Preoperative antithrombin supplementation in cardiac surgery: A randomized controlled trial

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Objectives: Purified antithrombin supplementation in cardiac surgery has been suggested for the treatment of heparin resistance and the prevention of thromboembolic complications. This study is a randomized controlled trial of preoperative purified antithrombin supplementation, with the primary end point of avoiding low (<58%) postoperative antithrombin activity levels and secondary end points including avoidance of heparin resistance, clinical outcome, and safety end points.

Methods: Two hundred patients were randomly allocated to the antithrombin group and the control group. Patients in the antithrombin group received a dose of purified antithrombin to reach an antithrombin activity value of 120%, whereas patients in the control group did not receive antithrombin.

Results: The antithrombin activity values were significantly higher in the antithrombin group at all postoperative determinations until discharge. Antithrombin activity levels <58% at admission to the intensive care unit were found in 26.6% of patients in the control group versus none in the antithrombin group ($P = .001$). Heparin resistance rate was significantly ($P = .001$) higher in the control group (38.2%) versus the antithrombin group (17%). Patients in the antithrombin group had a significant but clinically irrelevant (8 mL/hour) higher postoperative bleeding, with no differences in transfusion rates. No differences were found for clinical outcomes, and no safety issues were identified.

Conclusions: Preoperative antithrombin supplementation prevents heparin resistance and avoids excessive postoperative decrease of antithrombin activity. (J Thorac Cardiovasc Surg 2013;145:1393-9)

Antithrombin (AT) supplementation in cardiac operations with cardiopulmonary bypass (CPB) is still an open issue. Low levels of AT before and during CPB are associated with a poor response to heparin, commonly defined as ''heparin resistance'' (HR), which occurs at a variable rate between 10% and 30% depending on the definition.[1-4] The use of purified AT to treat HR has been suggested as an alternative to fresh frozen plasma administration.[5] Four randomized controlled trials demonstrated the efficacy of purified AT for the treatment of HR before or during CPB,[6-9] and the recently released update (2011) of the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Guidelines on Blood Conservation Clinical Practice[10] states that HR should be treated with AT concentrates before CPB (class IA).

During CPB, thrombin generation is mainly triggered by tissue factor released as a consequence of the surgical procedure and less importantly by contact with foreign surfaces. Heparin may only partially suppress thrombin generation, and the excessive hemostatic system activation may lead to coagulation factors consumption. Moreover, AT consumption during CPB may trigger postoperative thromboembolic complications, in presence of high thrombin generation. One observational study demonstrated an inverse relationship between postoperative AT levels and the incidence of a number of complications, including thromboembolic events, adverse neurologic events, bleeding, and prolonged intensive care unit (ICU) stay.[11] Furthermore, guidelines[10] place AT supplementation for the prevention of thromboembolic complications in selected patient populations in class IIB.

In the light of these arguments, it is reasonable to believe that preoperative supplementation with purified AT may represent a viable strategy for decreasing the hemostatic system dysregulation, preventing HR, and reducing postoperative morbidity in cardiac surgery operations with CPB.

This study is a phase II randomized controlled trial on pre-CPB purified AT supplementation aimed to investigate the effects of this treatment in maintaining postoperative AT values within the normal range, avoiding HR, and limiting postoperative complications.

MATERIALS AND METHODS

Study Design

This study is a phase II single center, single blinded, randomized, controlled trial designed to evaluate preoperative AT supplementation in patients undergoing cardiac surgery with CPB. The clinicians giving the

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Abbreviations and Acronyms
AE = adverse event
AT = antithrombin
CPB = cardiopulmonary bypass
HR = heparin reistance
ICU = intensive care unit
SAE = serious adverse event

treatment were not blinded; patients and clinicians assessing outcome measurements were not aware of patient allocation.

The study was approved by the local ethics committee and national health authority and properly registered at a public trials registry, www.clinicaltrial.gov (trial ID NCT00823082). Written informed consent was obtained from all patients before their participation.

The study was supported by Instituto Grifols S.A. (Barcelona, Spain). Representatives were involved in designing the study but not in collecting, analyzing, or interpreting the data. They read and approved the final manuscript but had no influence in making the decision to submit for publication.

Study Population

Inclusion criteria were: male or female patient aged at least 18 years needing an elective heart surgery with CPB. To be eligible, subjects had to present a baseline AT activity <100% and >60% and be willing to comply with all aspects of the protocol, including blood sampling, for the total duration of the study.

Exclusion criteria included heart transplant operations, nonelective surgery, participation in another investigational study during the past 3 months, documented AT deficiency, history of anaphylactic reaction(s) to blood or blood components, allergies to excipients, and pregnancy.

From June 2009 to April 2011 patients undergoing elective cardiac surgery with CPB were considered for enrollment at a single institution (IRCCS Policlinico San Donato, Milan, Italy). One thousand ninety patients were evaluated for screening (Figure 1) of which 1407 patients did not meet the eligibility criteria (136 patients suffered from congenital heart disease, 60 patients had missing baseline AT level values, 16 had baseline AT levels <60%, 1056 had baseline AT activity ≥100%, and 139 patients were enrolled in other randomized controlled trials), and 377 patients declined to participate or were not able to give consent because of their clinical condition. Screening, eligibility, and enrollment of patients are shown in Figure 1.

Study Interventions

The randomization scheme was electronically generated by an independent biostatistician and delivered to the center in sealed numbered envelopes.

The investigational drug (purified human plasma derived AT, Anbinex; Instituto Grifols S.A., Barcelona, Spain) was administered immediately after anesthesia induction as a single dose targeted to achieve a level of 120% according to the formula

$$\text{AT(IU)} = (120 - \text{actual AT activity}) \times (\text{weight in kg}) \times 0.8$$

Patients randomized to the control group did not receive any dose of the study drug. Postoperative AT administration was excluded by the study protocol.

The value of 120% was decided based on the fact that the normal AT activity range is considered 80% to 120%,[12] and that using chromogenic tests the value of 120% is considered as the upper limit of the normal range by the majority of the manufacturers, including the one providing the assays used in this study.

Intraoperative Anticoagulation

Unfractionated heparin was intraoperatively administered before CPB to reach and maintain a target activated clotting time of 450 seconds during CPB.

The heparin loading dose was assessed using a heparin monitoring system (Medtronic Inc, Minneapolis, Minn), which provided the estimated dose to reach an activated clotting time of 450 seconds and the heparin sensitivity index (seconds/IU/mL) as a measurement of the patient's sensitivity to heparin. The latter tests were performed before administration of the study drug, and repeated in patients of the AT group after receiving the study drug. In the AT group, the heparin loading dose was established according to the post-AT administration test.

Further heparin doses during CPB were administered as a bolus of 100 IU/kg if needed to maintain the desired activated clotting time value.

Heparin was reversed with protamine sulphate at a 1:1 ratio with the heparin loading dose; a second protamine dose (0.5 mg/kg) was administered if required.

AT Activity Determinations

All AT activity determinations were performed in the same local hospital laboratory with a coagulometer Sysmex CA-6000 (Toa Medical Electronics, Milan, Italy) through a calibration curve prepared by serial dilution of a human normal plasma pool and expressed as percentage of activity.

Data Collection and Time Points

Clinical data collected during this study were the usual ones routinely collected in the institutional database: patient demographics, medical history, comorbidities, risk stratification according to the EuroSCORE, and intraoperative details (eg, type of operation, CPB and aortic crossclamp time duration, lowest hematocrit on CPB, heparin and protamine dose, and heparin sensitivity index).

Laboratory data included complete blood count, biochemistry (eg, serum creatinine and liver enzymes) and coagulation tests (eg, AT activity, activated partial thromboplastin time, prothrombin time, international normalized ratio, and fibrinogen).

Throughout the study clinical data were collected at 8 separate time points: recruitment visit (within 14 days before the operation), preoperatively (the day of the operation), operatively (during the operation), at ICU admission, on postoperative days 1 and 2, at ICU discharge, and at the follow-up visit (1 month after the operation).

Study Outcomes: Assessment of Efficacy

The primary efficacy end points of the study were (1) AT activity levels at ICU admission higher in the AT group versus control group and (2) lower percentage of patients with AT activity <58% in the AT group versus control group. The value of AT activity settled at 58% was not arbitrary, being based on our previous study[11] where we could identify this cut-off value at the arrival in the ICU as the most specific and sensitive value predicting a prolonged ICU stay.

AT levels were measured at the recruitment visit and postoperatively immediately after the ICU admission, on postoperative days 1 and 2, and at discharge from the ICU.

Secondary efficacy end points were: HR (failure to reach an activated clotting time >450 seconds after a dose of up to 400 IU/kg heparin or to maintain this value despite heparin supplementation of 100 IU/kg), blood loss (in the first postoperative 12 hours), number of plasma and packed red cells units needed during the ICU stay, mechanical ventilation duration (hours), ICU and hospital stay (days), and prolonged (>7 days) ICU stay. Additional secondary end points were related to the postoperative complication rate (safety outcomes), which included surgical re-exploration (due to bleeding), low cardiac output syndrome (need for inotropic support >48 hours), myocardial infarction, adverse neurologic outcome, acute kidney injury (peak serum creatinine level >2 mg/dL and twice the baseline), thromboembolic events (myocardial infarction, stroke, mesenteric infarction, or peripheral or pulmonary thromboembolism), and in-hospital mortality.

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