Use of activated clotting time for monitoring anticoagulation during cardiopulmonary bypass in infants and children with congenital heart disease

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The use of a fixed dosage schedule was compared with the use of activated clotting time (ACT) for determining heparin and protamine dosages during and after cardiopulmonary bypass disease. Use of the ACT resulted in a statistically significant increase in heparin dosage and a statistically significant reduction of postoperative blood loss. With ACT use, chest tubes were retained for a shorter period of time, and the incidence of serious postoperative hemorrhage was reduced from 44% to 18%. These results confirm the superiority of the ACT method for monitoring intraoperative anticoagulation in pediatric patients with congenital heart disease.

In the past 25 years, cardiopulmonary bypass (CPB) has become standard in the repair of cardiovascular defects. Heparin anticoagulation

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before CPB and protamine reversal after CPB have become accepted practice, and more than 30 protocols have been described for the administration of these drugs.[1] In 1975, Bull and associates[2] demonstrated that individual responses to a single loading dose of heparin vary greatly. These authors recommended that activated clotting time (ACT) be used in monitoring intraoperative heparin and protamine therapy. Although subsequent reports confirmed the usefulness of this method in adults with acquired heart disease,[3-7] its value remained unconfirmed in pediatric cases. The following study was undertaken to determine the usefulness of the ACT method in infants and children undergoing surgery for congenital heart disease.

Patients and Methods

One hundred fourteen consecutive patients under 22 years of age who underwent CPB for the correction of congenital heart defects between October 1975 and July 1977 and left the operating room alive were studied retrospectively (Tables I and II). The first 57 patients (Group I) underwent open heart surgery prior to the use of the ACT method; the second 57 patients (Group II) underwent surgery after the ACT method had been instituted for intraoperative use. Three infants who died in the operating room within 1 hour after CPB were excluded from Group II. These nonsurvivors had total anomalous pulmonary venous connection, Type B interrupted aortic arch, or severe pulmonic stenosis with extensive right ventricular fibrosis, respectively. All operations were performed by the same surgical team.

Cardiopulmonary Bypass Equipment and Techniques

Cardiopulmonary bypass equipment consisted of a Sarns Model 5000 console with roller pump, a Harvey disposable bubble oxygenator, and arterial and cardiotomy line filters (20 micron). The pump priming solution consisted of lactated Ringer's solution, 0.5 gm of mannitol/kg body weight, and enough whole blood to yield CPB hematocrit of 25%-30%. Blood was transferred from the patient to the heart-lung machine with individual caval cannulae, and oxygenated blood was returned via an ascending aortic cannula of a size that created a pressure gradient of less than 100 mm Hg. A perfusion rate of 1.8 to 2.4 L/min/M^2 of body surface area was used in all cases. Normothermia was used for simple repairs such as secundum atrial septal defect and pulmonic valvotomy; moderate hypothermia (26°-30°C) was used in patients larger than 10 kg who underwent more complex operations; and deep hypothermia (less than 18°C) with temporary circulatory arrest was used for complex procedures in some infants under 10 kg (Group I, n = 3; Group II, n = 1). All patients with right-to-left cardiac shunts received transfusions of fresh frozen plasma and platelets immediately after CPB.

Heparin and Protamine

Prior to CPB, the first 57 patients (Group I, median age 5 years) received a fixed heparin dose of 3 mg/kg body weight if they were under 2 years of age, or 2 mg/kg body weight if over 2 years of age. An additional 100 mg was added to the pump priming solution. After each hour of bypass, an additional dose equivalent to half of the previous heparin dose was given. After bypass, heparin was neutralized by protamine sulfate equal to 1.5 times the total heparin dosage. Additional doses of protamine were given if indicated.

In the second 57 patients (Group II, median age 6 years), protamine dosages were determined by the method of Bull and associates.[2] After control ACT had been established, an initial heparin dose of 2 to 3 mg/kg body weight was given and the ACT was again determined. The heparin dosage necessary to achieve an ACT of greater than 400 sec was established by means of a dose-response curve, and an appropriate additional dose was given. Prior to CPB, a final ACT was ascertained to confirm the predicted value. Hourly ACTs were determined while the pa-

TABLE I. Decriptive Data for Group I Patients (Non-Activated Clotting Time)

Operation (Repair)	# of Patients	Age (yrs)	Weight (kg)	Mortality & Cause
Aortic Insufficiency with VSD	1	8	21	
Aortic Insufficiency with PS, VSD	1	3	14	
AS (Valvular)	3	9, 11, 15	31, 26, 50	
Aortic Valve Replacement	1	18	65	
Subvalvular AS	2	9,14	26,52	
ASD (Primum)	3	4, 4, 5	12, 17, 18	
ASD (Primum) with MR & VSD	1	5	19	
ASD (Secundum)	6	5, 5, 7 9, 14, 22	16, 15, 20 29, 55, 73	
ASD with PAPVC	2	3, 12	14, 22	
A-V Canal, Complete	4	3, 5, 7,10, 14	12, 17, 23, 51	
Cor Triatriatum	1	(.8)	(8)	Died 2 days PO (low CO).
Double Outlet Right Ventricle with VSD	3	3, 4, 5, 7	14, 17, 23	
Pulmonary Atresia & Potts Shunt with VSD	1	12	37	
PS (Valvular)	5	3, 5, 11, 12, 13	10, 17, 43, 37, 65	
Total Anomalous Pulmonary Venous Connection	3	.6, 6, 8	6, 16, 23	
TOF	3	4, 6, 16	14, 14, 64	
TOF with AS & Tricuspid Atresia	1	15	23	
TGA with PS (Mustard Procedure)	1	.5	7	
TGA with PS & VSD	1	5	19	
Truncus Arteriosus, Type II	1	(4)	(12)	Died 7 hrs PO (severe PVO).
VSD	13	.4, (.4), 2 2, 3, 3, 3, 4, 4, 4, 4, (4), 5	3, (3), 10, 10 10, 13, 13, 13, 15, 15, 16, (11), 19	One 3 kg pt died 1 day PO (low CO + small RV). One 11 kg pt died 2 days PO (low CO + residual band obstruction).

AS = Aortic Stenosis; ASD = Atrial Septal Defect; CO = Cardiac Output; MR = Mitral Regurgitation; PAPVC = Partial Anomalous Pulmonary Venous Connection; PO = Postoperative; PS = Pulmonic Stenosis; PVO = Pulmonary Vascular Obstructive Disease; RV = Right Ventricle; TGA = Transposition of the Great Arteries; TOF = Tetralogy of Fallot; VSD = Ventricular Septal Defect; ( ) = Age & Weight of Patient(s) Who Expired.

tient was on bypass, and additional heparin was given to maintain the ACT above 400 sec. Protamine sulfate was administered in a dosage calculated by means of the dose-response curve, and the ACT was determined at the end of CPB. To neutralize 1/3 mg of heparin, 1/3 mg of protamine was utilized.

Determination of Postoperative Blood Loss

Postoperative blood loss was measured and the length of time that chest tubes were maintained in place (duration of postoperative blood loss); the patient's body weight was also recorded. Bleeding rate was determined by dividing total blood loss per kg of body weight by the number of hours the chest tubes were in place. Serious hemorrhage was defined as the loss of 50% or more of calculated blood volume during the postoperative period. Blood volume was estimated as 80 ml/kg body weight for children up to 1 year of age; as 75 ml/kg body weight for those from 1 to 2 years; and as 70 ml/kg body weight for those over 2 years of age.

TABLE II. Descriptive Data for Group II Patients (Activated Clotting Time)

Operation (Repair)	# of Patients	Age (yrs)	Weight (kg)	Mortality & Cause
AS (Valvular)	7	1, 6, 10 11, 14, 19, 20	10, 22, 30 35, 48, 65 43	10, 22, 30
Aortic Valve Replacement	2	8, 11	27, 35	
Subvalvular AS	2	(2), 4	(10), 16	Died 3 hrs PO (low CO and aortic obstruction at site of a recurrent coarctation.
A-V Canal, Complete	1	(2)	(10)	Died 7 days PO (low CO & severe PVO).
ASD (Primum) with MR	1	11	28	
ASD (Secundum)	13	3, 5, 6, 7 7, 8, 10, 11 11, 11, 12 13, 14	18, 19, 18, 22, 24, 21, 25, 34 35, 40, 45, 42 48	
ASD (Secundum) with PS	2	5, 5	18, 20	
Mitral Regurgitation (Valvuloplasty)	1	14	35	
PS (Valvular)	4	5, 6, 6, 7	18, 18, 26, 27	
TOF	6	.8, 2, 5, 6 6, 10	8, 16, 19, 18, 21, 33	
Total Anomalous Pulmonary Venous Connection	2	(.02), .2	(3), 4	Died 1 day PO (low CO).
TGA (Mustard Procedure)	3	1, 1, 2	8, 9, 11	
VSD	10	1, 1, 4, 4, 4, 4, 4, 6, 7, 9	7, 7, 14, 17 17, 18, 19, 22, 22, 31	
VSD with AI	2	8, 15	27, 48	
VSD with AI and PS	1	3	14	

AS = Aortic Insufficiency; AS = Aortic Stenosis; ASD = Atrial Septal Defect; CO = Cardiac Output; MR = Mitral Regurgitation; PO = Postoperative; PS = Pulmonic Stenosis; PVO = Pulmonic Vascular Obstructive Disease; TGA = Transposition of the Great Arteries; TOF = Tetralogy of Fallot; VSD = Ventricular Septal Defect; ( ) = Age & Weight of Patient(s) Who Expired.

Data Analysis

Data were analyzed according to the unpaired t test. The x^2 test for 2 $\times$ 2 contingency tables was used to analyze the frequency of serious hemorrhage. The Mann-Whitney test was used to compare the ratio of protamine dose to heparin dose. The null hypothesis was rejected when $p < 0.5$. All data were expressed as mean $\pm$ standard error.

Results

Group I patients did not differ significantly from Group II patients with respect to age, body weight, preoperative hematocrit, and rate of blood loss (Table III). Group II patients received 34% more heparin ($p < 0.001$) than Group I patients, and also had lower ($p < 0.02$) protamine-to-heparin ratio. Cardiopulmonary bypass times were shorter in Group II than in Group I ($p < 0.05$). This was because three patients in Group I required unusually long periods of CPB. Group II patients required chest tubes for a shorter time ($p < 0.02$) and lost less blood ($p < 0.001$) postoperatively. Serious postoperative hemorrhage occurred in 25 Group I patients (44%) and in ten Group II patients (18%). This difference was significant at the $p < 0.005$ level. One patient in Group II required secondary exploration for bleeding.

Discussion

Despite advances in the preoperative assessment of blood coagulation, improvements in heart-lung machine design, and reductions in mechanical trauma associated with CPB, excessive postoperative bleeding remains a serious complication. The incidence of life-threatening hemorrhage after CPB is reported at between 5% and 25%.[8,9] Since the introduction of the ACT method of monitoring anticoagulant therapy during CPB, a decrease in postoperative blood loss in patients with acquired heart disease has been reported.[5,7] Some authors have failed to confirm this observation but still advocate the use of the ACT method intraoperatively.[3,6]

In the present study of infants and children with congenital heart disease, reduced postoperative blood loss in the ACT group may have been due to a number of factors. Because patients in Group I (non-ACT) received 1.62 times as much protamine as heparin, this excess protamine may have acted as an anticoagulant, with deleterious cardiovascular effects.[8,10] The empirical anticoagulation protocol used in Group I may also have been the cause of inadequate anticoagulation. The formation of microclots may have produced a consumption coagulopathy. In two cases, the arterial-line filters became seriously occluded during CPB. In five pediatric patients undergoing open heart surgery for congenital defects, Young and associates[9] found limited amounts of debris in the car-

diotomy reservoir filters when the ACT was kept within a range of 400-600 sec. If the ACT had been measured in our Group I patients, the levels might have been found inadequate (< 400 sec) to insure proper anticoagulation.

In our Group II patients, the mean dosage of heparin (4.35 mg/kg) was greater than that reported by other authors for adults,[3,6] but was within the range reported by Akl and associates[3] for 20 pediatric patients. Jaberi and colleagues[10] and Akl and associates[3] have demonstrated that, because pediatric patients are less sensitive than adults to heparin, they require higher dosages to reach the same level of

TABLE III. Statistical Comparison of Group I and Group II Patients

	Group I (N = 57)	Group II (N = 57)
Age (yrs)	6.90 ± 0.65* (0.42-22.0)	6.83 ± 0.62 (0.02-20.0)
Weight	23.56 ± 2.23 (3.87-73.75)	23.76 ± 0.71 (3.3-48.8)
Hematocrit (%)	40.39 ± 0.56 (30.0-54.7)	41.15 ± 0.92 (30.5-62.8)
Time on CPB[1] (min)	104.51 ± 7.1 (17-278)	82.56 ± 6.77** (20-196)
Heparin Dose (mg/kg)	3.24 ± 0.14 (1.95-4.65)	4.35 ± 0.17§ (1,8-7.87)
Protamine Dose (mg/kg)	5.15 ± 0.26 (1.57-11.01)	4.97 ± 0.26 (2.02-9.07)
Protamine/Heparin Ratio	1.62 ± 0.07 (0.32-2.75)	1.15 ± 0.05*** (0.46-2.13)
Postoperative Blood Loss (ml/kg)	49.1 ± 6.02 (5.5-162.52)	23.7 ± 2.80 (4.1-99.64)
Duration of Postoperative Blood Loss (hrs)	49.2 ± 3.3 (7.5-133.0)	36.24 ± 1.82*** (3-77)
Bleeding Rate (ml/kg/hr)	1.21 ± 0.28 (0.14-14.99)	0.68 ± 0.08 (0.17-3.85)
Serious Hemorrhage[2] (no. of patients)	25	10†

* = Mean ± standard error (range)
** = $p < 0.05$
*** = $p < 0.02$
† = $p < 0.005$
§ = $p < 0.001$
[1]Three patients in Group I were on CPB >200 min. If these patients are excluded, the difference in time on CPB is no longer significant; however, all other parameters remain the same
[2]Serious hemorrhage is defined as loss >50% of calculated blood volume.

anticoagulation. The protamine dosages administered to our Group II patients were also higher than those reported by other authors using the ACT method, but this difference reflected our increased heparin requirements. In Group II patients, the mean protamine/heparin ratio of 1:15 was comparable to the ratios reported by other authors.[6,7]

Our data might suggest that CPB time was the prime determinant of the differences in postoperative blood loss in both groups. Whereas no patient in Group II had a CPB time longer than 200 minutes, three patients in Group I were on CPB longer than 200 minutes. If these three cases are discounted, the difference in pump time is no longer statistically significant ($p < 0.2$), although all other data (heparin, protamine/heparin ratio, blood loss, time of postoperative blood loss, and serious hemorrhage) remain significant. Therefore, time on CPB was not an important factor in determining differences in postoperative blood loss.

At our institution, few patients have required reoperation to control postoperative bleeding. During the current study, only one child (in Group II) underwent secondary exploration. From 1973 to 1976, which was prior to our use of the intraoperative ACT method, seven of 265 (2.6%) infants and children underwent re-exploration. From 1976 through 1979, three of 249 patients (1.2%) in whom the ACT method was used required exploration for bleeding.

We have found the ACT method useful for confirming satisfactory anticoagulation under unusual circumstances. By ascertaining adequate anticoagulation before CPB, the surgeon can prevent inadvertent subcutaneous injection of heparin through an infiltrated intravenous line. Because heparin activity may vary among different vials, and heparin metabolism may vary during CPB, the ACT method is useful for accurately predicting protamine requirements. This is often valuable with infants who have undergone profound hypothermia, a technique that is popular in the repair of complex congenital cardiac anomalies.

Our data indicate that the ACT provides an accurate method of monitoring anticoagulant therapy during CPB in infants and children with congenital heart disease. In our patients, heparin dosage was significantly higher with the ACT method than with use of an empiric formula. Total postoperative blood loss was also significantly decreased. We recommend the ACT method for the management of anticoagulation during CPB in pediatric patients undergoing surgery for congenital heart disease.

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