Original Article

Remifentanil Prevents Increases of Blood Glucose and Lactate Levels during Cardiopulmonary Bypass in Pediatric Cardiac Surgery

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Abstract

Introduction: Cardiopulmonary bypass (CPB) can cause stress response that increases levels of cytokine and catecholamine in plasma, resulting in hyperglycemia. In adults, it has been demonstrated that remifentanil infusion during CPB could prevent increases of cytokine, catecholamine, and blood glucose levels, but such effects of remifentanil in children have not been elucidated. **Aim:** In this study, we investigated the preventive effects of remifentanil on blood glucose and lactate levels during CPB in children. **Materials and Methods:** This retrospective study included children who underwent ventricular septal defect or atrial septal defect closure. Data for patients who did not receive, during CPB period, remifentanil infusion (non-Remi group) and patients who received remifentanil infusion at 0.5 μg/kg/min (Remi group) during CPB were used for analysis. Primary outcomes were lactate and blood glucose levels just before and after CPB. Data are presented as medians and interquartile ranges. Data were analyzed by the Mann–Whitney U-test and Chi-square test. A $P < 0.05$ was considered statistically significant. **Results:** During CPB, 13 and 11 patients were allocated into Remi and non-Remi groups, respectively. Pre-CPB lactate and blood glucose levels were not significantly different between the two groups, but post-CPB lactate and blood glucose levels in the Remi group were significantly lower than that in the non-Remi group. **Conclusion:** 0.5 μg/kg/min remifentanil infusion during CPB suppresses the increases of blood glucose and lactate levels in children.

Keywords: *Cardiopulmonary bypass, children, hyperglycemia, hyperlactatemia, remifentanil*

Introduction

Cardiopulmonary bypass (CPB) is essential for cardiac surgery, for example, congenital heart disease repair, at CPB period. However, CPB can cause inflammatory responses that increase cytokine[1,2] and catecholamine levels in plasma, resulting in hyperglycemia[3-6] and hyperlactatemia.[7] Moreover, perioperative hyperglycemia and hyperlactatemia exacerbate postoperative outcomes.[5-7] In adults, it has been demonstrated that remifentanil infusion during CPB could prevent increases of cytokine,[1] catecholamine,[8] and blood glucose levels,[9] but such effects of remifentanil in children have not been elucidated. In this study, we investigated the preventive effects of remifentanil on the increases of blood glucose and lactate levels during CPB in children.

Materials and Methods

We retrospectively reviewed anesthetic records of patients with 0–7 years old, American Society of Anesthesiologists Physical Status - I or II, who received ventricular or atrial septal defect (ASD) closure during a 12-month period from April 2014 to March 2015. Exclusion criteria included the patients who had congenital metabolic disease which may influence aerobic metabolism (e.g., mitochondrial encephalomyopathy), abnormal glucose tolerance, anemia (hemoglobin <9.0 g/dL), and hyperlactatemia (lactate >10 mg/dL) preoperatively.

All anesthetic procedures were standardized. Anesthetic induction was performed by slow induction with 5% sevoflurane under O_2 4 L/min and N_2O 6 L/min. Two peripheral venous and an arterial cannula were inserted, and 0.6–0.8 mg/kg rocuronium was administered, and children were tracheary intubated. After intubation, central venous catheter was inserted from the right internal jugular vein. Noninvasive blood pressure, invasive blood pressure, central venous pressure,

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heart rate, electrocardiography, core body temperature, SpO_2, end-tidal CO_2, and cerebral tissue oxygen index were continuously recorded. During pre-CPB period, anesthesia was maintained with 1.5% sevoflurane, fentanyl, and 0.25–0.5 μg/kg/min remifentanil. Just after start of CPB, sevoflurane inhalation was stopped, and 10 mg/kg/h propofol, 0.7 μg/kg/h dexmedetomidine, and remifentanil infusion were started. During CPB, anesthesiologist decided whether to administer 0.5 μg/kg/min remifentanil or not at all. Concurrently, with the end of CPB, propofol infusion was stopped, and sevoflurane inhalation was started again. After the operation procedure, all children were transferred to the Intensive Care Unit with tracheary intubation and 0.7 μg/kg/h dexmedetomidine infusion. Blood gas analysis was performed at just before and after CPB period.

Intraoperative data were obtained from anesthetic and CPB records. Patients were divided into two groups; Remi group included patients who received 0.5 μg/kg/min remifentanil infusion, and non-Remi groups included patients who did not receive remifentanil infusion during CPB. Primary outcomes were blood glucose and lactate just before and after CPB. Secondary outcomes include base deficit before and after CPB, dose of $NaHCO_3$ and chlorpromazine, perfusion pressure and cerebral tissue oxygen index during CPB, urine output, and dose of furosemide during a postoperative 24-h period.

Ethics

Hokkaido Medical Center for Child Health and Rehabilitation Institutional Review Board approved this study (Date of approval: July 2015, 28, Approval code: 142). This study was in accordance with the ethical standards of our institution and with the Helsinki Declaration of 1975.

Statistics

Statistical analysis was performed with Mann–Whitney U-test for primary outcomes. Secondary outcomes were analyzed with Chi-square test and Mann–Whitney U-test. A $P < 0.05$ was considered statistically significant. Data were presented as absolute number or median (interquartile range).

Results

Twenty-three patients were included this retrospective study. Thirteen and 11 patients were included in Remi and non-Remi groups, respectively. There was no significant difference in characteristics between two groups, including CPB time, aortic clamp time, and flow rate of CPB [Table 1]. Fentanyl dose was slightly lower in Remi group, but this was not significantly. Pre-CPB blood glucose was not significantly different (Remi group; 93 [88–100], non-Remi group; 101 [85–101] mg/dL, $P = 0.395$) [Figure 1a], but post-CPB blood glucose was significantly lower in Remi group (Remi group; 111 [105–138], non-Remi group; 174 [162–194] mg/dL, $P < 0.05$) [Figure 1b]. Similarly, pre-CPB lactate was not significantly different (Remi group; 6.0 [5.7–7.0], non-Remi group; 6.5 [5.0–8.0] mg/dL, $P = 0.552$) [Figure 2a], but post-CPB lactate was significantly lower in Remi group (Remi group; 8.0 [7.0–9.2], non-Remi group;

Table 1: Characteristics of the patients

	Remi	Non-remi	*p* value
Number	n = 13	n = 10	
VSD / ASD	10 / 3	9 / 1	$p = 0.412$
Age (month)	14 (2 – 66)	3 (2-19)	$p = 0.316$
Height (cm)	75 (58 – 110)	60 (55 – 80)	$p = 0.191$
Weight (kg)	9 (4.5 – 16.5)	5.6 (4.5 – 10)	$p = 0.401$
Qp/Qs	1.8 (1.3 – 1.9)	2.0 (1.3 – 2.3)	$p = 0.462$
CPB time (min)	72 (52 – 93)	80 (71 – 83)	$p = 0.963$
Aorta Clump time (min)	39 (26 – 56)	44 (42 – 45)	$p = 0.615$
Minimum temperature during CPB (°C)	36.4 (36.0 – 36.7)	36.0 (35.7 – 36.4)	$p = 0.170$
Fentanyl dose ($\mu g \cdot kg^{-1}$)			
Pre CPB	11 (10 – 16)	17 (14 – 24)	$p = 0.118$
Total	15 (14 – 22)	21 (16 – 28)	$p = 0.152$
CPB flow rate ($mL \cdot kg^{-1} \cdot min^{-1}$)	138 (112 – 157)	146 (130 – 159)	$p = 0.340$

Data were presented as median (IQR) and absolute number. IQR: Interquartile range

12.0 [10.7–13.5] mg/dL, $P < 0.01$) [Figure 2b]. Secondary outcomes were presented in Table 2. Perfusion pressure during CPB in Remi group was significantly lower in non-Remi group. On the other hand, cerebral tissue oxygen index was not significantly different. Doses of $NaHCO_3$ and chlorpromazine during CPB were not significantly different but tend to be higher in non-Remi group. Postoperative serum creatinine, urine output, and dose of furosemide, relating to renal function, were not significantly different between two groups.

Discussion

Our study has three major findings. First, this study indicates remifentanil has the preventive effect on increases of blood glucose and lactate levels during CPB in children. In adult, this effect of remifentanil has been reported.[9] It is well known that CPB induces a systemic inflammatory response and stimulates cytokine signaling.[1,2] Von Dossow *et al*. reported that remifentanil infusion for coronary artery bypass graft surgery decreased the interferon (INF)-γ/interleukin (IL)-6 ratio and suppressor of cytokine signaling-3 gene expression,[1] which is known as a feedback inhibitor of cytokine receptor signaling and negative regulator of $CD4^+$ T-cell differentiation.[10,11] Moreover, remifentanil infusion suppresses post-CPB stress hormone levels such as norepinephrine, antidiuretic hormone compared with intermittent fentanyl administration.[8] These stress hormones have potent vasoconstrictive effects, inducing the disturbance of peripheral tissue perfusion. At low-perfusion tissue, oxygen delivery was exacerbated and anaerobic metabolism was facilitated, resulting in hyperglycemia and

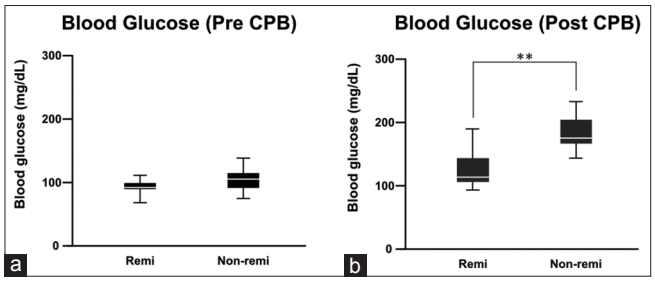

Figure 1: The results of blood glucose levels at pre- and post-cardiopulmonary bypass period. (a) Precardiopulmonary bypass glucose, (b) postcardiopulmonary bypass glucose. *$P < 0.05$ CPB: Cardiopulmonary bypass

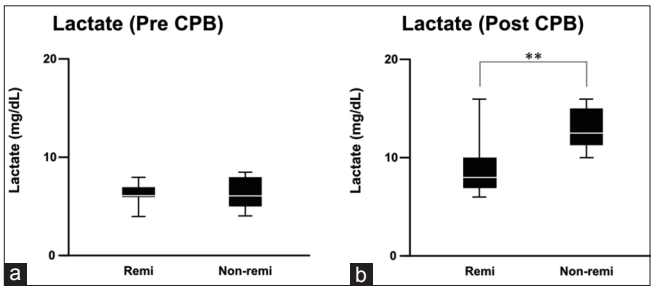

Figure 2: The results of lactate levels at pre- and post-cardiopulmonary bypass period. (a) Precardiopulmonary bypass lactate, (b) postcardiopulmonary bypass lactate. **$P < 0.01$. CPB: Cardiopulmonary bypass

Table 2: The result of secondary outcomes

	Remi	Non-remi	*p* value
Perfusion pressure (mmHg)	42 (32 – 44)	49 (45 – 50)	$p = 0.024$
Cerebral tissue oxygen index (%)	56 (55 – 62)	58 (55 – 61)	$p = 0.962$
Base deficit (mmol/L)			
Pre CPB	2.9 (0.4 – 3.3)	2.1 (0.3 – 3.2)	$p = 0.749$
Post CPB	2.5 (1.8 – 2.5)	3.1 (1.7 – 4.8)	$p = 0.289$
$NaHCO_3$ (mg/kg)	214 (143 – 326)	364 (240 – 470)	$p = 0.105$
Chlorpromazine (mg/kg)	0 (0 – 0.03)	0.13 (0 – 0.25)	$p = 0.368$
Serum creatinine (mg/dL)			
Pre operation period	0.25 (0.21 – 0.35)	0.22 (0.21 – 0.25)	$p = 0.382$
Post operation period	0.23 (0.22 – 0.31)	0.26 (0.22 – 0.26)	$p = 0.914$
Urine output during postoperative 24 hour (mL/kg/day)	76 (69 – 96)	89 (63 – 94)	$p = 0.766$
Furosemide dose during postoperative 24 hour (mg/kg)	0.9 (0.5 – 1.7)	1.4 (0.8 – 1.9)	$p = 0.419$

Data were presented as median (IQR). IQR: Interquartile range

hyperlactatemia. It is thought to be that remifentanil could suppress inflammatory response, stress hormone release and improve tissue perfusion, and consequently prevent blood glucose and lactate elevations.

Second, remifentanil infusion might be useful as antihypertensive agent during CPB period in children. In pediatrics, hypertension often occurs during CPB as a result of systemic vasoconstriction. To prevent hyperperfusion pressure, chlorpromazine and nitroprusside are useful as vasodilative drugs.[12,13] In this study, perfusion pressure was significantly lower in Remi group. In addition, chlorpromazine dose during CPB had a tendency to be lower in Remi group. This effect is thought to be the result of the anti-inflammatory effect of remifentanil as described above mention. Therefore, remifentanil infusion during CPB in children is also expected to fulfill a role as an antihypertensive agent.

Third, no adverse effect was observed in Remi group. In pediatric cardiac surgery, renal dysfunction is important complication, and the incidence is reported 42%.[14] In our results, secondary outcomes relating to postoperative renal function, such as urine output, serum creatinine, and dose of furosemide, were not different between the two groups. There is some possibility that remifentanil can use safely during CPB in pediatric cardiac surgery.

In addition, remifentanil infusion during CPB might improve postoperative outcomes. Intraoperative hyperglycemia and hyperlactatemia are known as the factors that exacerbate postoperative outcomes.[5-7] To prevent hyperglycemia, intensive insulin therapy is desirable,[15] but it might be harmful, because of a risk of hypoglycemia in pediatrics.[16-18] From this point, stress-free perioperative management, stabilizing blood glucose, and lactate levels are thought to be apposite. Remifentanil may incarnate this management and improve postoperative outcomes for children.

In the current study, pre-CPB and total fentanyl dose were higher in non-Remi group. These differences were not significant but might influence some outcomes. In pediatrics, CPB induction causes the huge increases of circulatory and drug distribution volume, resulting in the change of pharmacokinetics and pharmacodynamics, compared with adults. Koren *et al*. reported that plasma fentanyl concentration does not change between before and during CPB periods.[19] According to this study, it is thought that the plasma fentanyl concentrations were different between Remi and non-Remi group in this study. However, Stanley *et al*. reported that approximately 100 mcg/kg fentanyl administration could not suppress the elevations of stress hormones during CPB.[20] Consequently, it is seems that the differences of fentanyl dose (6 mcg/kg) were too slight to affect our blood glucose and lactate results.

We use blood glucose and lactate levels as the results of stress responses caused by CPB, but inadequate sedation also affects these values. In our institution, 10 mg/kg/h propofol infusion was applied as a sedative during CPB period. In pediatrics, because the dimension of their forehead is limited, bispectral index was not monitored routinely. There is possibility that insufficient sedation and anesthesia-induced stress response resulting in blood glucose and lactate increases in the current study. Dawson *et al*. investigated the effects of CPB on total and unbound plasma concentrations of propofol.[21] According to their results, after CPB start, total plasma propofol concentration decreased transiently, but unbounded portion of propofol increased. As a result, unbounded plasma propofol concentration, which had drug efficacy, small increased and the depth of anesthesia became deeper. Our 10 mg/kg/h propofol infusion rate for anesthetic maintenance is advocated by McFarlan *et al*. in 1999 and widely used for many years clinically.[22] Moreover, in pediatric cardiac surgery, 4–8 mg/kg propofol infusion is recommended.[23] In summary, 10 mg/kg/h propofol infusion was sufficient for anesthetic maintenance during CPB in children and did not influence increase levels of blood glucose and lactate in non-Remi group in this study.

This current study has four limitations. First, it is unclear that our 0.5 μg/kg/min remifentanil infusion rate is optimal to prevent CPB stress. In adult, various infusion rates were applied during CPB to elucidate the effect of stress response suppression.[1,8,24] Sato *et al*. reported that 1 μg/kg/min remifentanil infusion was effect for suppression of stress responses.[9] Considering the difference of pharmacokinetics and pharmacodynamics between adult and children, higher infusion rate might be necessary to perform the maximum antistress effect of remifentanil during CPB. Second, this study is retrospective trial and based on small sample size and does not include quantitative evaluation of stress hormones or inflammatory cytokines. In our institution, the surgeons changed the CPB priming fluid, from 5% glucose to bicarbonate Ringer solution at March 2014; therefore, we cannot collect only 23 patients. These hormone and cytokine values are not measured routinely, and usage of remifentanil infusion during CPB is imperative by surgeon's request. For measurement of these items, huge amount of blood sample is mandatory, and it induces severe anemia for children. From these reasons, we could not add more number of cases and construct prospective comparative study including stress response measurement. Third, our anesthetic management includes the routine dexmedetomidine infusion during CPB. Bulow *et al*. reported that dexmedetomidine was associated with a significant reduction of IL-1, IL-6, tumor necrosis factor-alpha, and INF-γ levels.[25] This effect resembling remifentanil may affect synergistically and result in present results. Fourth, we selected the only patients who underwent ASD or ventricular septal defect closure for this study. It was not elucidated that this remifentanil effect was beneficial to the patients with complex congenital heart disease, for example, hypoplastic left heart syndrome.

Because these patients have complicated hemodynamic state, remifentanil effect might induce worse outcome in the management of such children. To resolve these limitations, more detail, controlled prospective comparative study is warranted.

Conclusion

Remifentanil infusion suppresses increases of blood glucose and lactate levels and may act as vasodilator during CPB in pediatrics. Moreover, any side effect was observed in the current study. However, the remifentanil infusion rate, which is optimal for preventive effect on the elevations of blood glucose and lactate, is unclear. More detail prospective, randomized, controlled study should be taken to elucidate the effect of remifentanil during CPB in children.

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Conflicts of interest

There are no conflicts of interest.

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