CLINICAL CIRCULATION III

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Title INFLUENCE OF APROTININ ON COAGULATION PATTERNS AND BLOOD LOSS IN INFANTS UNDERGOING SURGERY FOR CONGENITAL HEART DEFECTS

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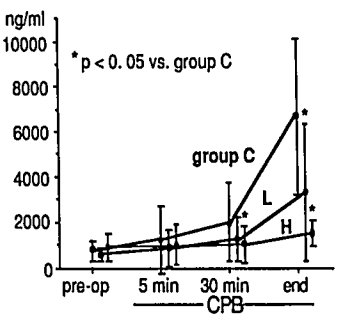
Recent studies in adult patients undergoing cardiac surgery showed a beneficial effect of the proteinase inhibitor aprotinin in terms of an attenuated activation of hemostasis during cardiopulmonary bypass (CPB), thus leading to a decrease in blood loss and homologous blood requirement (1).

The aim of this study was to assess this effect in neonates and infants operated for congenital heart defect.

Methods. After institutional approval 60 patients (pts.) with a body weight less than 10 kg undergoing open heart surgery for different congenital lesions were randomly assigned to one of 3 groups. Pts. in group L (n=20) received a bolus of 15000 KIU/kg aprotinin prior to surgery plus an equal bolus at the start of CPB, and in group H (n=20) 2x 30000 KIU/kg. Pts. in group C (n=20) without aprotinin served as control. The bubble oxygenator was primed with 500 ml blood.

Postoperative blood loss was measured. Beside other coagulation parameters total degradation products (TDP), D-dimers (DD), fibrin and tissue plasminogen activator (tPA) were determined by means of monoclonal-antibody-based immunoassay. Kruskal-Wallis-test was used for statistics.

Results. Pts. data were comparable among the groups. All pts. were operated in hypothermia (< 24°C), 37 pts. in deep hypothermia and circulatory arrest (< 20°C). The 6 h postop. blood loss was significantly ($p < 0.05$) lower in group H (5.6±1.8 ml/kg) compared to group L (8.7±6.3 ml/kg) and group C (9.4±5.3 ml/kg). Aprotinin plasma concentration 5 min. after onset of CBP was 57±32 (group L) and 76±32 KIU/ml (group H). Hemostasiologic data at the end of CPB are given in the table. No side effects attributable to aprotinin occured.



TDP plasma concentration

Group	TDP(ng/ml)	DD(ng/ml)	Fibrin(µg/ml)	tPA(ng/ml)
C	6677±3486	1341±809	28.3±13.3	8.8±8.5
L	3276±3033*	597±775*	18.6±17.3	12.5±5.2
H	1501±575*	414±334*	20.6±4.3	10.7±6.1

Table: Concentration at End of CBP *p < 0.05 vs. group C

Discussion. By the use of aprotinin postoperative blood loss is significantly reduced; the clinical importance, however, of this finding remains questionable, because no patient received more than one unit of homologous blood in the postoperative period.

The aprotinin plasma levels are markedly lower than those found in adults (2), presumably due to a greater dilution in the prime volume.

Plasmin activity is dose dependent suppressed, causing a reduced formation of fibrin(ogen) degradation products, but attenuation of thrombin generation by aprotinin in the present study seems to be less effective compared to the studies performed in adults. At any rate a more physiological state of hemostasis is maintained.

Aprotinin treatment can therefore be recommended in this subgroup of cardiac surgical patients and the use of higher doses should be considered.

References. (1) Bidstrup B.P., et al.: Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin. J Thorac Cardiovasc Surg 97: 364-372, 1989.

(2) Dietrich, W., et al.; Influence of high-dose aprotinin treatment on blood loss and coagulation pattern in patients undergoing myocardial revascularization. Anesthesiology 73 :1119-1126, 1990.

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EFFECTS OF PROTAMINE ON ACT AND ANTITHROMBIN III-HEPARIN COMPLEX DURING CARDIAC SURGERY

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INTRODUCTION: Protamine is used to neutralize heparin in cardiovascular surgery. Protamine 0.6 mg to 1.5 mg for each mg of heparin given is usually administered. Higher doses of protamine may be hazardous because of untoward cardiovascular effects and its own anticoagulant effect. On the other hand, inadequate heparin reversal causes bleeding. The rational use of protamine is very important. Therefore we examined the dose-response of protamine on activated clotting time (ACT), activated partial thromboplastin time (aPTT), plasma heparin (H), and antithrombin III (AT III)-heparin complex during cardiac surgery.

METHODS: Nine patients (age 51-66) scheduled for elective cardiac surgery were studied after institutionally approved informed consent was obtained. Patients were premedicated with morphine, scopolamine, and hydroxyzine intramuscularly. Patients were anesthetized with fentanyl, diazepam, and enflurane if necessary.

Beef lung heparin was given in increments: 50 U/kg, 100 U/kg, and 100 U/kg (for a total of 250 U/kg) before cardiopulmonary bypass (CPB). Heparin 125 U/kg was added to the priming solution of CPB. Moderate hypothermia with blood temperature between 25 to 28° C was used during CPB. No additional heparin was administered.

After CPB was terminated, incremental doses of protamine sulfate 0.5 mg/100 U of heparin were administered over 5 mins. A total of 1.5 mg of protamine sulfate/100 U of heparin was administered, regardless of ACT. The following parameters were measured: ACT, aPTT, plasma heparin level, AT III-heparin complex level, and AT III activity. Plasma heparin and AT III-heparin complex levels were measured by chromogenic assay. Blood samples were obtained 3 minutes after each dose of heparin or protamine. Data were analyzed by t-test and regression analysis. $p<0.05$ was considered significant.

RESULTS: ACT returned to baseline after P 0.5 mg/H 100U although significant levels of heparin and AT III-H complex existed, and aPTT was prolonged. No significant decreases in plasma H and ATHC were seen after P 1.0 mg/H 100 U.

CONCLUSION: Protamine 0.5 mg/H 100 U is adequate to correct ACT after 2hr of hypothermic CPB. However, protamine 1.0 mg/H 100 U is required to neutralize heparin completely. Protamine 1.5 mg/H 100 U does not further improve nor degrade ACT or aPTT.

SAMPLE #	ACT (sec)	aPTT (sec)	Heparin (U/ml)	ATHC (U/ml)
1. before H	150±5	33.5±1.3	0	0
2. H 50U/kg	259±10	>300	0.67±0.05	0.47±0.03
3. H 150U/kg	410±18	>300	2.46±0.16	0.72±0.05
4. H 250U/kg	510±32	>300	3.71±0.23	1.13±0.09
5. before P	569±30	>300	2.44±0.20	0.51±0.07
6. P 0.5 mg/H 100U	144±7	52.2±3.5	0.38±0.06	0.14±0.02
7. P 1.0 mg/H 100U	146±4	47.9±3.6*	0.13±0.04$	0.04±0.02$
8. P 1.5 mg/H 100U	148±4	47.3±2.9*	0.10±0.04$	0.04±0.02$

mean±SEM, H=heparin, P=protamine sulfate, ATHC=antithrombin III-heparin complex, *P<0.05 compared with sample #6. $P<0.001 compared with sample #6

Changes of ACT, aPTT, plasma heparin, and antithrombin III-heparin complex level