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A Comparison of Washed Red Blood Cells Versus *Packed Red Blood Cells (AS-1) for Cardiopulmonary Bypass Prime and Their Effects on Blood Glucose Concentration in Children*

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The effects on blood glucose concentrations of packed red blood cells (AS-1) (group I) *versus* washed red blood cells (group II) for cardiopulmonary bypass prime were compared in 20 infants weighing less than 10 kg undergoing cardiac surgical procedures. All patients were anesthetized with N_2O/O_2/isoflurane/fentanyl and received lactated Ringer's solution prior to bypass. Blood glucose concentrations prior to bypass were 85 ± 15 mg/dl (mean ± SD) in group I and 81 ± 14 mg/dl in group II. Blood glucose concentrations were 210 ± 21 mg/dl *versus* 78 ± 14 mg/dl ($P < 0.001$) 10 min after initiation of bypass, 241 ± 48 mg/dl *versus* 107 ± 28 mg/dl ($P < 0.001$) prior to separation from bypass, and 214 ± 52 mg/dl *versus* 97 ± 19 mg/dl ($P < 0.001$) after protamine administration in group I and group II, respectively. The use of washed red blood cells for cardiopulmonary bypass priming solution in infants significantly attenuates the increase in blood glucose concentration otherwise observed during cardiopulmonary bypass. (Key words: Surgery, cardiac: cardiopulmonary bypass. Glucose: hyperglycemia. Packed red blood cells: transfusion. Pediatrics: congenital heart disease.)

NEUROPSYCHIATRIC complications following cardiopulmonary bypass may occur in up to 28.9% of patients.[1] Severe permanent neurologic deficits occur in approximately 1% of patients after cardiac surgery.[2,3] Causative factors may include cerebral vascular disease, air or particulate emboli, and perioperative hypotension, all leading to focal or global ischemia. A correlation between blood glucose concentration and outcome following cerebral ischemia has been demonstrated in primates and some humans.[4–6] Hyperglycemia in brain tissue prior to ischemia may result in significantly greater intracellular lactic acid levels following ischemia and consequent increase in acidosis, depletion of high-energy phosphates, structural damage, and reperfusion abnormalities.[7–9] However, these observations are not without controversy. Clearly, the effect of glucose concentration on neurologic damage during ischemia in humans has not yet been completely defined.[10,11]

Cardiac surgical procedures in infants frequently result in large increases in blood glucose concentrations during cardiopulmonary bypass.[12,13] There has been no prospective randomized controlled study performed to demonstrate that hyperglycemia during cardiopulmonary bypass or total circulatory arrest results in adverse neurologic outcome. However, in a small group of infants[6] who underwent profound hypothermic circulatory arrest, a trend was noted towards increased incidence of neurologic deficits in infants with blood glucose concentrations above 215 mg/dl immediately prior to initiation of circulatory arrest.

Because in certain instances the adverse effects of elevated glucose concentrations outweigh potential benefits obtained from glucose administration, it is recommended to maintain the blood glucose concentration within normal limits whenever brain ischemia may occur intraoperatively.[10]

Removal of glucose-containing solutions in the immediate preoperative period is ineffective in preventing elevations of blood glucose levels during cardiopulmonary bypass.[14] Due to the small blood volume of infants relative to the volume required to prime the cardiopulmonary bypass apparatus, red blood cells must be added to the circuit to prevent excessive hemodilution. Red blood cells suspended in AS-1 preservative solution (adenine-glucose-mannitol-saline) contain glucose concentrations in excess of 400 mg/dl and could contribute to increases in blood glucose concentrations upon institution of cardiopulmonary bypass in infants.[15] Washing of red blood cells with isotonic saline decreases glucose concentrations to 30–60 mg/dl. The intent of this randomized prospective study was to determine if washed red blood cells when used for bypass prime in infants can prevent the large increase in blood glucose concentrations during cardiopulmonary bypass observed when red blood cells suspended in AS-1 preservative solution are used.

Methods

Twenty infants weighing less than 10 kg scheduled for cardiac surgical procedures were included in the study. The study was approved by the Mayo Clinic Institutional Review Board and informed consent was obtained from the parents or legal guardian(s) of each patient. The pa-

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tients were prospectively randomized into two groups. Group I patients received packed red blood cells (AS-1) and group II patients received washed red blood cells for cardiopulmonary bypass prime. Children with diabetes mellitus or other endocrine disturbances that could result in an abnormal response to glucose were excluded.

None of the infants studied received iv fluids prior to entering the operating room. All children were monitored by ECG, blood pressure cuff, precordial stethoscope, and pulse oximetry. General anesthesia was induced in all patients with N_2O/O_2/isoflurane. The total amount of fentanyl received by each patient before and on initiation of cardiopulmonary bypass was 67 ± 51 μg/kg (group I) and 82 ± 49 μg/kg (group II). The difference was not statistically significant.

Tracheal intubation was performed after adequate muscle relaxation was obtained with pancuronium 0.1 mg/kg. Additional monitoring included femoral arterial and central venous pressures, nasal temperature, and end-expired carbon dioxide concentration. Lactated Ringer's solution was the only iv fluid administered prior to cardiopulmonary bypass.

Prior to cardiopulmonary bypass, dexamethasone 0.5 mg/kg and mannitol 0.5 g/kg were given. Immediately after institution of cardiopulmonary bypass, thiopental 100 mg (10 mg/kg with a minimum of 100 mg) was administered. Nine of the 20 study patients underwent circulatory arrest which was instituted within 12 min after the start of cardiopulmonary bypass.

The bypass priming solution consisted of 250 ml albumin 5%, 220 ml fresh frozen plasma, and the amount of packed or washed red blood cells calculated to yield a hematocrit of 25% during bypass. The blood volume of all patients was calculated by multiplying their weight in kilograms by 85 ml/kg. The hematocrit used to calculate priming volumes was 65% for both packed red blood cells and washed red blood cells. Glucose concentrations ranged between 400–700 mg/dl in the packed red blood cells and 30–60 mg/dl in the washed red blood cells. The Sci-Med® membrane oxygenator (minimal priming volume 900 ml) was used in all cases. Additional red blood cells to replace intraoperative blood loss were administered in accordance to which group the patient had been randomized.

Arterial blood samples for measurement of blood gas and glucose were taken after induction (A), prior to (B), and 10 min after (C) initiation of cardiopulmonary bypass, 10 min prior to separation from bypass (D), and after protamine administration (E). The samples were immediately analyzed using alpha-stat methods for arterial blood gas analysis. Blood glucose concentrations were measured by the glucose oxidase method.

The data were analyzed using repeated measures analysis of variance within each group. Paired Student's *t* tests with Bonferroni correction were used for comparisons within each group between control (A) and each of the successive values (B, C, D, E). Between groups, paired comparisons between corresponding values at different times were carried out with Student's *t* tests after testing for equality of population variances with the F test. $P < 0.05$ was considered statistically significant. All values are reported as mean ± SD.

Results

Tables 1 and 2 describe the demographic characteristics of the subjects in each group. There were no significant differences between groups I and II except in height.

Blood glucose concentrations were significantly higher in group I patients receiving packed red blood cells at all intervals after initiation of cardiopulmonary bypass (fig. 1). Blood glucose levels were similar at 93 ± 24 mg/dl and 95 ± 24 mg/dl after induction and 85 ± 15 mg/dl and 81 ± 14 mg/dl prior to bypass in group I and group II, respectively. Two patients, one in each group, had a blood glucose concentration less than 60 mg/dl in the

TABLE 1. Demographic Data, Packed Red Blood Cell Group (Group I)

Patient	Age (months)	Height (cm)	Weight (kg)	Cardiopulmonary Bypass Time (min)	Circulatory Arrest (min)	Diagnosis
1	6	64	6	101	49	Tetralogy of Fallot
2	5	62	5.2	108	61	Complete AV canal
3	8	68	7.9	103	0	Tricuspid atresia
4	15	75	9.3	103	13 + 29	Interrupted aortic arch; pulmonary artery stenosis
5	4	61	4.8	163	10	Truncus arteriosus
6	11	72	6	80	0	Ventricular septal defect
7	7	62	7.1	75	0	Ventricular septal defect
8	16	74	7.9	69	0	Tetralogy of Fallot
9	6	60.5	5.3	98	0	Complete AV canal
10	6	67	5.5	74	34	Ventricular septal defect; patent ductus arteriosus
Mean	8.3	66.6	6.5	97		
SD	4	5.5	1.5	27		

TABLE 2. Demographic Data, Washed Red Blood Cell Group (Group II)

Patient	Age (months)	Height (cm)	Weight (kg)	Cardiopulmonary Bypass Time (min)	Circulatory Arrest (min)	Diagnosis
1	5	59	4.3	113	0	Complete AV canal
2	4	53	3.5	60	40	Ventricular septal defect
3	8	61	4.6	117	0	Complete AV canal
4	16	65	7.7	168	5 + 10	Transposition of the great arteries
5	2	58	4.7	87	42	Ventricular septal defect
6	1	51	3.5	183	26	Transposition of the great arteries
7	8	66	7.2	114	0	Complete AV canal
8	13	66	5.1	205	0	Transposition of the great arteries
9	10	67.5	6.5	111	0	Complete AV canal
10	3	59	4.2	112	0	Truncus arteriosus
Mean	7	60.6*	5.1	127		
SD	4.9	5.8	1.5	48		

* $P < 0.05$ with respect to packed red blood group.

prebypass period.¶ Glucose concentrations in the bypass priming solution prior to initiation of cardiopulmonary bypass were 374 ± 46 mg/dl in group I and 92 ± 27 mg/dl in group II ($P < 0.001$). Ten minutes after initiation of cardiopulmonary bypass, blood glucose concentrations were 210 ± 21 mg/dl in group I and 78 ± 14 mg/dl in group II ($P < 0.001$). Prior to separation from bypass, blood glucose concentration was 241 ± 48 mg/dl in group I and 107 ± 28 mg/dl in group II ($P < 0.001$). Blood glucose concentrations remained significantly different after administration of protamine 214 ± 52 mg/dl *versus* 97 ± 19 mg/dl ($P < 0.001$) in group I and group II, respectively.

Discussion

In an attempt to decrease the incidence and severity of ischemic damage to the brain during cardiopulmonary bypass and circulatory arrest, hypothermia,[16] thiopental,[17] and control of *p*H[18] and blood glucose[6] concentrations have been suggested. Decreased insulin release and inhibition of peripheral glucose use combined with elevated levels of plasma catecholamines, glucagon, and cortisol may result in elevation of blood glucose concentrations with the initiation of cardiopulmonary bypass.[19,20] In this setting, the ability to deal with large glucose loads is significantly impaired. High-dose opioid anesthesia and avoidance of glucose in the prebypass period may reduce increases in blood glucose concentrations during bypass.** However, hyperglycemia during hypothermic cardiac surgical procedures occurs in most infants and children.[10,11]

The small blood volume of infants and the high concentration of glucose in AS-1 red blood cells used to prime the cardiac bypass circuit expose these patients to a large source of exogenous glucose. The glucose concentrations in the priming solution prior to initiation of extracorporeal circulation were significantly higher in the AS-1 red blood cell group. This large glucose load in the setting of decreased glucose tolerance resulted in significantly higher glucose concentrations at all intervals measured after initiation of cardiopulmonary bypass. There was no significant difference in the anesthetic management of group I and group II patients. Likewise, the bypass priming solution was similar in both groups with the exception of the type of red blood cells administered. Therefore, the large differences in blood glucose concentrations must be attributable to the high concentration of glucose in the AS-1 preserved red blood cell units.

The avoidance of glucose-containing solutions in the prebypass period has been advocated as a means of preventing hyperglycemia during cardiac surgical procedures in children.[11] However, this does not insure control of glucose concentrations; patients in group I still experienced significant increases of blood glucose concentrations during cardiopulmonary bypass. As hypoglycemia may occur in 1–30% of fasting children prior to surgery,[21–23] glucose concentrations are closely monitored throughout the operative period. Patients in this study were NPO for 4–8 h prior to surgery and did not receive glucose-containing solutions prior to bypass, except when indicated. Two of 20 patients experienced hypoglycemia (glucose

¶ In the patient in the packed cell group, a repeat blood sample showed stabilization (59 mg/dl) of the glucose concentration, and this patient subsequently did not receive treatment because onset of cardiopulmonary bypass was imminent. The patient in the washed cell group received two doses of 150 mg/kg glucose at an interval of 15 min. This patient's blood glucose concentration increased from 35 mg/dl to 55 mg/dl up to 63 mg/dl shortly before start of cardiopulmonary bypass.

** Hickey PR, Anderson N: Deep hypothermic circulatory arrest: A review of pathophysiology and clinical experience as a basis for anesthetic management. J Cardiothorac Anesth 1:137–155, 1987.

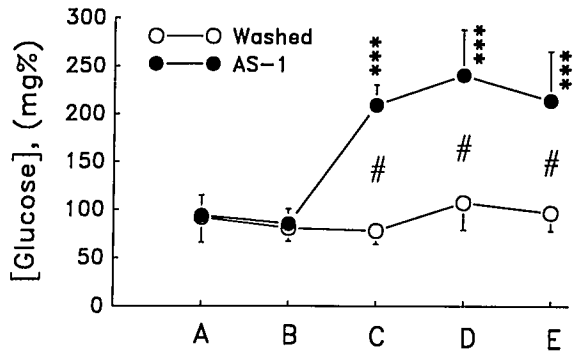

FIG. 1. Blood glucose concentrations (mean ± SD) at different stages of anesthesia in the washed red blood cell group (O) and AS-1 (●) group. ***$P < 0.001$ (Student's paired t test between B, C, D, E, and A, respectively). #$P < 0.001$ (Student's t test between washed red blood cells and AS-1 groups). A) after start of anesthesia; B) before bypass; C) 10 min after start of bypass; D) before discontinuation of bypass; E) after protamine administration.

concentration < 60 mg/dl). In group II patients, the use of fresh frozen plasma (glucose concentration 380–440 mg/dl) prevented administration of a large volume of hypoglycemic priming volume upon institution of cardiopulmonary bypass. Blood glucose concentrations of the washed red blood cell group priming solution averaged 92 ± 27 mg/dl and no hypoglycemia occurred during bypass. In some institutions, CPDA-1 red blood cells are used in the priming solution for small infants on cardiopulmonary bypass. Compared with fresh red cells stored in AS-1 solution, fresh CPDA-1 red cells contain approximately 50% less glucose. Therefore, the use of CPDA-1 red cells as priming solution for small infants is expected to cause less hyperglycemia during bypass. However, few blood banks routinely continue to provide CPDA-1 red cells (citrate-phosphate-dextrose-adenine-1) because their shelf life is shorter than that of AS-1 red blood cells.

In conclusion, glucose concentrations were significantly higher in infants weighing less than 10 kg undergoing cardiac surgical procedures when packed red blood cells stored in AS-1 solution were used as a component of the bypass priming solution when compared with washed red blood cells.

References

1. Slogoff S, Girgis KZ, Keats AS: Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass. Anesth Analg 61:903–911, 1982
2. Bojar RM, Najafi H, DeLaria GA, Serry C, Goldin MD: Neurological complications of coronary revascularization. Ann Thorac Surg 36:427–432, 1983
3. Furlan AJ, Breuer AC: Central nervous system complications of open-heart surgery. Stroke 15:912–915, 1984
4. Lanier WL, Stangland KJ, Scheithauer BW, Milde JH, Michenfelder JD: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. ANESTHESIOLOGY 66:39–48, 1987
5. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F: Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 74: 540–544, 1983
6. Steward DJ, DaSilva CA, Flegel T: Elevated blood glucose levels may increase the danger of neurologic deficit following profoundly hypothermic cardiac arrest (letter). ANESTHESIOLOGY 68:653, 1988
7. Welsh FA, Ginsberg MD, Rieder W, Budd WW: Deleterious effect of glucose pretreatment on recovery from diffuse cerebral ischemia in the cat. II. Regional metabolite levels. Stroke 11:355–363, 1980
8. Rehncrona S, Rosen I, Siesjo BK: Brain lactic acidosis and ischemic cell damage. I. Biochemistry and neurophysiology. J Cereb Blood Flow Metab 1:297–311, 1981
9. Kalimo H, Rehncrona S, Soderfeldt B, Olsson Y, Siesjo BK: Brain lactic acidosis and ischemic cell damage. II. Histopathology. J Cereb Blood Flow Metab 1:313–327, 1981
10. Sieber FE, Smith DS, Traystman RJ, Wollman H: Glucose: A reevaluation of its intraoperative use. ANESTHESIOLOGY 67:72–81, 1987
11. Ibayashi S, Fujishima M, Sadoshima S, Yoshida F, Shiokawa O, Ogata J, Omae T: Cerebral blood flow and tissue metabolism in experimental cerebral ischemia of spontaneously hypotensive rats with hyper-, normal and hypoglycemia. Stroke 17:261–266, 1986
12. Kunkel R, Hagel S, Richter JA, Habermeyer P, Sebening F: The effects of deep hypothermia and circulatory arrest on systemic metabolic state of infants undergoing corrective open heart surgery: A comparison of two methods. Thorac Cardiovasc Surg 27:168–177, 1979
13. Benzing G III, Francis PD, Kaplan S, Helmsworth JA, Sparling MA: Glucose and insulin changes in infants and children undergoing hypothermic open-heart surgery. Am J Cardiol 52: 133–136, 1983
14. Zucker HA, Nicolson SC, Steven JM, Jobes DR, Betts EK: Blood glucose concentrations during anesthesia in children undergoing hypothermic circulatory arrest (abstract). ANESTHESIOLOGY 69: A739, 1988
15. Heaton A, Miripol J, Aster R, Hartman P, Dehart D, Rzad L, Grapka B, Davisson W, Buchholz DM: Use of Adsol® preservation solution for prolonged storage of low viscosity AS-1 red blood cells. Br J Haematol 57:467–478, 1984
16. Michenfelder JD, Theye RA: Hypothermia: Effect on canine brain and whole body metabolism. ANESTHESIOLOGY 29:1107–1112, 1968
17. Nussmeier NA, Arlund C, Slogoff S: Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. ANESTHESIOLOGY 64:165–170, 1986
18. Blayo MC, LeCompte Y, Pocidalo JJ: Control of acid-base status during hypothermia in man. Respir Physiol 42:287–298, 1980
19. Kuntschen FR, Gallitti AN, Hahn C: Glucose-insulin interactions during cardiopulmonary bypass: Hypothermia vs. normothermia. J Thorac Cardiovasc Surg 91:451–459, 1986
20. Kuntschen FR, Galletti PM, Hahn C, Arnulf JJ, Isetta C, Dor V: Alterations of insulin and glucose metabolism during cardiopulmonary bypass under normothermia. J Thorac Cardiovasc Surg 89:97–106, 1985
21. Bevan JC, Burn MC: Acid-base and glucose levels of pediatric cases at induction of anaesthesia: The effects of preoperative starvation and fasting. Br J Anaesth 45:115–118, 1973
22. Watson BG: Blood glucose levels in children during surgery. Br J Anaesth 44:712–715, 1972
23. Welborn LG, McGill WA, Hannallah RS, Nisselson CL, Ruttimann UE, Hicks JM: Perioperative blood glucose concentrations in pediatric out-patients. ANESTHESIOLOGY 65:543–547, 1986