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Removal of Glucose from the Cardiopulmonary Bypass Prime: A Prospective Clinical Audit

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Abstract: To quantify our decision for the removal of glucose and the use of mannitol as a substitute osmotic agent in the cardiopulmonary bypass prime, we conducted a prospective clinical audit to evaluate the effects of this change on patient outcomes. Data were prospectively collected for 172 consecutive routine cardiac surgery patients. The first 85 patients (Surgeon A, 42 patients [Group 1], Surgeon B, 43 patients [Group 2]) received 1000 mL Plasmalyte 148 + 5% glucose as per institutional protocol. The remaining priming volume for each group consisted of 500 mL hemaccel or 4% albumin, 50 mL 8.4% sodium bicarbonate, 100 mL Hartmann's solution. The change to a glucose-free prime was then initiated, substituting Plasmalyte 148 (without 5% glucose) for the Plasmalyte 148 + 5% glucose, in addition 12.5 g mannitol was administered following delivery of cardioplegia to the patients operated on by Surgeon B. Surgeon A would not include mannitol at this time. Forty-one patients operated by Surgeon A (Group 3) subsequently received Plasmalyte 148, and 46 patients operated on by Surgeon B (Group 4) received Plasmalyte 148 plus mannitol. Analysis was performed stratified by surgeon to quantify the effects of removing glucose from the prime. Comparisons were made between groups 1 and 3, and 2 and 4. Net fluid changes were recorded from pre-CPB, up to 24-h postoperatively. Intraoperative data collection included serum glucose, hematocrit, osmolality, return to rhythm, arrhythmias, and blood transfusions. Post-operative variables, including cardiac enzymes, arrhythmias, intubation time, length of stay, and mortality were also collected. Removal of glucose from the CPB prime resulted in a lower serum glucose concentration (mmol/L) during CPB (Gp 1 [13.6] vs. Gp 3 [5.4]; Gp 2 [14.7] vs. Gp 4 [5.4], $p < .05$). The addition of 12.5 g of mannitol to the CPB prime resulted in a significantly lower net fluid gain (mL) 24 h postoperatively (Gp 2[2792] vs. Gp 4 [1970], $p < .05$) and greater CPB hematocrit (%) (Gp 2 [24.3] vs. Gp 4 [26], $p < .05$). No other results were found to be significant (except CPB plasma osmolality (Groups 2 and 4) and sodium concentration [Groups 1 and 3]). The results of our audit provide an evidence base to support our change in practice to utilize nonglucose primes. **Keywords:** glucose, mannitol, cardiopulmonary bypass, clinical audit. *JECT. 2004;36:240–244*

INTRODUCTION

The evolution of priming solutions used for cardiopulmonary bypass (CPB) has involved a trend toward asanguinous solutions as the major constituent. The hemodilution and subsequent reduction in viscosity created by the use of these solutions increases flow through the microcirculation, and oxygen delivery to the tissues is still maintained. In this way, a compromise is reached in order to provide optimal physiological conditions during CPB. One of the principles of selection of priming solutions is to maintain normal physiological parameters within the fluid compartments of the body, both in terms of electrolyte composition and reduction of fluid shifts. We used Plasmalyte 148 solution containing 5% glucose (Baxter Healthcare, Old Toongabbie, NSW, Australia) as part of our CPB prime to maintain osmolality, and to provide a substrate for energy production during myocardial ischemia.

Following a literature review on the use of glucose in the CPB prime, we concluded that the evidence suggests that hyperglycemia may contribute to worsened postoperative outcomes. According to a review on the glucose modulation of ischemic brain injury (1), hyperglycemia is associated with a worsening of post ischemic brain injury. Mechanisms for this injury include intracellular lactic acidosis and formation of free radicals (1–3). A reduction in

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plasma glucose concentration during cardiac surgery has been shown to reduce the rate of wound infections in diabetic patients (4) as a result of improved neutrophil function. Hyperglycemia has also been identified as a risk factor for renal dysfunction following coronary artery bypass surgery (5).

To remove glucose from the prime, a substitute osmotic agent should be used. Osmitrol has been shown to reduce positive fluid balance during cardiopulmonary bypass (6), and to cause an increased diuresis during CPB (7). To quantify the outcomes of our decision for the removal of glucose and the use of mannitol as a substitute osmotic agent, we conducted a prospective clinical audit to evaluate the effects of this change.

MATERIALS AND METHODS

The audit involved prospective data collection on 172 consecutive routine cardiac surgery patients performed by two surgeons. The first 85 patients (Surgeon A, 42 patients [Group 1], Surgeon B, 43 patients [Group 2]) received 1000 mL Plasmalyte 148 + 5% glucose as per institutional protocol. The remaining priming volume for each group consisted of 500 mL *Haemaccel* (Hoechst Marion Roussel, Lane Love, NSW, Australia) or 4% albumin (CSL), 50 mL 8.4% sodium bicarbonate (Pharmacia and Upjohn, Bentley, WA, Australia), 100 mL Hartmann's solution (Baxter Healthcare, Old Toongabbie, NSW, Australia). The change to a glucose-free prime was then initiated, substituting Plasmalyte 148 (without 5% glucose) for the Plasmalyte 148 + 5% glucose, in addition 12.5 g mannitol was administered following delivery of cardioplegia to the patients operated on by Surgeon B. Surgeon A would not include mannitol at this time. Forty-one patients operated on by Surgeon A (Group 3) subsequently received Plasmalyte 148, and 46 patients operated by Surgeon B (Group 4) received Plasmalyte 148 plus mannitol. To quantify the effects of removing glucose from the prime, analysis was performed stratified by surgeon. Comparisons were made between groups 1 and 3, and 2 and 4.

General anesthesia was induced with fentanyl (10–30 μg/kg) and supplemented with isoflurane and/or propofol. Cardiopulmonary bypass was instituted using ascending aortic cannulation and either two-stage or bicaval venous cannulation via the right atrium. The perfusion circuit components consisted of a Capiox SX25 oxygenator (Terumo Corporation, Tokyo, Japan), Quart 40 μm arterial filter (Jostra, Hirrlingen, Germany), 0.2 μm prebypass filter (Pall, East Hills, NY), and Myotherm cardioplegia heat exchanger (Medtronic, Minneapolis, MN). Cannulas used were DLP 22Fr or Argyle 21Fr arterial, Sarns two-stage 36/51Fr or dual 36 Fr venous. A cardiac index of 1.6–2.4 L/min/m^2 and a mean arterial pressure >40 mmHg was maintained during CPB. Myocardial protection consisted of antegrade infusion of blood/crystalloid cardioplegia solution (4:1 ratio) at 32°C, with a potassium concentration of 25 mEq/L or 30 mEq/l. Patient systemic temperature was maintained at 34°C during aortic cross clamping.

Administered fluid was recorded pre, during, post CPB, and in the intensive care unit (ICU) up to 24 h postoperatively. Fluid loss was recorded as urine and blood loss during the same time period. Net fluid gain was calculated as the total fluid volume administered minus the total fluid loss. Cardiac markers (CK, CKMB, and Troponin T) were measured preoperatively, 6, 12, and 24 h following cross clamp application. Detailed data collection was maintained for all patients and included intraoperative (serum glucose, hematocrit, and osmolality [measured by the ABL 700 blood gas analyzer, Radiometer, Copenhagen], spontaneous return to rhythm following cross clamp removal, arrhythmias, and number of blood transfusions) and post-operative (arrhythmias, intubation time, length of stay, and mortality) variables.

Continuous data are presented as the mean ± SD, unless otherwise stated, categorical data as percentages. Continuous variables were screened for normality, and analyzed using one-way analysis of variance (ANOVA), while categorical variables were compared using chi square (χ^2) statistic. All statistical analyses were performed using the *SPSS* software package (SPSS Inc, Chicago, IL). An $\alpha \leq .05$ was considered statistically significant, with the Bonferroni correction for multiple analyses applied when necessary.

RESULTS

The demographic and procedural data in Table 1 show that there were no major differences between groups, although there were significantly more males and a shorter CPB time in Group 4 as compared to Group 2. All four groups were also comparable in the use of diuretics preoperatively and in the incidence of congestive

Table 1. Demography and procedural data.

	Surgeon A		Surgeon B	
	Group 1 (Glucose) $n=42$	Group 3 (No Glucose) $n=41$	Group 2 (Glucose) $n=43$	Group 4 (No Glucose with Mannitol) $n = 46$
Mean Age (years)	61.6 ± 14.1	66.7 ± 10.3	65.3 ± 14.1	65.0 ± 10.8
Sex (% male)	76.2	82.9	58.1	81.4*
CPB time	58.2 ± 17.2	57.9 ± 18.5	60.8 ± 24.9	50.4 ± 16.0*
X Clamp time	37.6 ± 12.0	36.5 ± 11.4	37.4 ± 18.3	30.9 ± 12.9

*$p < .05$; CPB, cardiopulmonary bypass time; x clamp, cross clamp.

Table 2. Haematological data.

	Surgeon A		Surgeon B	
	Group 1 (Glucose) $n=42$	Group 3 (No Glucose) $n=41$	Group 2 (Glucose) $n=43$	Group 4 (No Glucose with Mannitol) $n=46$
Pre CPB Hb (g/L)	13.5 ± 1.7	13.6 ± 1.3	13.6 ± 2.9	13.9 ± 1.2
CPB Hct (%)	25.7 ± 3.7	28.2 ± 7.5	24.3 ± 3.5	26.0 ± 3.3*
No. of blood units on CPB	0.2 ± 0.8	0 ± 0.2	0.2 ± 0.5	0 ± 0.2
(median (range)	0 (0–4)	0 (0–1)	0 (0–2)	0 (0–1)

*$p < .05$; CPB, cardiopulmonary bypass; Hb, haemoglobin; Hct, haematocrit.

heart failure, diabetes, renal disease, and pulmonary dysfunction.

The hematocrit was significantly greater during bypass in Group 4 as compared to Group 2 (Table 2). There was a reduction in blood transfusions in the nonglucose groups; however, this was not statistically significant.

As hypothesized, the removal of glucose from the prime resulted in a significant reduction in serum blood glucose concentration during CPB (1 vs. 3 and 2 vs. 4, $p = .000$, Table 3). Approximately 9% of the nonglucose group was diabetics, and 15% in the mannitol group. In the groups that received glucose, approximately 17% were diabetics in Group 1 and 7% in Group 2. One of these patients exceeded a serum glucose concentration of 20 mmol/L. Electrolyte analysis demonstrated a significant difference in sodium concentration (1 vs. 3, Table 3) and osmolality (2 vs. 4, Table 3).

There were no significant differences in the incidence of spontaneous return to rhythm, the incidence of sinus rhythm, or the requirement for pacing intraoperatively, or in the incidence of arrhythmias postoperatively in the ICU (Table 3). The results of the fluid audit demonstrate that there was a significant reduction in net fluid gain 24 h postoperatively in Group 2 as compared with Group 4, $p = .037$ (Table 3). Twenty-four hours post-operative blood loss was comparable between groups. There were no significant differences in the incidence of perioperative infarction, hospital length of stay, intubation time, and there was no mortality.

Table 3. Clinical data.

	Surgeon A		Surgeon B	
Intraoperative	Group 1 (Glucose) $n=42$	Group 3 (No Glucose) $n=41$	Group 2 (Glucose) $n=43$	Group 4 (No Glucose with Mannitol) $n=46$
Spontaneous return to rhythm (%)	82.9	87.8	81.4	93.1
Rhythm (%) sinus	92.9	87.5	69	84.7
Other than sinus	2.4	5	16.7	8.5
Not sinus	2.4	5	11.9	3.4
AF	2.4	2.5	2.4	3.4
Pacing (%)	7.1	12.2	14	11.9
Fluid Audit				
Net fluid gain (mL) (median (range))	2710 (–2915–5790)	2150 (310–3924)	2787 (–815–689.3)	1906 (–1265–6282)
24 h blood loss (mL) (median [range])	640 (250–2750)	560 (120–1230)	690 (200–1570)	670 (140–4680)
CPB Electrolytes				
Osmolality (mmol/Kg)	283.3 ± 4.0	281.4 ± 6.6	284.8 ± 5.4	276.1 ± 5.3*
Glucose (mmol/L)	13.6 ± 2.6	5.4 ± 0.8*	14.7 ± 3.0	5.4 ± 1.0*
Na+ (mmol/L)	135 ± 1.9	137.8 ± 3.3*	134.7 ± 2.3	135.4 ± 2.5
K+ (mmol/L)	4.8 ± 0.6	4.9 ± 0.6	5.1 ± 0.7	4.9 ± 0.6
ICU Data				
Arrhythmia (%)	37	40	46.9	27.9
Intubation time (median (range))	11.8 (6.3–309.2)	11.4 (4.2–97.4)	15.5 (5.8–184.1)	12.0 (4.5–273.1)
Length of stay (median (range))	7.0 (4–35)	7.0 (4–41)	7.0 (4–34)	7.0 (4–23)
Enzyme changes (%)	14.3	9.5	7.3	10.9
Mortality (%)	0	0	0	0

*$p < .05$; CPB, cardiopulmonary bypass; AF, atrial fibrillation; ICU, intensive care unit.

DISCUSSION

Improvements in clinical practice often involve making changes to existing institutional protocols; however, strict guidelines for instituting changes are rarely present. The decision to remove glucose from the prime was based on the examination of the literature on the topic of hyperglycemia in CPB patients. The conduct of a prospective clinical audit can provide a method for evaluating the effectiveness of making changes by examining patient outcomes. This audit demonstrated that the incidence of hyperglycemia during CPB can be reduced without causing any major changes in other parameters measured. By conducting a clinical audit, we have been able to evaluate change in a structured manner. Although this study was not randomized, we were able to conduct the study over a very short period of time, include all patients undergoing surgery, and maintain the focus on the performance of a successful clinical procedure.

Serum glucose levels increase during CPB, even during normothermia (8). Hypothermia, surgery, and anesthesia elicit suppression of insulin secretion (8); therefore, the addition of glucose to the CPB prime may lead to marked hyperglycemia. It is well shown that hyperglycemia can give rise to increased neuronal injury in the presence of ischemia, via several different mechanisms (1,2,3,9). Hyperglycemia has also been linked to a greater incidence of wound infections in diabetic patients (4) and renal dysfunction postoperatively (5). The results of this study demonstrate that removal of glucose from the prime resulted in an overall reduction in serum glucose during CPB of approximately 58–65%. No patients in the glucose-free prime groups (Groups 3 and 4) exceeded the recommended limit of 13.8 mmol/L (250 mg/dL) during CPB (1). In contrast, 66% of patients in Group 1 and 52% of Group 2 exceeded this value. There were no cases of hypoglycemia (defined as < 3 mmol/L); therefore, we were able to achieve appropriate glucose management in the patients who did not receive glucose. We can only speculate on the benefits of this reduction because we have not looked at a large enough patient samples to demonstrate outcome benefits of tightly controlled glucose levels.

Small, nonrandomized trials have demonstrated a beneficial effect of solutions containing insulin and glucose on the recovery of myocardial metabolism and ventricular function after cardioplegic arrest and reperfusion. The Insulin Cardioplegia Trial conducted by Rao et al. (10) was designed to evaluate prospectively the ability of preischemic metabolic enhancement to improve the results of surgery in high-risk patients undergoing urgent, isolated CABG for unstable angina. This trial failed to demonstrate a clinical benefit of insulin-enhanced cardioplegic solution for this group of patients.

In coronary artery bypass patients, the time until preoperative weight is achieved is a simple function of the rate at which excess interstitial fluid is excreted (11). Excess fluid accumulation and slower return to pre-operative weight are significantly correlated with post-operative mortality, bleeding, use of the intra-aortic balloon pump, renal and respiratory failure (8,11), so preservation of renal function is a major factor in the elimination of retained fluid. The use of such diuretics as mannitol creates a correlation between the fluid retention during bypass and the fluid excretion during the first 24 h postoperatively (12,13). A number of benefits for using mannitol have been described, including a reduction in fluid accumulation (6), an improvement in renal function post CPB (7), and in dogs, an increase in postischemic myocardial functional recovery (14). We observed a significant reduction in fluid accumulation post CPB in the mannitol group (2792 vs. 1970 mL), which could explain the increase in hematocrit in both glucose-free groups (significant increase Group 4 as compared to Group 2).

Overall, there were few differences in terms of patient outcomes in this audit. A significant reduction in osmolality was observed in Group 4 as compared with Group 2; however, this was not considered clinically significant because there was significantly less fluid gain in Group 4. Likewise, the differences in electrolytes were also determined to be satisfactory. By reducing the incidence of hyperglycemia we have reduced the potential incidence of neurological injury in our practice, and through the use of a clinical audit, we have been able to quantify the effects of making a change in our institutional protocol.

Based upon the outcome of our audit, we have been able to facilitate a change to our institutional protocol to adopt the utilization of nonglucose primes, with an evidence base to support our practice.

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