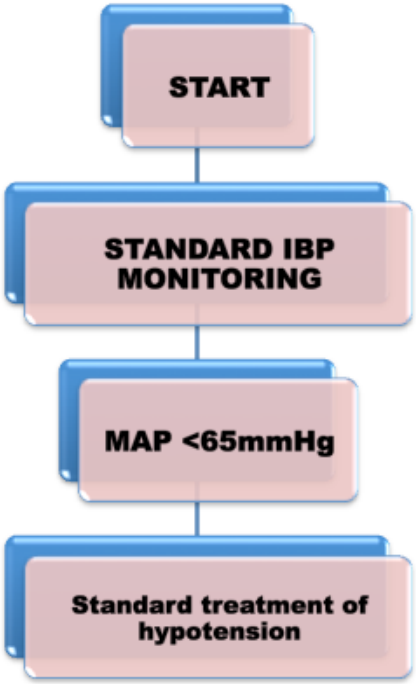

Figure 1: Treatment of patients of control group

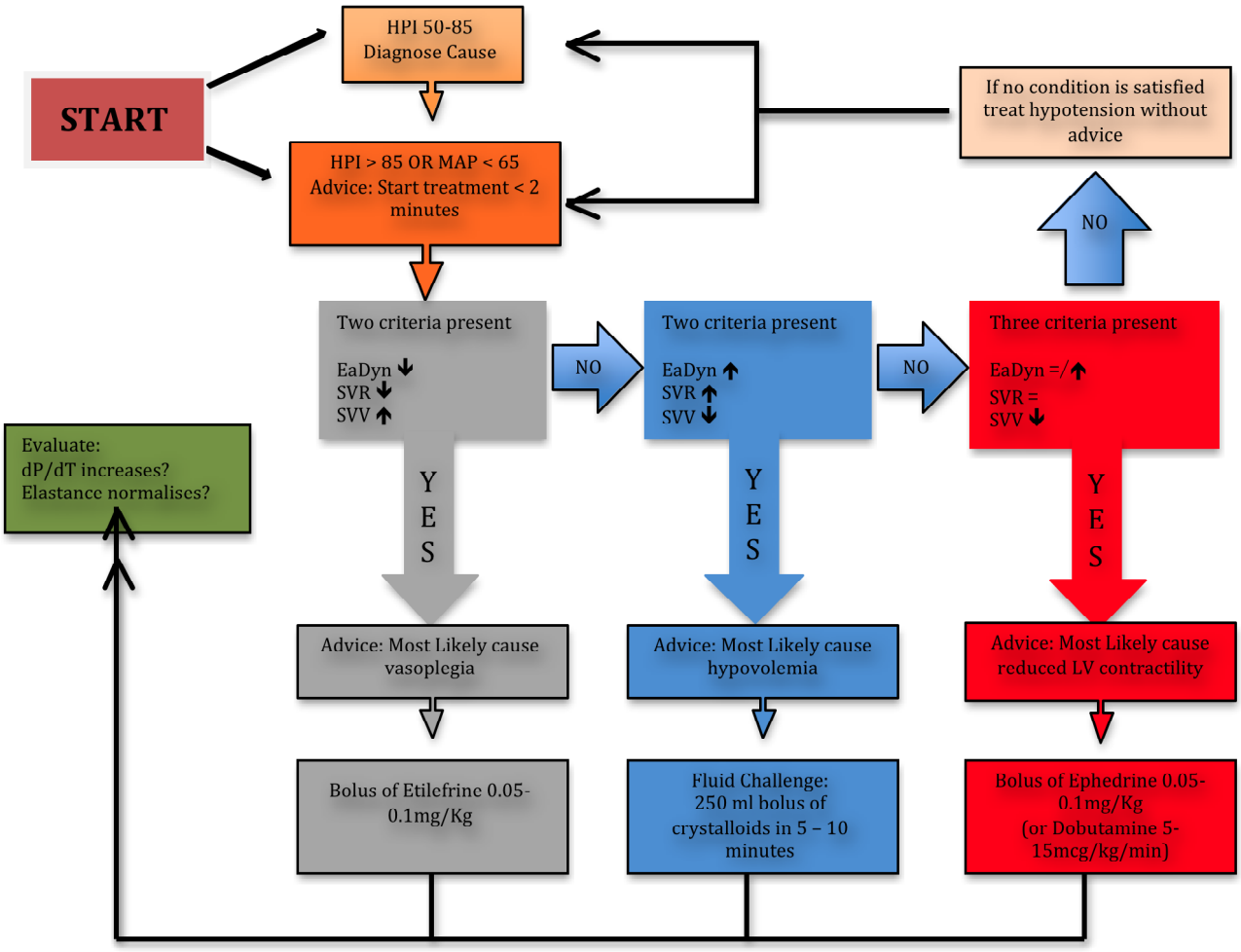

Figure 2. Treatment of patients of experimental group.

In both groups different blood samplings will be performed in order to assess biomarkers of specific organ dysfunction: T0 (baseline, before starting operating procedures); T1 (2 hours after starting anesthesia); T2 (at the end of surgical procedures). The following biomarkers will be assessed: neuron specific enolase and S100B (for brain monitoring) (7); high sensitive cardiac Troponine T (for heart monitoring) (8); Neutrophil Gelatinase-Associated Lipocalin (NGAL, for kidney monitoring) (9); circulating endothelial cells counting and cytofluorimetric analysis (for endothelial monitoring) (10). In addition we will also determine systemic effect of intraoperative hypotension as measured by inflammatory citokynes (IL-6, IL-1 beta and TNF-alfa), oxidative stress (reduced glutathione, lipid hydroperoxides) (11) and markers of hypoxia (HIF1alpha, lactate, acetylCoA, CoA) (11).

Various clinical informations will be collected at the same time: glomerular filtration rate, plasma electrolytes, creatinine, AST, ALT, blood gasses analysis, anion gap.
A telephone interview will be performed one month after surgery, in order to investigate general health condition and any re-admission to hospital.

Endpoints/Measurements:

- variation of biomarkers levels from basal (T0);
- incidence of hypotension during surgery;
- time spent in hypotension during surgery;
- patient-reported outcome.

Sample size calculation:

Given the pilot nature of the study, no formal justification of sample size has been made.

Statistical analysis:

For a test of normal distribution, the Kolmogorov–Smirnov test will be used. Continuous data with normal distribution will be tested with paired or unpaired t tests, non-normally distributed data using Mann–Whitney U test and Wilcoxon rank-sum test for unpaired and paired results, respectively.
Changes in biomarkers over time will be tested using analysis of variance (ANOVA) on repeated measurements. Categorical data will be tested using Chi-square test and Chi-square test for trend. Data will be presented as mean ± standard deviation when normally distributed and as median [interquartile ranges] in case of abnormal distribution. A $p < 0.05$ will be considered statistically significant for all tests.

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