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Research Article

Does Meticulous Blood Glucose Control During Cardiopulmonary Bypass Improves Outcome In Paediatric Patients?

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Abstract: ***Background:*** Fluctuations in glucose levels and prolonged hyperglycaemia is associated with poor outcomes concerning morbidity and mortality in cardiac surgery patients. Paediatric patients are more susceptible to adverse effects of hyperoxaemia during cardiopulmonary bypass (CPB) on glucose homeostasis. In this study, we tried to find out changes in blood glucose and the Insulin requirements intraoperatively in paediatric patients undergoing cardiac surgery requiring CPB. This is a prospective, single-centre study performed among 130 paediatric patients of either sex in the age group below 12 years with congenital heart disease scheduled for cardiac surgery requiring CPB. The parametric data were analyzed by paired t-test for intragroup comparison and unpaired *t*-test for intergroup comparisons. Differences were significant when the probability was less than 0.05 (p-value). Chi-square test was used for inferential data analysis. Blood glucose was meticulously monitored at various points of time as at baseline, after 10 min, then every half-hourly during bypass, 30 minutes after bypass, and after 10 min at intensive care unit (ICU). To control blood glucose on CPB inj. Insulin was used as per study protocol. Group I (n= 97) patients required insulin due to hyperglycaemia on CPB while Group II (n=33) no insulin was required on CPB. 74% of paediatric patients required insulin on cardiopulmonary bypass out of the 43% required insulin 30 min after starting CPB. There is significant blood glucose rise in children of congenital cardiac disease after induction of anaesthesia, and on CPB. The duration of CPB might not significantly affect the insulin requirement of patients. CPB significantly affected glucose homeostasis in children. Hence it seems prudent to administer a small amount of intravenous dextrose in the pre-bypass period to avoid hypoglycaemia. The insulin administration rate and dose should be adjusted on CPB as per patient requirements.

Keywords: Cardiopulmonary bypass, Glucose**,** Heart disease, Insulin (Source: MeSH, NLM).

INTRODUCTION

Blood glucose levels can increase due to surgery and /or cardiopulmonary bypass (CPB) known as hyperglycaemia. This "stress diabetes" occurs due to relative insulin resistance and an increase in hepatic glucose production (Vanhorebeek, I., & Langouche, L. 2009). Several studies have shown an association between hyperglycaemia and poor morbidity and mortality, irrespective of pathology. In 1971 Allison was first to study "Changes in insulin secretion during open-heart surgery since then various studies have been done to know glucose homeostasis during cardiac surgery (Allison, S. P. 1971). An increase in blood glucose levels is a result of counter-regulatory hormones like glucagon, growth hormone, catecholamines, and cytokines, such as interleukin-1, interleukin-6, and tumour necrosis factor-alpha that result in increased gluconeogenesis and glycogenolysis (Marik, P. E., & Preiser, J. C. 2010; & Ulate, K. P. *et al.,* 2012). In principle, once the stressors have been removed, euglycemia should be achieved by the action of insulin, which facilitates glucose entry into insulin-sensitive glucose channels (Ulate, K. P. *et al.,* 2012). High glucose levels affect several other aspects of physiology, some of which are hypothesized to play a role in postoperative outcomes, including oxidative injury, a pro-inflammatory response, clotting abnormalities, vascular reactivity, and decreased immune system effectiveness (Marik, P. E., & Preiser, J. C. 2010). It is thought that hyperglycaemia compromises all major components of the innate immune system, including opsonisation and phagocytosis (Alves, R. L. *et al.,* 2011), causing glycosylation and inactivation of circulating immunoglobulins. This contributes to an increased risk of infection and postoperative mortality (Bell, C. *et al.,* 1993).

Many studies have shown that the duration and intensity of hyperglycaemia are directly related to

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postoperative outcomes, and it is thought that this is due to prolonged exposure to a stressor. Recent emphasis is on good control of blood glucose intra operatively**.** The effect of anaesthesia and surgery are more pronounced during cardiac anaesthesia because of more stress and exposure to extreme un-physiological conditions like Cardiopulmonary bypass (CPB). Children are more vulnerable to the adverse effects of CPB on glucose homeostasis. Uncontrolled blood glucose intraoperatively has deleterious effects on the patients both intraoperatively as well as postoperatively.

METHODS

This research was single-centre, prospective study with the inclusion criteria as children between the age group of 6 months and 12 years undergoing cardiac surgery for congenital heart diseases. The exclusion criteria for the present study were parents/ guardian refusal on behalf of the patient, patients less than 6 months and more than 12 years, patients on steroids, anticonvulsant, children with hepatic/renal failure, Cushing disease, thyroid disorder, sepsis, glomerulopathy, intravenous glucose or fluid intake within 4 hours before surgery and surgical procedures requiring total circulatory arrest.

History of any systemic medical diseases, history of any previous surgery and anaesthesia, history of any drug intake, and drug-allergy was evaluated. A thorough preoperative assessment of the patient was done including all the systems as per hospital protocol. The nature of the study was explained to all the parents/ guardians of paediatric patients included in the study and written informed valid consent was taken from the parents /guardian of the patient on the separate consent form. With institutional ethics committee approval and written informed consent of parents, 130 children in the age group of 6 months to 12 years and undergoing cardiac surgery on CPB were randomly included in this prospective study.

Procedure

In Operation Theatre (OT) baseline blood glucose was taken**.** After fasting for 4 hours and children were premedicated with injection (inj.) Midazolam 0.5 mg/kg and inj. Ketamine 5 mg/kg along with inj. Glycopyrrolate by oral route. The children over 5 years of age received inj. Midazolam 0.03 mg /kg and inj. Ketamine 0.5 mg/kg IV or inj. Ketamine 5 mg/kg IM children were monitored by electrocardiogram, pulse oximetry, and arterial pressure. The induction of anaesthesia was performed with opioids (inj. Fentanyl 10 ug/kg) and benzodiazepines (inj. Midazolam 0.1mg/kg) inj. Pancuronium (0.1mg /kg) was used as muscle relaxant intubation was performed after adequate muscle relaxation with Pancuronium. In all children, additional monitoring included central venous pressure, rectal and nasal temperatures. Anaesthesia was maintained with an infusion of inj Midazolam 0.02 mg/kg/hr and inj. Fentanyl 2 ug/kg/hr. After the inj. of 300 International Unit (IU) /kg of heparin, CPB was accomplished using a non-pulsatile pump with a membrane oxygenator. Core cooling was used in all patients, monitored by rectal and oesophageal temperature. After CPB, the reversal of heparin was accomplished with Protamine sulfate (1.3 mg/1 mg Heparin). No child received intravenous fluids before entering the operating room. Immediately after induction of anaesthesia a continuous infusion of Isolyte-P 10 mL/kg/hr was initiated.

Blood samples for blood glucose measurements were drawn after induction of anaesthesia and before 30 min after induction of anaesthesia (T1), 10 minutes after the beginning of CPB (T2), and half-hourly till he/she was on the bypass (T3-T7). Samples were taken from the bypass machine. One sample was taken after 30 minutes of bypass (T8) and one sample was taken in the immediate post-operative period in the ICU (T9). At each point of time about ½ cc blood was taken as a sample. Blood glucose was measured by the HemoCue-beta-glucose photometer. Hypoglycaemia was defined as a blood glucose concentration lower than 40 mg/dL and hyperglycaemia greater than 200 mg/dL. Those who had blood glucose >200mg% had received inj. Insulin 5 units and those with >300mg% received 10 units on the pump as per our hospital protocol and blood glucose was monitored.

Statistical analysis

The parametric data were analyzed by paired t-test for intragroup comparison (blood glucose trend) levels of significance and unpaired *t*-test for intergroup comparisons. A Chi-square test was used for inferential data analysis of cyanotic and acyanotic children. Differences were significant when the probability was less than 0.05 (p-value). The results were expressed as mean ± Standard Deviation (SD) in the text and the tables.

Results

We had examined 130 pediatric patients going on CPB for cardiac surgery. Blood glucose was monitored in patients who did not require inj. Insulin (Group II) on bypass for hyperglycaemia (n=33) while 97 patients required insulin (Group I) on bypass because of hyperglycaemia. Table 1 shows demographic data in the study population. There was a significant difference ($P<0.05$) between age (month) of group I (51.21±43.55) and group II (73.91±46.18) and weight (kg) of group I (12.22±6.71) and group II (15.67±8.13) patients.

Table 1: Demographic data in study population:

Variables	Study population Mean ± SD	Group I (insulin) n=97	Group II (no insulin) n= 33
Age (months)	56.78 ±44.84	51.21 ± 43.55*	73.91 ±46.18*
Weight (kg)	13.09 ±7.23	12.22 + 6.71*	15.67 ± 8.13*
CPB duration (min)	82.15±28.6	84.55 + 26.70	75.12 ±33.02
Clamp duration(min)	65.11±25.9	67.47±23.70	60.06±31.60

* Statistical significance (p <0.05), CPB= Cardiopulmonary bypass, min= minutes

Table 2: Blood glucose level at a different time on CPB:

Sample collection time	Blood glucose level (mg %)
Preoperative (basal)(T0)	106.27±22.57
After induction (T1)	135.73±23.07*
On bypass 10 min (T2)	131.6±9.78
On bypass 30 min (T3)	158.85±23.29*
On bypass 60 min (T4)	164.25±18.88*
On bypass 90 min (T5)	171.20±17.52*
On bypass 120 min(T6)	179.8±15.51*
After bypass 30 min(T8)	176.3±33.11*
In ICU 10 min(T9)	166.7±27.52*

* Statistical significance (p <0.05) mg= milligram, ICU=intensive care unit, T=time

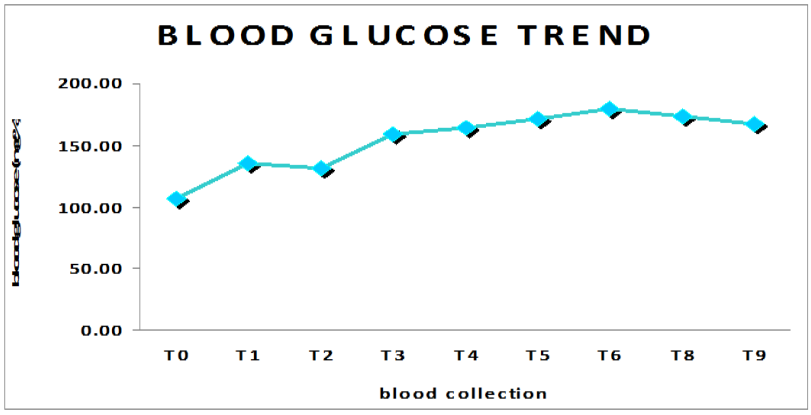

Figure 1: Blood glucose level at a different time:

Blood glucose levels preoperative (T0) as compared to after induction of anaesthesia (T1) increased from 106.27±22.57 mg % to 135.73±23.07 mg % was statistically significant as shown in Table 2. After starting CPB the blood glucose levels showed statistically insignificant fall from (T1) 135.73±23.07 mg% to (T2) 131.6±19.7 mg% while from T2 (10 min on bypass) to T6 (120 min on bypass) there was significant rise at each point in blood glucose level [no patients in this group II were on bypass for 150 min (T7)]. The sample of blood glucose collected 30 min post bypass (T8) and after 10min in ICU (T9) shows significantly lower 176.3±33.1mg% and 166.7±27.5mg% glucose level than (T6) 179.8±15.51mg% (p<0.05) as shown in Figure 1 and Table 2. The type of heart disease cyanotic or acyanotic did not seem to affect hyperglycaemia on CPB as shown in Table 3.

Table 3: Distribution of patients according to their congenital heart disease:

Variables	Group I (Insulin)	Group II (no insulin)
Cyanotic	37	11
Acyanotic	57	22

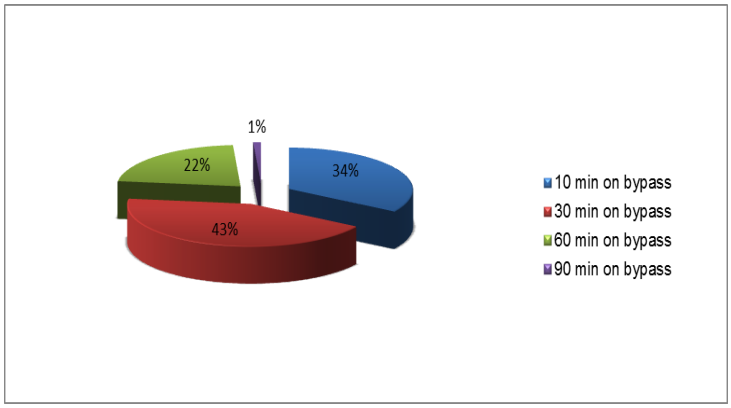

Figure 2: Distribution of patient requiring insulin at a different point of time:

The patients who required inj. insulin on CPB required insulin at a different time interval, once or frequently. Analysis of data showed that maximum patients (43%) required insulin 30 min on bypass (T3) first time, followed by 34% at 10 min on the bypass (T2), whereas 22% received insulin first time 60 min on bypass and only 1% received insulin 90 min on CPB as depicted in Figure 2.

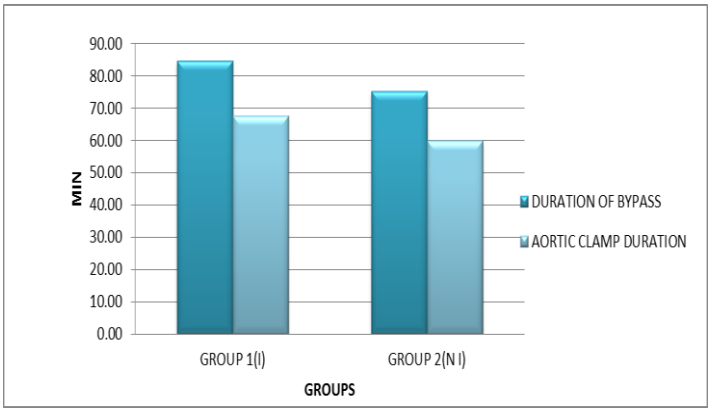

Figure 3: Duration of bypass and aortic clamp duration:

Only one patient required 25 International Unit (IU) of insulin on CPB. The average insulin required on CPB was 11.08 IU/child. Figure 3 showed that maximum patients required 10 IU of insulin and only one required 25 IU of insulin.

DISCUSSION

Each year in the US approximately 20,000 operations are carried out for the correction of congenital heart defects. The incidence of hyperglycaemia is estimated up to 90% in these patients, but the correction of which risks iatrogenic hypoglycaemia that may cause damage to the brain (Agus, M. S. *et al.*, 2012). During paediatric cardiac surgery, a large increase in blood glucose has been reported when exogenous glucose was added intraoperatively (Vanhorebeek, I., & Langouche, L. 2009). However, when glucose was excluded, hypoglycaemia occurred (Nicolson, S. C. *et al.*, 1992). Hypoglycaemia when blood glucose <40mg/dL in children during surgery can be deleterious. When it is severe and prolonged then even can lead to irreversible neuronal damage (Ballweg, J. A. *et al.*, 2007).

Hyperglycemia occurs when blood glucose >200mg/dL during cardiac surgery results from several factors. These alterations in glucose metabolism are related to some extent to the metabolic response to surgical trauma, mostly to specific aspects of CPB, such as hypothermia, re-warming, and heparinization (Lee, K. U. *et al.*, 1988; & Kuntschen, F. R. *et al.*, 1986). The etiology of the disturbance of the plasma glucose-insulin relationship, which consistently occurs during CPB, includes inadequate insulin secretion. Hypothermic CPB increased catecholamines, cortisol, and glucagon which stimulate glycosis, hepatic gluconeogenesis, and glucose production, decrease total body glucose uptake enhance renal absorption of filtered glucose, and decrease exogenous insulin activity. High concentrations of anti-insulin humoral factors also contribute to a rise in blood glucose (Marik, P. E., & Preiser, J. C. 2010; & Ulate, K. P. *et al.*, 2012).

The degree and duration of hyperglycaemia differ with the type of anaesthesia, duration of CPB, degree of haemodilution, depth of hypothermia, and duration (Singh, S. *et al.*, 2013; & Nuutinen, L. S. *et al.*, 1977). Whether Intraoperative hyperglycaemia can

affect the neurological outcome in patients of cardiac surgery is debatable. As in a study by De-Ferranti *et al.*, no adverse neurological effect was seen in 1 to 8 years age group children having intraoperative hyperglycaemia during CPB for cardiac surgery (de Ferranti, S. *et al.*, 2004).

Hyperglycaemia has been shown in Sieber *et al.*, study to worsen neurological injury after focal and global cerebral ischemia, probably because of anaerobic glycolysis induced conversion of glucose to lactate. These lactates cause impairment of cellular metabolism and intracellular acidosis (SIEBER, F. E., & TRAYSTMAN, R. J. 1992). Hyperglycaemia provokes deleterious effects on myocardium as ischaemia during the reperfusion process. As seen in dogs with diabetes and hyperglycaemia that the myocardial infarct size is strongly correlated with blood glucose concentration (Kersten, J. R. *et al.*, 2000). Moreover, high blood glucose concentration abolishes ischaemic preconditioning and amplifies reperfusion injuries (Kersten, J. R. *et al.*, 2000; & Singh, S. *et al.*, 2020). To perform a study with homogenous conditions, children between the age of 6 months to 12 years were operated under hypothermic CPB without circulatory arrest were included in our study. Procedures with total hypothermic circulatory arrest are mainly used on newborn children and induce a striking metabolic response to surgical stress (Anand, K. J. *et al.*, 1990). It was found that glucose withdrawal in this population can induce threatening hypoglycaemia during the pre-bypass period. This risk was prevented by moderate intraoperative glucose intake (0.5gm/kg/hr) without any major hyperglycaemia. Before induction of anaesthesia children were kept fasted for 6 hours and no low blood glucose levels were recorded in 130 children in our study. No exogenous glucose was infused in this group. There was no incidence of hypoglycaemia in our study, but previous studies show a trend to an increase in this incidence when glucose was excluded. Nicholson *et al.*, have already reported similar results, suggesting that hypoglycaemia in fasting children with congenital heart disease is not rare (Nicolson, S. C. *et al.*, 1992). This incidence depends on fasting duration, nutritional condition, and energy requirements. Because of their great metabolic needs and their higher oxygen consumption, infants with congenital heart disease are not able to maintain normal blood glucose during fasting. Their glycogen storage is relatively less than in adults and is exhausted more rapidly. Nishina *et al.*, conducted a study in healthy infants during minor surgery, reported that during glucose-free infusion, a major lipid mobilization (lipolysis) occurred to maintain normal glycaemia after fasting (Ballweg, J. A. *et al.*, 2007). In children with higher energy needs, this physiological compensation is probably insufficient and hypoglycaemia can occur. This emphasizes the necessity of the low rate of glucose infusion in this population. Our study data showed that preoperative blood glucose levels may be a factor that significantly affects blood glucose levels on CPB.

The children, in our study, were premedicated as per unit protocol. This was done to reduce the rise in blood glucose level due to induction as earlier reported by Aono *et al.*,. Their study observed that blood glucose values of crying and agitated children before induction were significantly higher than those of calm children during the perioperative period (Aono, J. *et al.*, 1992). There is a paucity of literature in children showing any significant relationship between age and weight of child and blood glucose level on CPB. Our study findings were suggesting that the paediatric patients with higher age group II (73.91 ±46.18)] and weight (15.67 ± 8.13) have less increase in blood glucose compared to less age (51.21 ± 43.55) and weight (12.22 ± 6.71) as seen in group I on CPB.

Both the type of congenital heart disease either cyanotic or acyanotic does not found to affect blood glucose on CPB. None previous studies data concluded the same. The patients were induced with a high dose of opioids (inj. fentanyl 10 ug/kg) and benzodiazepines (0.1mg/kg) to reduce the stress response. Inj. pancuronium was used as a muscle relaxant. After induction, there was a significant increase in blood glucose levels from 106.27+22.57 mg% to135.73+23.07 mg% ($p<0.05$). This increase in blood glucose level was also attributable to inhibition of peripheral glucose uptake during anaesthesia combined with elevated levels of plasma catecholamine, glucagons, and cortisol in response to surgical stress (Weale, N. K. *et al.*, 2004; & Singh, S. *et al.*, 2013). However study performed by Lehot *et al.*, noted that no change in blood glucose levels after induction of anaesthesia in adult patients (Lehot, J. J. *et al.*, 1992).

The priming solution used contained no dextrose and volume is increased by ringer's lactate solution. If required then blood was added to maintain CPCV >25%. The addition of blood to priming solution increases its glucose content as stored CPD blood contains 7 to 22 mmol/lit of glucose. Keidan *et al.*, showed that when stored CPD is added to priming solution, blood glucose level increases more with blood stored more than 5 days in the first 20 min of CPB (Keidan, I. *et al.*, 2004). In our unit, we used less than 5 days old blood. McKnight *et al.*, found that blood glucose concentration decreased by 36±9 mg% immediately on the institution of CPB in 12 non-diabetic adult patients undergoing open-heart surgery with cardiopulmonary by-pass using priming fluids free of glucose (Keidan, I. *et al.*, 2004). The blood glucose fall in our study is insignificant. The decrease in blood glucose can be explained by dilution of blood by prime fluid. The subsequent blood glucose reading showed an increasing trend throughout the bypass. The results were similar to previous studies (Lehot, J. J. *et al.*, 1992; & Keidan, I. *et al.*, 2004). In our study, the

increase in blood glucose is neither significant with the duration of bypass nor with the clamp duration. Our result was similar to Doenst *et al.*, and others (Singh, S., & Annamalai, A. 2017; & Doenst, T. *et al.*, 2005).

The causes of an increase in blood glucose on CPB are already discussed above. The significant increase in blood glucose levels during the rewarming phase is due to changes in hormonal levels. There is a surge in adrenalin and noradrenalin as the body's response to return to normothermia, which increases glycogenolysis and gluconeogenesis. Similarly, the direct stimulatory effect of increasing temperature on the enzyme system involved in glucose production cannot be ruled out (Lehot, J. J. *et al.*, 1992). In our study blood glucose level in children coming off bypass decreased but remains above the normal level.

Our study findings showed that the duration of neither CPB nor aortic clamp was significantly increased blood glucose levels and the requirement of insulin on the pump. This was contrary to the result obtained by Nuutinen *et al.*,. They found the blood glucose remained at a high level until the second postoperative day and was significantly higher in the long perfusion group than in the short perfusion group (Nuutinen, L. S. *et al.*, 1977). Studies on blood glucose on bypass show different results and opinions still differ whether hyperglycaemia in a short span of CPB affects the outcome of patients (Lehot, J. J. *et al.*, 1992). Attempts are continuing to control blood glucose on CPB. To control blood glucose on the CPB pump in our study we used inj. Insulin. In various previous studies, different regimens had been tried to control blood glucose levels during cardiac surgery, like glucose, insulin, and potassium (GIK) drip, insulin glucose drip, insulin infusions, Insulin bolus (Doenst, T. *et al.*, 2005). Almost 74% of paediatric patients required insulin on the pump to control blood glucose levels at different points of time. The total requirement ranging from 5 IU to 25 IU these results are comparable to those obtained by Quattara *et al.*, in adult patients who showed that 37% patient requires insulin on the pump to control blood glucose level on the pump (Ouattara, A. *et al.*, 2005). Apart from the control of blood glucose level during surgery insulin has been shown to improve the patient's outcome by its other effect avoiding glucose toxicity to vital organs (Ellger, B. *et al.*, 2006) and preventing mitochondrial damage (Vanhorebeek, I. e al 2005).

Results have been so varied that the American College of Physicians has actively recommended against the use of intensive insulin therapy in children (Srinivasan, V. 2013). Finally, the studies on blood glucose, insulin, and perioperative period in cardiac surgery & intensive care suggested that the degree of intraoperative hyperglycaemia may merely reflect the severity of underlying "stress" (Gandhi, G. Y. *et al.*, 2005, July). On the other hand, being too cautious and start tight glycaemic control, exposing children to hypoglycaemia come with its risks of causing significant disability in children whose neurological systems are immature.

CONCLUSION

Blood glucose rise in paediatric congenital heart disease patients was significant after induction of anaesthesia, hypothermic CPB, rewarming phase, and addition of blood to the priming solution. The duration of CPB might not significantly affect insulin requirements in paediatric patients. There is simply not enough evidence to suggest that tight glycaemic control would be of benefit in this patient population because the risks of hypoglycaemia are felt to be too great. CPB significantly affects glucose homeostasis in children, hence it seems prudent to administer a small amount of dextrose in prebypass period to avoid hypoglycaemia but the rate and dose of insulin should be adjusted as it may affect blood glucose level on CPB. Most of the previous studies were in adult and there is a need for more extensive study in the paediatric population.

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