Supplementary material for Holm J, et al. Preoperative NT-proBNP independently predicts outcome in patients with acute coronary syndrome undergoing CABG. Scandinavian Cardiovascular Journal. 2013;47:28–35.

Appendix

Preoperative NT-proBNP independently predicts outcome in patients with acute coronary syndrome undergoing CABG

A prespecified substudy of the GLUTAMICS-trial – GLUTAmate for Metabolic Intervention in Coronary Surgery (ClinicalTrials.gov Identifier: NCT00489827).

The glutamics trial

The Glutamics trial was an investigator-initiated prospective randomized controlled trial evaluating metabolic intervention with intravenous glutamate infusion in association with surgery for acute coronary syndrome (ACS). The main purpose was to determine whether intravenous glutamate can protect the heart from myocardial injury, postoperative heart failure and death in association with CABG in ACS.

The study was approved by the Swedish Medical Products Agency (151:2003/70403) and the Regional Ethical Review Board in Linköping (M76-05). Amendments were accepted by the Swedish Medical Products Agency 2006-08-31, 2007-05-08, 2007-11-01, and 2007-11-19.

External randomization in variable block sizes was done by Apoteket AB, Produktion & Laboratorier (APL), Box 6124, SE 90604, Umeå, Sweden.

External monitoring of all key data was done by an independent professional monitoring team (Clinical Research Support: http://www.orebroll.se/crs). Recording of adverse events was done according to Good Clinical Practice standard.

Intervention

Glutamate solution

500 ml 0.125 M solution of L-glutamic acid with pH 6.0 and 280 mosmol/kg containing L-glutamic acid 9.2 g, NaCl 0.8g, H_2O ad 500 ml and NaOH quantum satis.

Production of glutamate solution and quality control was done by Apoteket AB, Produktion & Laboratorier (APL), Box 6124, SE 90604 Umeå, Sweden.

Inclusion criteria

Inclusion criteria were coronary artery bypass surgery for acute coronary syndrome. Patients were eligible for inclusion regardless if the procedure was done on-pump or off-pump or if the patient had a simultaneous valve procedure.

Exclusion criteria

Exclusion criteria were, informed consent not possible because of critical condition or other reason, preoperative use of inotropic drugs or mechanical circulatory assist, preoperative dialysis, redo-procedure, unexpected intraoperative finding or event that increased the magnitude of the procedure to overshadow the originally planned operation, age >85 years, body weight >125 kg and food allergy known to have caused flush, rash or asthma.

Criteria for endpoints of the substudy

Left ventricular failure at weaning from cardiopulmonary bypass or after completion of off-pump surgery

Patients were considered to have left ventricular failure at weaning from cardiopulmonary bypass or after completion of off-pump surgery if criteria a + b or a + c or a + d were fulfilled.

(a) Consensus reached by Endpoints committee that left ventricular failure was evident at weaning from cardiopulmonary bypass based on available records and hemodynamic data.

(b) Cardiac index $<$ 1,9 L/min m^2 BSA with SAP <100 mm Hg

(c) SvO_2 criteria in relation to systolic arterial blood pressure (SAP) below fulfilled at weaning from cardiopulmonary bypass, five minutes after main dose of protamine sulphate and on admission to ICU that could not be explained by shivering, anemia or hypovolemia[4–6].

$SvO_2 < 50\%$ SAP < 130 mm Hg
$SvO_2 < 55\%$ SAP < 110 mm Hg
$SvO_2 < 60\%$ SAP < 90 mm Hg
$SvO_2 < 65\%$ SAP < 70 mmHg

(d) Use of intraortic balloon pump or need for at least one inotropic agent in dosages listed below remaining on admission to ICU

Severe circulatory failure

Patients were considered to have had severe circulatory failure if criteria 1 + 2 + 3 or 2 + 4 were fulfilled.

(1) ICU stay ≥ 48 hours
(2) Consensus reached by endpoints committee that heart failure presenting at weaning from cardiopulmonary bypass or later had occurred. This decision was based on Cardiac Index or SvO_2 data identical to those prespecified for the primary endpoint left ventricular failure at weaning from CPB.
(3) Use of intraortic balloon pump or need for at least one inotropic agent in dosages listed below ≥ 24 hours after admission to ICU
(4) Mortality Dosages of inotropes required for criteria above:

Epinephrine ≥ 0,033 μg/kg BW/minute
Milrinone ≥ 0,375 μg/kg BW/minute
Dopamine ≥ 4 μg/kg BW/minute
Dobutamine ≥ 4 μg/kg BW/minute
Levosimendan regardless of dose + additional inotropic treatment in dosages above.

Clinical management

Clinical management was standardized and similar at the three participating centers with minor differences concerning choice of anesthetic drugs. After an overnight fast patients received beta-blockers and calcium antagonists orally whereas antihypertensive and antidiabetic agents were withheld. Standard premedication consisted of orally administered flunitrazepam 0,5–1,0 mg or diazepam 5–10 mg and ketobemidone 0,1–0,2 mg/kg body weight or morphine 0.1–0.2 mg/kg body weight. Anesthesia was induced with thiopentone (2–3 mg/kg body weight) or propofol (2 mg/kg body weight) supplemented by a bolus dose of fentanyl 3–5 μg/kg body weight. Muscle relaxation was achieved with pancuronium 0.1 mg/kg body weight or rocuronium 0.6 mg/kg body weight. Anesthesia was maintained with isoflurane, sevoflurane or propofol supplemented with intermittent doses of fentanyl.

Standard monitoring was used consisting of 5-lead echocardiogram, pulse oximetry, continuous arterial blood pressure monitoring using a cannula in the radial artery, central venous pressure and transesophageal echocardiography. A surgical pulmonary artery catheter was introduced in all patients (4,5).

Standard surgical techniques were employed. A median sternotomy was performed in all patients. Use of cardiopulmonary bypass, single-clamp technique for aortic cross-clamping, method for myocardial protection and off-pump surgery is presented in Table I.

Postoperative sedation was achieved with propofol. Postoperative analgesia regimen consisted of ketobemidone 7–15 μg/kg body weight administered intermittent intravenously and acetaminophen 1 g every 6th hour.

Extubation was performed when body temperature reached a level above 37° C, hemodynamic values were stable including a mixed venous saturation exceeding 55%, PO2 was above 10 kPa with FiO2 0,4 and PCO2 was below 6,5 kPa with a respiratory rate less than 30 and drainage loss was less than 100 ml per hour and declining.

ROC analyses in groups with or without intervention

Based on the aspect of possible disturbance of the intervention in interpreting data, the group without intervention was analyzed individually.

In patients with isolated CABG who did not receive glutamate (n = 181) ROC analysis showed an area under the curve (AUC) of 0.76 (95% CI 0.67–0.86; p = 0.12) for in-hospital mortality with a best cut-off value for preoperative NT-proBNP of 1028 ng/L providing a sensitivity of 66.7% and a specificity of 79.8%.

In patients with isolated CABG who did not receive glutamate (n = 181) ROC analysis showed an AUC of 0.87 (95% CI 0.78–0.96; p = 0.002) for severe circulatory failure postoperatively with a best cut-off value for preoperative NT-proBNP of 1028 ng/L providing a sensitivity of 83.3% and a specificity of 81.1%.

The number of events in the group treated with intravenous glutamate with regard to severe circulatory failure (n = 1) and in-hospital mortality (n = 2) was too few for statistical analysis but these patients had a preoperative NT-proBNP of 2000 ng/L or above.