Extended Extracorporeal Support Utilizing Minimal Heparin and Iloprost (ZK36374)

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Abstract

Iloprost (ZK36374), a prostacyclin analogue, has been shown to preserve platelet ultrastructure and reactivity. In an effort to reduce adverse platelet alterations, iloprost was utilized in three patients undergoing extended extra-corporeal support (EECS).

EECS times ranged from 21 to 46 hours. One patient was able to be weaned from EECS. Iloprost allowed EECS in one patient who was heparin sensitive. All three patients demonstrated no platelet aggregation when challenged by ADP during iloprost infusion. Platelet reactivity returned to normal in the patient who was successfully weaned from EECS after iloprost was discontinued. Iloprost allowed EECS to be performed with minimal heparinization.

We conclude that minimal heparinization and iloprost may be a valuable addition for those patients requiring extended extra-corporeal support.

Introduction

Investigators have shown that while circulation of blood through an extra-corporeal circuit is known to affect several hemostatic functions, "acquired platelet dysfunction appears to be the most significant abnormality."[1] Contact of the blood to the foreign surfaces of the extra-corporeal circuit reduces both platelet number and function.[2] This leads to prolonged bleeding times and significant blood loss. These platelet abnormalities can be even more pronounced when the extra-corporeal circuit is used for extended support of a patient exceeding 12 hours.[3-4]

Recent reports in the literature seem to indicate that iloprost (ZK36374),[a] a prostacyclin analogue, may mitigate some of these platelet alterations.[5] Iloprost is an effective inhibitor of platelet reactivity to ADP, in animal as well as clinical trials.[6-7] Platelet reactivity as well as numbers are regained following termination of iloprost at the conclusion of extra-corporeal support.

During the course of clinical trials utilizing iloprost, three patients were presented with an urgent need for extended extra-corporeal support. Because of the proven ability of iloprost to inhibit platelet reactivity, we obtained special permission to utilize iloprost in an attempt to reduce the platelet alterations and bleeding that occurs with extra-corporeal support.

Patient Summary

Patient 1 (JAM) was an 18-year-old male involved in a motor vehicle accident, suffering from multiple trauma, including a closed head injury, fractures of the right femur, left tibia, fibula, and mandible. He also had multiple lacerations and a splenic tear. He underwent a splenorrhaphy upon admission and was placed in a barbiturate coma for his head injury. Over the next few days, he developed adult respiratory distress syndrome (ARDS) with progressive deterioration of respiratory function. His respiratory status became such that he could not be maintained on 100% oxygen and 18 cm. of PEEP. In an effort to maintain oxygenation EECS was instituted in conjunction with iloprost.

Patient 2 (JPJ) was a 28-year-old male with a history of scarlet fever as a child, who was diagnosed as having mitral valve prolapse in 1982. He did well until November 1986 when he presented with flu-like symptoms. He indicated that he had been using cocaine intravenously on a daily basis. He was diagnosed as having bacterial endocarditis of staphylococcal origin

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and mitral insufficiency. Echocardiogram indicated vegetations on the anterior mitral leaflet. He was admitted and placed on antibiotic therapy for 30 days. He was accepted for the iloprost protocol and underwent mitral valve replacement. He tolerated the surgery well; however, it was noted that he exhibited some sensitivity to heparin and may have suffered platelet embolization to the kidneys. The evening of surgery, he became hypotensive. Cardiac index fell to 0.91 LPM, cardiac output was 1.6 LPM, SVO2 fell to 22% and the SVR rose to 2400. An intra-aortic balloon (IAB) was inserted and an infusion of cathecholamines was begun. Echocardiogram demonstrated that the inferior and posterior walls were akinetic. Despite high doses of cathecholamines and IABP support the patient continued to deteriorate. EECS was instituted and because of his previous demonstration of heparin sensitivity, an iloprost infusion was begun.

Patient 3 (GM) was a 57-year-old male in good health until he developed chest pain and shortness of breath. He was diagnosed as having an acute myocardial infarction. Acute intervention was not attempted because of the delay in the patient arriving for treatment. The patient continued to have pain and coronary arteriography demonstrated severe triple vessel disease with an ejection fraction of 15%. The patient requested medical therapy which was continued. Two days later the patient developed a murmur. He was restudied and a large ventricular septal defect (VSD) was identified. Because of his deteriorating condition, an IAB was inserted; and he underwent a patch closure of the VSD and a double coronary artery bypass. He was weaned from cardiopulmonary bypass with the use of cathecholamines and IABP support. He did well until 48 hours postoperatively when he removed the IAB. It was reinserted, however his hemodynamic condition deteriorated, despite maximal cathecholamine support. EECS and iloprost were instituted because of his good neurological status.

Materials and Methods

The EECS system consisted of standard heart/lung tubing,[b] a centrifugal pump,[c] and a membrane oxygenator. A hollow fiber[d] was used on two patients and a spiral coil[e] was used on the third (JAM). The system was primed with 1000 cc's of a balanced electrolyte. All patients and/or their family gave informed consent to the use of iloprost and EECS. Permission was obtained from the manufacturer of iloprost for the compassionate use of this drug.

Vascular access was from the patient's femoral vein to the centrifugal pump and then through the oxygenator. The return of oxygenated blood was directly from the oxygenator to a graft sewn end to side to the axillary artery. Ten minutes prior to cannulation, 12 ng/kg of iloprost infusion was started. Two minutes prior to cannulation, 7,000 units of sodium heparin was given as a bolus injection. After cannulation EECS flow was started and maximal flows were obtained. EECS flows were regulated to maintain venous saturation above 60%.

The oxygenator was ventilated with an FiO_2 ranging from 80 to 100% with a sweep of 1 liter of compressed air. Patient ventilator settings were regulated to achieve normal arterial blood gas results.

Activated clotting times (ACT) were done initially and every 30 minutes of EECS time. ACTs were maintained around 300 seconds, with the use of a heparin drip.

Laboratory tests included hemoglobin, hematocrit, electrolytes, creatine, BUN, glucose, platelets, protein, albumin, calcium, arterial blood gases, and oxygenator blood gases throughout the procedure. Electrocardiogram, arterial and pulmonary artery pressure and venous saturation were continuously monitored through indwelling catheters.

Because of the vasodilatory effects of iloprost, the infusion was slowly reduced to 3 ng/kg for the duration of EECS. Cathecholamines were infused to maintain arterial pressure above 50 mm Hg.

Patient body temperatures were maintained at 35° C. with the use of a heating blanket. All patients were kept paralyzed and sedated.

The first attempt at weaning the patient from the EECS system did not occur until after 12 hours of support. Except during weaning EECS flow was not allowed to drop below one LPM. If the patient was able to be weaned, the heparin infusion was stopped and the iloprost infusion was increased to 12 ng/kg until decannulation and repair of the femoral and axillary vessels, at which time the infusion was discontinued. All laboratory work was repeated 15 minutes after discontinuation of iloprost.

Results

Patient 1 (JAM) underwent EECS for 53 hours. He experienced marked improvement of lung oxygenation. 15 hours into EECS increased bleeding was noted from the cannulation sites and iloprost was discontinued for five hours. 51 hours into EECS, intra-abdominal bleeding was noted. The iloprost was discontin-

b TBG63, American Bentley, Irvine, CA 92714
c Model 600, Bio-Medicus, Inc., Minneapolis, MN 55344
d SK1380, J & J Cardiovascular, King of Prussia, PA 19406
e 25002A, SciMed Life Systems, Minneapolis, MN 55441

ued. However, the bleeding increased which coincided with a drop in the platelet count (Figure 1). It was felt by the patient's referring physician that surgical intervention not be attempted. EECS was then discontinued and the patient expired. An autopsy was not performed.

Patient 2 (JPJ) was placed on EECS for 21 hours. During this time he showed marked improvement in ventricular function and wall motion. Platelet aggregation demonstrated no response when challenged by ADP. His platelet count remained fairly stable (Figure 1). The patient was weaned from EECS in satisfactory condition and platelet function returned to normal. However, over the next 10 days, the patient's condition deteriorated. Renal failure occurred, and dialysis was started. He suffered a cardiac arrest on the 12th day and could not be resuscitated. Autopsy revealed multiple fungal abscesses throughout the heart, brain, lungs, and kidneys. These were thought to be related to his IV drug abuse.

Patient 3 (GM) was placed on EECS for a period of 37 hours. His condition appeared to improve and his neurological status remained intact. However multiple attempts at weaning were unsuccessful. Because of his status, arrangements to transfer the patient to another institution for cardiac transplantation were begun. His platelet count remained stable until 25 hours into EECS. At 32 hours the patient began to bleed from multiple sites and he required large amounts of blood and fluid replacement. He eventually arrested and could not be resuscitated. An autopsy was not performed.

All three patients showed an improvement in their hemodynamic status while on EECS initially. Patient arterial blood gases were satisfactory throughout the EECS procedures (Figures 2–4). Platelet aggregation studies demonstrated no response when challenged by ADP. Mean arterial pressures averaged about 50 mmHg throughout the procedures. There was a slightly positive correlation (r = 0.2888) between pump flow and MAP (Figure 5). ACTs averaged 280 seconds on minimal amounts of heparin (Figure 6). There was no correlation between the amount of heparin and the resultant ACT (r = 0.0044). Two of the three patients stabilized their platelet counts until about 25 hours into EECS when the counts dropped dramatically. All three patients required minimal blood replacement until the advent of spontaneous bleeding in two of the three patients.

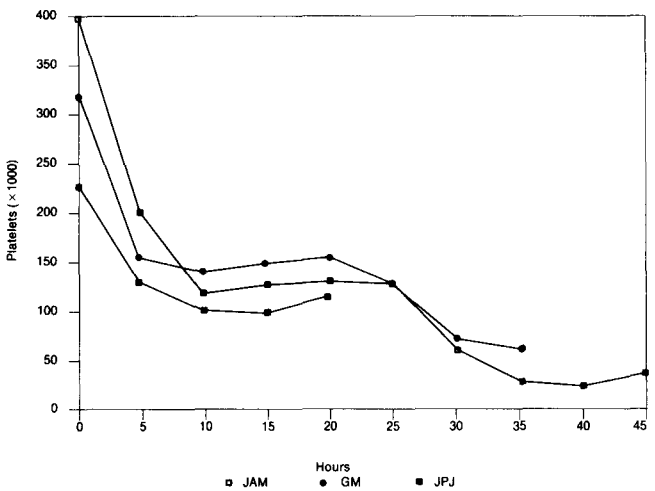

Figure 1. Platelet Count

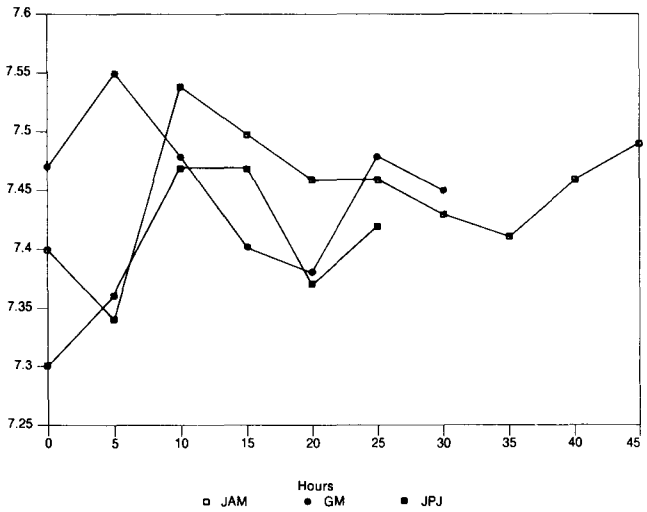

Figure 2. pH

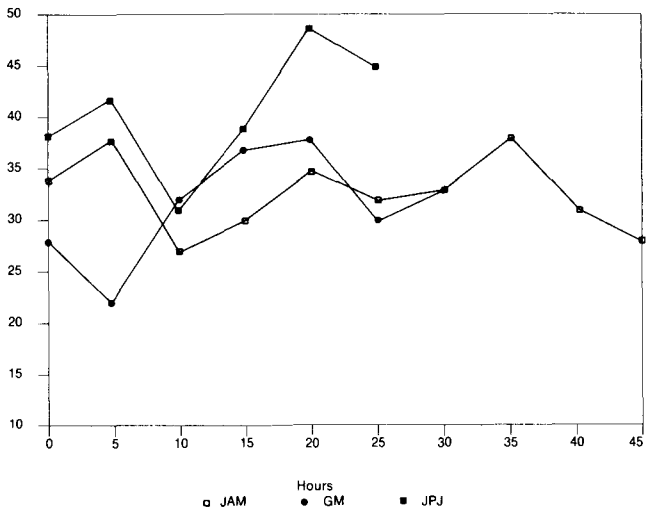

Figure 3. pCO_2

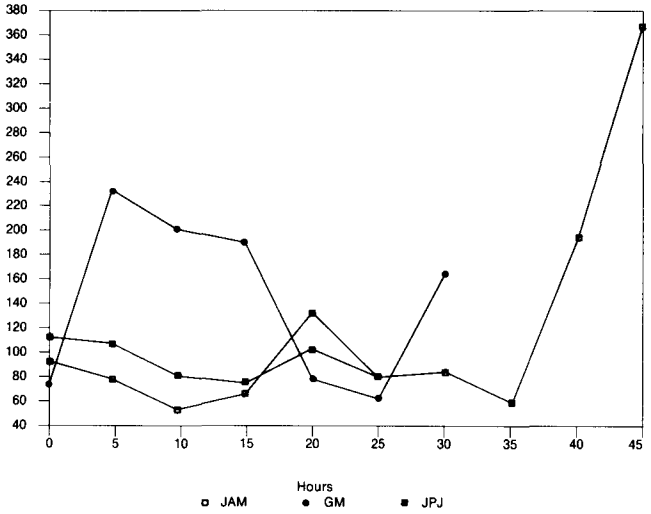

Figure 4. pO_2

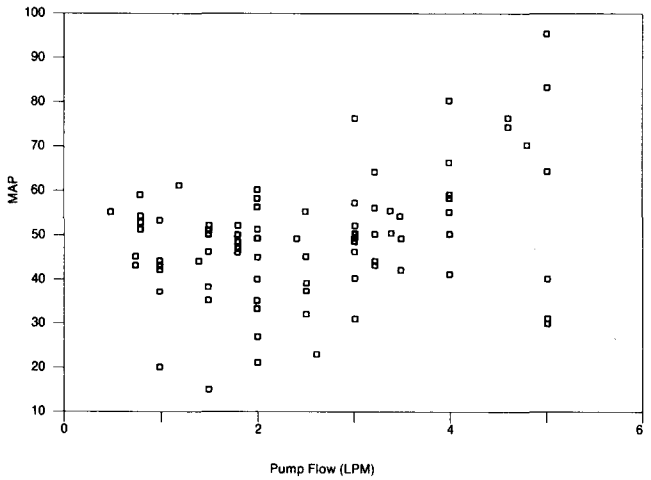

Figure 5. Pump Flow plotted against Mean Arterial Pressure (MAP). There was a slightly positive correlation (r = 0.2888).

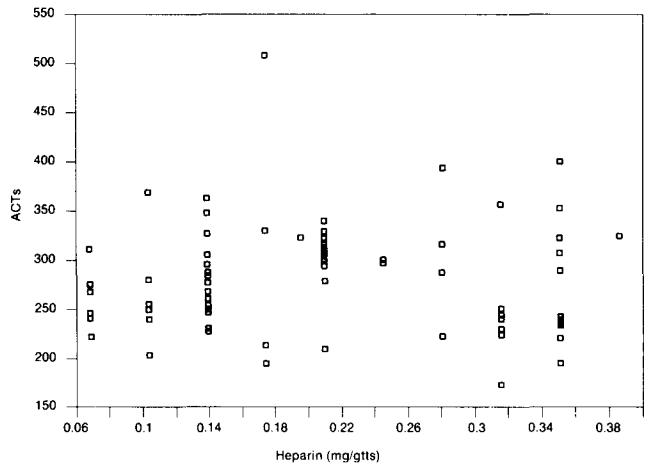

Figure 6. Heparin administration plotted against Activated Clotting Times (ACT). There was no correlation (r = −0.0044).

Discussion

Worldwide experience with EECS has shown that a major complication is bleeding.[8-9] The best results of EECS are in infants and neonates[10-11] There has been limited experience with adult EECS in the past several years, although there is an occasional report of its use. Among the reasons cited are ARDS,[12-13] postoperative cardiac failure refractory to IABP and inotropes,[14] severe asthma attacks,[15] and pulmonary lavage.[16]

Bleeding associated with EECS can usually be traced to a loss of platelet function and numbers caused by the contact of the blood to the synthetic surfaces of the extra-corporeal circuit over an extended period. Iloprost has been shown to be effective in preventing these surface-induced changes. Therefore it was thought that the use of iloprost may help mitigate these platelet alterations over the extended period of extra-corporeal support.

The results indicated that there was some protection in the earlier stages of EECS. However two of the patients experienced a continual loss of platelets, despite replacement, that resulted in spontaneous bleeding. EECS was terminated and the patients expired. It was encouraging to note however that in Patient 1 (JAM), there was a significant improvement in pulmonary function which may indicate that iloprost has a role in reversing platelet aggregation which could be a causative factor ARDS.

Patient 2 (JPJ) was the only patient to be successfully weaned from EECS. He also exhibited no spontaneous bleeding and required no platelet replacement. He did exhibit some platelet loss post-EECS, but it was secondary to the use of amrinone. He also exhibited some degree of heparin sensitivity during earlier testing. The use of iloprost allowed us to institute EECS in an effort to reverse his deteriorating myocardial function. It is important to note however that the support period was the shortest of the three patients which may have allowed us to escape the continued platelet loss. His death was attributed to the abscesses caused by *Candida* and *aspergillosis* fungal infections. These organisms have been implicated in the mortality of IV drug abusers.[17-18]

Iloprost is still an experimental drug which is currently undergoing clinical trials. Compassionate use permission had to be obtained from the manufacturer as well as the hospital investigational drug use committee. All patients and their families were informed as to the use of iloprost and consent was obtained.

Although iloprost will continue to need further investigational work into its role in EECS, it may be a valuable tool in preventing surface induced platelet changes over a long period. The use of minimal heparin for anticoagulation and iloprost may prove to be

invaluable for those patients requiring long term support.

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Question from the Audience

Question: Can you tell me what is the average dose of iloprost for administration and how to reverse it? Also, what is the half life of iloprost?

Answer: We placed all patients on 12 nanograms per kilo. Because of the vasodilatory effect of iloprost, after bypass was established and we were comfortable with everything, we dropped the dosage down to 3 nanograms per kilo and maintained it at that level throughout bypass. When we were able to wean the one patient that we were able to wean, we turned off the heparin drip and ran the iloprost back up to 12 nanograms until we were decannulated. There is no reversal. When you turn off the iloprost, the effect ends right there at that spot and the platelets start functioning again.