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SCA22

COMPARISON OF THE EFFECTS OF TRANEXAMIC ACID, APROTININ AND PLACEBO ON BLOOD CONSERVATION, FIBRINOLYSIS AND PLATELET FUNCTION WITH EXTENSIVE HEART SURGERY. A RANDOMIZED CLINICAL TRIAL.

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Introduction: CPB results in fibrinolysis as reflected by increased plasmin concentrations and fibrin degradation products, both of which have deleterious effects on platelet function.

We designed a study to compare the effects of a high dose of aprotinin (A), tranexamic acid (TA) and no treatment (P) on blood loss, transfusion of blood products, fibrinolysis and platelet function during and after heart surgery.

Methods: After IRB approval, 60 consecutive consenting patients undergoing combined aortic valve replacement surgery with CABG were studied. They were randomized to either: high-dose A (280 mg loading dose, 70 mg/h infusion rate and 280 mg in the prime)(n=20); TA (100 mg/kg loading dose, 1 mg/kg/h infusion rate)(n=20); or saline (n=20).

The effect of A and TA on some markers for the activation of thrombin formation and fibrinolysis was studied (D-dimer, plasminogen, α2-antiplasmin, antithrombin and glycocalicin, a fragment of the platelet-membrane GPIb). Sampling was at induction (t1), at the start and end of CPB (t2, t3), and at 1, 4 and 24 h after CPB (t4, t5, t6).

Analysis of variance for repeated measurements was applied for statistical comparisons between groups. p values < 0.05 were considered as significant. Data are expressed as mean values ± SEM.

Results: Study groups did not differ with regard to demographic data and type of operation. Blood loss and chest tube drainage was significantly less in the A and TA group as compared with the P group at all time points and was accompanied with the use of less blood products, volume replacement and higher hemoglobin levels. The duration of the surgical post-CPB period was significantly shorter in the A and TA groups (55 ± 18, 71 ± 19 and 84 ± 26 min respectively). There was no difference in platelet count between groups. There were no re-explorations for postoperative bleeding. Inhibition of fibrinolysis was significant with both antifibrinolytic drugs (D-dimers 578±81, 550±105 and 3603±440 mcg/mL at t4). During and after the operation the D-dimers were much higher in the placebo group. α2-antiplasmin levels were higher in the A group compared with the TA and P groups. This effect was present until 24 h after CPB. TA had no effect on this parameter. Plasminogen levels were lower in the TA group at t4, t5 and t6. TA patients more often received additional boluses of heparin to maintain ACT > 480 s during bypass (15/20 patients versus 9/20 and 8/20 patients in the A and P groups respectively). aPTT values were significantly prolonged at the end of CPB in the A group. Antithrombin values were significantly higher in the A group at t3, t4 and t5. Glycocalicin values were slightly higher in the TA group during bypass.

Discussion: TA can inhibit fibrinolytic activity by blocking plasmin(ogen) activity measured as D-dimer, but seems to have no influence on neutralization of plasmin by α2-antiplasmin. Both A and TA effectively suppress the appearance of markers of fibrinolysis as compared with placebo. The results also suggest that the antifibrinolytic effects of TA and A can reduce blood loss in patients undergoing extensive CPB surgery.

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SCA23

DETERMINANT OF COMPLICATIONS WITH RECOMBINANT FACTOR VIIA (RFVIIA) THERAPY IN PATIENTS WITH EXCESSIVE BLOOD LOSS AFTER CARDIAC SURGERY

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Introduction: Blood loss that becomes refractory to standard hemostatic interventions is a serious complication of cardiac surgery that is associated with increased morbidity and mortality [1]. Recombinant factor VIIa (rFVIIa), a hemostatic agent currently approved for hemophiliac patients, is increasingly being used in the treatment of refractory excessive blood loss (EBL) after cardiac surgery. Its "off label" use in this setting is currently based on several case series and case-control studies that support its effectiveness for this indication. The high rate of serious adverse events in the majority of these reports, however, has raised concerns about its safety in this setting [2]. The purpose of this observational study was to identify the determinants of complications associated with rFVIIa therapy in a cohort of cardiac surgical patients with EBL.

Methods: In this single-institution observational study, we compared the unadjusted and adjusted perioperative complication rates, expressed as observed to expected (O/E) ratios, in 114 consecutive cardiac surgical patients who received rFVIIa for refractory EBL with 552 concurrent patients who developed EBL but did not require rFVIIa. The primary outcome was a composite perioperative complication outcome that included death, stroke, renal failure, myocardial infarction, and major vein thrombosis. For risk adjustment, a logistic regression model for this outcome was constructed that adjusted for known confounders.

Results: Whereas the unadjusted complication rate was 88% higher in patients who received rFVIIa (O/E =1.88; 95% CI =1.58-2.19), the adjusted rate was comparable to those who did not receive rFVIIa (O/E =1.06; CI =0.85-1.28). In addition, late versus early rFVIIa therapy (relative to the amount of blood loss with patients dichotomized to greater than or less than the 50th percentile median RBC units transfused before rFVIIa therapy) was associated with an increased risk-adjusted complication rate (late O/E =1.32; CI =1.00-1.63; early O/E =0.83; CI 0.54 – 1.12; P =0.03).

Discussion: The results of this study suggest that the observed association between rFVIIa therapy and postoperative adverse events is due to the effect of confounders. The results also suggest that rFVIIa therapy late in the course of blood loss may be associated with increased morbidity and mortality. Late rFVIIa therapy may be harmful because as patients bleed more, they are more likely to become hemodynamically unstable and develop disseminated intravascular coagulation (DIC), and rFVIIa therapy in the presence of DIC may increase the risk of thrombotic complications.

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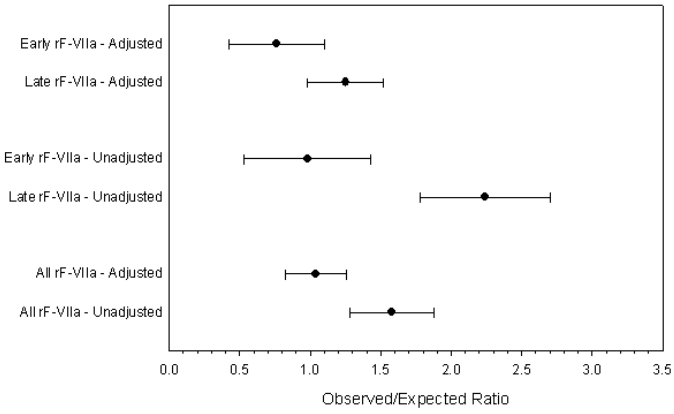

ANESTH ANALG
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SCA24

PROTAMINE INFUSION TO ELIMINATE RESIDUAL ANTI-XA ACTIVITY AFTER CARDIAC SURGERY.

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Introduction: Postoperative infusion of protamine sulphate (25mg/hr) has been shown to reduce bleeding after cardiac surgery (1) but detectable anti-Xa levels persist despite this strategy. While not causing bleeding in most patients, residual anti-Xa activity may explain the increased bleeding seen after supplemental antithrombin III (ATIII) administration during cardiac surgery (2) and may be important to avoid antigenic circulating heparin in cardiac surgery patients with HIT receiving heparin and an antiplatelet agent.(3) Therefore we tested the hypothesis that a higher dose of protamine sulphate could eliminate measurable anti-Xa activity after cardiac surgery.

Methods: With IRB approval 42 adult primary CABG patients at the Durham Veterans Affairs Medical Center received, in addition to standard intraoperative heparin anticoagulation with protamine reversal, an infusion of protamine sulphate at 50mg/hr for 6 hours after separation from CPB or an equal volume of saline in this randomized, placebo controlled, double blind study. Redo surgeries and patients with coagulopathies or renal insufficiency were excluded from enrollment. Blood samples were taken at baseline and hourly for the 6 hours following the start of study drug infusion. Platelet poor plasma was frozen at -70C and batch analyzed by ELISA for anti-Xa activity. Fisher's Exact Test was used to compare the number of samples per group with detectable anti-Xa activity.

Results: Two patients from the protamine group were excluded, as surgery was cancelled, and 13 patients (7 from the protamine group) were receiving heparin at baseline. The incidence of detectable antiXa effect in the post-op period was significantly less in the protamine group (p=0.0066); 66.67% of the placebo group had a detectable anti-Xa activity at some postop period whereas only 10% of the protamine group did. The incidence of detectable anti-Xa activity at each timepoint is illustrated in the figure.

Discussion: Our results indicate that it is possible to effectively eliminate circulating heparin in the postoperative period by infusing protamine sulphate at 50mg/hr. Further study with larger patient groups is needed to determine the effect of this on bleeding and transfusion. These results may be important in HIT patients, patients receiving supplemental ATIII or patients receiving postoperative FFP transfusion.

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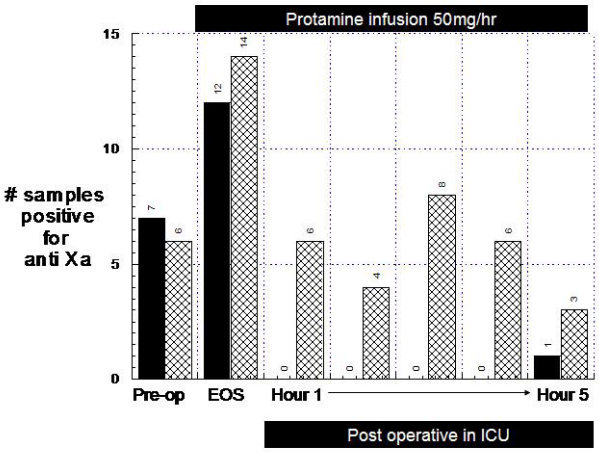

SCA25

IMPLEMENTATION OF A TRETMENT PROTOCOL FOR EXCESSIVELY BLEEDING CARDIAC SURGICAL PATIENTS MAY IMPROVE CLINICAL OUTCOMES

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Introduction: Excessive blood loss (EBL) is a common complication of cardiac surgery that is associated with increased morbidity and mortality [1-3]. Treatment protocols aimed at cardiac surgical patients with EBL may improve outcomes by allowing for prompt and optimal care. To date, however, such protocols have been primarily directed towards improving blood product utilization rather than improving clinical outcomes [4,5]. The objective of this observational study was to assess the independent effect of a blood management treatment protocol on the outcome of cardiac surgical patients with EBL.
Methods: In November 2002, an institutional treatment protocol for rapid identification and aggressive treatment of excessively bleeding cardiac surgical patients was implemented in order to determine the patients' eligibility for treatment with recombinant factor VIIa. The independent relationship between protocol implementation and adverse outcomes was measured by comparing the outcomes of patients with EBL who underwent surgery at the study institution during the three years before protocol implementation with those who underwent surgery during the two and a half years after protocol implementation. Multivariate logistic regression analysis was used to control for the effects of confounders. EBL was defined as 4 or more units of packed red blood cells transfused within 24 hour of surgery. A composite adverse event that included death, renal failure, stroke, and sepsis was the primary outcome. Bootstrapping and sensitivity analyses were used to confirm the validity of the results.
Results: 11,324 patients underwent surgery at our Institution during the study period, 1863 (16%) of whom were classified as having had EBL. Of those with EBL, 954 were in the pre protocol period and 909 were in the post protocol period. After controlling for all measured confounders, protocol implementation was associated with a 36% reduction (95% Confidence interval 24%-52%) in the odds of the primary composite outcome. This estimate was stable across different modeling conditions as well as in bootstrap sampling.
Discussion: In conclusion, in this large before/after study, we found that the implementation of a practical blood management protocol for cardiac surgical patients with EBL was independently associated with a marked reduction in adverse postoperative events. Randomized controlled trials are required to determine whether or not this is a cause-effect relationship.
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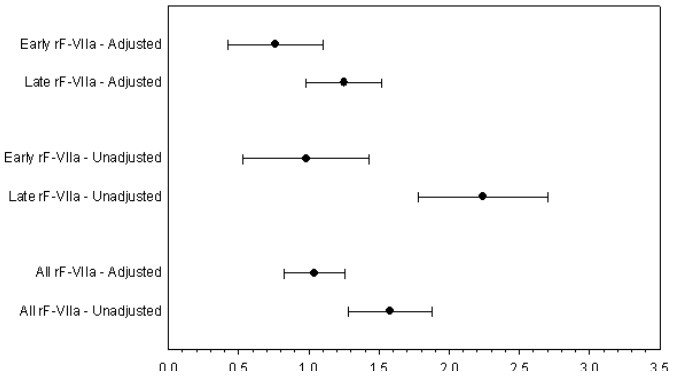

ANESTH ANALG
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SCA26

COMBINATION ANTICOAGULATION MINIMIZES THROMBIN GENERATION DURING EXPERIMENTAL CARDIOPULMONARY BYPASS

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Introduction: Thrombin generation during cardiopulmonary bypass (CPB) activates a procoagulant and inflammatory response resulting in adverse outcome after cardiac surgery. This occurs despite high dose heparin anticoagulation, which does not effectively suppress tissue factor mediated thrombin generation [1]. Our overall hypothesis is that adjunctive anticoagulant therapy (using the direct thrombin inhibitor bivalirudin in addition to heparin) can optimize anticoagulation during CPB by inhibiting the tissue factor mediated thrombin generation, while simultaneously avoiding problems associated with high dose alternative anticoagulants.

Methods: With IRB approval, 45 male Sprague-Dawley rats were anesthetized, surgically cannulated for CPB and assigned to one of 4 groups : Sham (n=6 analyzed prior to others to validate model); Heparin (H; n=13) 0.3-0.4 units/g IV heparin prior to CPB with 50 units heparin in the pump prime [2]; full dose bivalirudin (B; n=13) 1mg/g bolus followed by 1mg/g/hr infusion and heparin plus half dose bivalirudin (H[SPCHAR(B)] n=13)[3]. We compared thrombin-antithrombin complex (TAT) levels, using ELISA, after 60 minutes of CPB. Values were expressed as % change from baseline measured just prior to initiation of CPB. A 3-group Wilcoxon Rank Sum test was used to test for a difference between groups with a post-hoc test comparing between groups. With correction for multiple comparisons, the alpha level was 0.017.

Results: Sham operated animals (identical surgery and anesthesia but no CPB) had minimal detectable TAT complexes. As illustrated in the Figure, thrombin generation after 60 minutes CPB was significantly different among groups (chi-square 12.3, p= 0.0017). Post-hoc analysis showed that thrombin generation in group H&B was significantly lower than in group H (chi-square 13.3, p= 0.0003). No difference was found between groups H&B and B (chi-square 0.71, p=.34).

Discussion: Consistent with human CPB, heparin anticoagulation failed to suppress thrombin generation in this animal model of CPB. In contrast, combination anticoagulation using the direct thrombin inhibitor bivalirudin, effectively suppressed thrombin generation. This was achieved with half the dose effectively used as a sole anticoagulant for CPB. Elucidating the dose response relationship in this model may guide human studies where minimal bivalirudin doses can be used to augment heparin anticoagulation while minimizing risk of increased bleeding.

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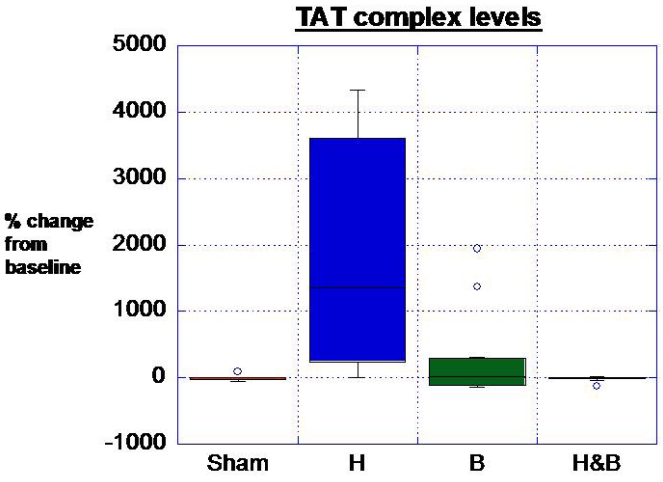

SCA27

COLLAGEN WHOLE BLOOD PLATELET AGGGREGOMETRY PREDICTS MYOCARDIAL INJURY AFTER CORONARY ARTERY BYPASS GRAFT IN ASPIRIN TAKING PATIENTS

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During CABG (Coronary Artery Bypass Graft), the endothelium of coronary vessels is injured by surgical manipulations and then the integrity of the endothelium may be lost. When the platelets are exposed to subendothelial collagen matrix and activated, they may initiate coagulation cascade and release potent vasoconstrictors. Subsequently, it may increase the organ injury by thrombosis or spasm. Although aspirin is usually used to prevent the platelet activation during CABG, some of the patients are resistant to it and aspirin blocks only a part of the platelet activating pathways.

We hypothesized that during CABG, even if the patients take the aspirin, the variance of the platelet response to the platelet agonists may correlate with the myocardial and renal injury. Thus, for 44 patients taking aspirin who were scheduled for elective CABG, we studied preoperative WBAs (whole blood aggregometry) and investigated the relationship of those with the postoperative myocardial and renal injury.

Before the induction of anesthesia, WBA in the presence of collagen 2 μg/ml, 5 μg/ml and ADP 5 μg/ml as stimulant agents was performed by the impedance method.

After CABG, myocardial injury was evaluated with enzyme analysis (creatine kinase [CK], creatine kinase-MB [CK-MB], lactate dehydrogenase [LD] at the end of operation, 6, 24, 48, 72 and 120 hr after operation) and electrocardiograms (at the end of operation, 6, 24, 72 and 120 hr). For the evaluation of renal injury, Ccr was measured at postoperative 0, 6, 24, 72 and 120 hr.

Preoperative WBA with collagen (5 mcg/ml) had significant correlation with the increase of cardiac enzymes. The myocardial enzyme levels were increased in CK at postoperative 6, 48 and 72 hr (P=0.049, 0.049 and 0.045 respectively), CK-MB at postoperative 48, 72 hr (P= 0.024 and 0.031 respectively) and LD at postoperative 24 hr (P=0.020). There were no significant relationship between preoperative WBA and postoperative Ccr. In conclusion, this study showed that in patients taking aspirin who undergo CABG, preoperative platelet response to collagen (5 mcg/ml) is correlated with the postoperative myocaridial injury in contrary to low dose collagen and ADP. And that emphasize the importance of collagen mediated platelet activation during CABG.

ANESTH ANALG
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SCA28

HEPARIN ANTIBODIES ARE ASSOCIATED WITH SEVERE ADVERSE OUTCOMES IN THE EVOLUTION TRIALS

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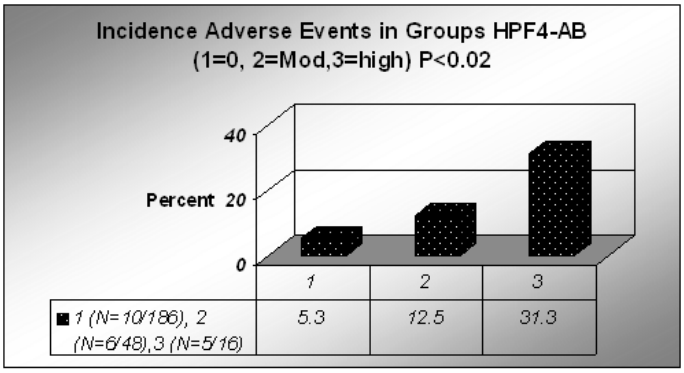
Introduction: Heparin induced thrombocytopenia (HiT) is caused by antibodies to heparin/platelet factor-4 (HPF4-AB). In cardiology HPF4-AB are associated with adverse outcomes even without thrombocytopenia. Bivalirudin (Biv), a short acting direct thrombin inhibitor is used as a replacement for unfractionated heparin (UFH)in cardiology. The EVOLUTION trials were designed to assess the use of bivalirudin in cardiac surgery. We investigated tne icidence of HPF4-AB and their impact on clinical outcome in the EVOLUTION trials.

Methods: The trials were 2:1 prospective, randomized, open label utilizing Biv versus UFH. Antibodies were analyzed with ELISA by a reference laboratory: collected at baseline, seven and 30 days after surgery. Patients were not treated due to their HPF4-AB status, as it was not known until after the study. Patients randomized to Biv may have received UFH in the cath lab or post-operatively as there was no restriction of UFH except as the primary anticoagulant for operation. HPF4-AB levels were considered negative at all times if < 0.4 optical density (OD), moderate >0.4-1.0 OD and strong >1.0 OD. Serious adverse events included: death, Q-wave myocardial infarction (Q-MI), stroke or severe adverse bleeding. Adverse events were examined either as composites or individually. Data were examined at each of the three time points as well as in cohorts that sero-converted. In patients that sero-converted the level of antibody was tested for association with the incidence of adverse events.

Results: See Tables and Firgures.

Discussion: Five percent of patients presented with HPF4-AB. Sero-conversion was common and numerically more (P=.1) in the UFH group. Presence of antibodies at day seven was associated with an ascending and impressive difference in composite adverse event incidence. Sero-conversion, especially with development of high levels of HPF4-AB was associated with the highest incendence of adverse events. Pre-operative presence of antibodies was associated with severe bleeding whereas sero-conversion was assocaited with Q-wave MI and composite endpoints. Although the use of Biv vs UFH as the primary anticoagulant for heart surgery did not show statistical differences in either HPF4-AB formation or sero-conversion the trends were always towards Biv having less antibody and in some sub-groups fewer adverse events (Stroke and Q-wave MI).



Event	No Change (N=176)	>0.4- 1.0 (N=52)	>1.0 (N=15)	P value
Q-MI	1 (0.6)	3 (5.8)	2 (13.3)	0.02
Stroke	3 (1.7)	2 (3.9)	1 (6.7)	0.28
Death	2 (1.1)	0 (0.0)	0 (0.0)	1.00
Major Bleed	5 (2.8)	5 (9.6)	2 (13.3)	0.10
Composite	10 (5.9)	9 (17.31)	4 (26.7)	0.02

Table 1: Patient numbers and (percent incidence) of adverse events in patients who sero-converted from no HiT antibodies to >0.4 or more at day 7.

Time	Biv	UFH	Overall
Baseline	6.0	4.6	5.5
7 day	18.6	25.0	20.9
30 day	29.2	34.3	30.9

Table 2: Incidence in percent of HiT antibodies within drug groups and overall for the Evolution study.

SCA29

MAGNESIUM THERAPY DOES NOT PREVENT PLATELET OR LEUKOCYTE ACTIVATION DURING CARDIAC SURGERY

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Introduction: Magnesium is important in the regulation of vascular tone, heart rhythm, and thrombosis. Recently, low serum magnesium levels have been associated with a 2-fold increase in the risk of death or myocardial infarction (MI) after CABG surgery(1). To investigate potential mechanisms underlying magnesium-induced reductions in adverse cardiac events, we hypothesized that intraoperative high-dose magnesium supplementation reduces the platelet and leukocyte activation commonly seen during cardiac surgery with cardiopulmonary bypass (CPB).

Methods: Following IRB approval, 100 patients >= 55 years in age and undergoing primary CABG and/or valve surgery were enrolled into this prospective, randomized, double-blind, placebo controlled trial. Patients were excluded if they had a history of symptomatic cerebrovascular disease, alcoholism, psychiatric illness, or renal failure (creatinine >2.0 mg/dl), had < 7th grade education, were pregnant, or had a Mini-Mental State Examination score < 24 on baseline cognitive testing. Patients were randomized to receive either placebo or magnesium administered immediately after induction of anesthesia as a 50 mg/kg bolus infusion over 20 minutes followed by another 50 mg/kg infusion over 3 hours (total dose=100 mg/kg). Blood samples were drawn at baseline, end-bolus, 10 minutes after cross-clamp release, end-surgery, and 24 and 48 hours postoperatively. Mean CD11b fluorescence and percentage of platelets expressing CD62P were determined on a flow cytometer as respective markers of leukocyte and platelet activation. The association of platelet and leukocyte activation with magnesium treatment group was tested using repeated measures analysis of variance. Log transformation was conducted on the positively skewed cellular activation data in order to meet assumptions of normality; $p<0.05$ was considered significant.

Results: Fifty patients were randomized to receive magnesium and fifty to a placebo bolus and infusion. 72.5% of the study population underwent CABG only, 15.7% CABG + Valve, and 11.8% Valve only. There were no differences between the magnesium and placebo groups with respect to age, gender, race, ejection fraction, bypass and cross-clamp time, number of grafts, and a history of hypertension, MI, or diabetes. There were also no differences between treatment groups in platelet (Figure 1) and leukocyte activation or in platelet-leukocyte binding ($p>0.05$). Sensitivity analysis revealed that with a sample size of 100, we had 80% power to detect a difference in log-transformed values of > 0.5.

Conclusions: High-dose magnesium supplementation does not decrease platelet and leukocyte activation during cardiac surgery with CPB. The previously reported association between low magnesium levels and increased MI and mortality rates after cardiac surgery is unlikely to be related to perioperative platelet or leukocyte activation.

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