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Original Article

High Ionized Calcium Concentration Is Associated With Prolonged Length of Stay in the Intensive Care Unit for Postoperative Pediatric Cardiac Patients

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Objective: There has been controversy regarding the beneficial effects of calcium on myocardial contractility and the harmful effects on myocardial cells, especially in children. The aim of this study was to investigate an association between ionized calcium concentration (iCa) and outcomes for pediatric patients after cardiac surgery.

Design: A retrospective, single-center study from May 2013 to December 2014.

Setting: Referral high-volume pediatric cardiac center in a tertiary teaching hospital.

Patients: Patients < 72 months old with congenital heart disease who underwent palliative or definitive surgery.

Interventions: None.

Measurements and Main Results: The association between pH-corrected iCa within 24 hours after surgery and intensive care unit (ICU) length of stay (ILOS) was defined as the primary outcome. The highest iCa (iCa_{max}), lowest iCa (iCa_{min}), and time-weighted average iCa (iCa_{ave}) were stratified and compared with the outcomes. The authors reviewed 5,468 ionized calcium measurements from 357 consecutive pediatric patients during the study period. One patient died at postoperative day 34 in the ICU. Significant differences in ILOS were observed among patients after cardiopulmonary bypass (CPB) according to iCa_{ave}, iCa_{max}, and iCa_{min} but not among patients without CPB. Patients with CPB and an iCa_{ave} value of 1.31-to-1.40 mmol/L, 1.41-to-1.50 mmol/L, 1.51-to-1.60 mmol/L, and > 1.60 mmol/L stayed in the ICU for 7 (interquartile range [IQR] 4-10) days, 8 (IQR 6-16) days, 10 (IQR 8-14) days, and 19 (IQR 12-38) days, respectively, which was significantly longer than the ILOS of 5 (4-8) days for patients with an iCa_{ave} of 1.21-to-1.30 mmol/L. Even after adjustment for other predictors of ILOS using multivariable analyses, there were significant relationships of ILOS with iCa_{ave} and iCa_{min} values of > 1.50 mmol/L among patients with CPB.

Conclusions: Higher iCa within 24 hours after congenital cardiac surgery using CPB was independently associated with longer LOS in the ICU.

Key Words: calcium; pediatric; cardiac surgical procedures; heart defects; intensive care units; length of stay

CALCIUM EXISTS IN the body in a protein-bound form, an ionized or unbound form, and a chelated form. The blood ionized calcium concentration (iCa) is strictly regulated by parathyroid hormone and vitamin D within narrow limits. Ionized calcium (Ca^{2+}) has been shown to be essential for

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myocardial excitation-contraction coupling,[1] and variations in Ca^{2+} are directly correlated with clinically significant changes in myocardial contractility[2] and changes in blood pressure.[3] It has been suggested that the immature myocardium depends more on extracellular calcium levels in neonates and infants because intracellular calcium stores are limited[4]; therefore, iCa is monitored closely in the pediatric intensive care unit (ICU)[5] and calcium replacement therapy is given to maintain serum Ca^{2+} levels with the aim of providing hemodynamic stability.[6–8]

On the other hand, Ca^{2+} also has negative effects on the cardiovascular system. Some observational studies have shown that serum calcium concentration was positively associated with the risk of heart failure.[9,10] Ca^{2+} also was shown to have detrimental effects on myocardial cells and cardiovascular function after ischemia-reperfusion injury including cardiopulmonary bypass (CPB).[11–14] Specifically, neonatal immature myocytes have reduced recovery of myocardial function after cardioplegia, possibly because of a reduced capacity to handle the intracellular Ca^{2+} load.[15] In addition to the necrotic myocardium, calcium deposition also is implicated in cerebral death accompanying neuronal injury of varying etiologies.[16,17] In a clinical study including post-cardiac surgical infants, the use of calcium during cardiopulmonary resuscitation was associated with worse survival.[18] Based on these concerns, the American Heart Association in 2000 recommended that the use of a calcium agent during pediatric cardiopulmonary resuscitation should be limited to select circumstances.[18]

Regarding the potentially opposite effects of Ca^{2+}, there is no evidence about an association between iCa and any outcomes for pediatric patients after cardiac surgery. In order to investigate whether there is an association between iCa and outcomes, the authors retrospectively studied the association between iCa within 24 hours after cardiac surgery and length of ICU stay and other adverse outcomes.

Materials and Methods

Design

The authors conducted a single-center, retrospective study that was approved by the Okayama University Hospital Ethics Committee. The committee waived the need for informed consent for studies involving the use of a database.

Study Population

This study was conducted in a tertiary teaching hospital that had 865 beds in the hospital and 8 beds in the pediatric cardiac ICU. Patients <72 months old with congenital heart disease who underwent palliative or definitive surgery and were admitted to the pediatric cardiac ICU in the hospital from May 2013 to December 2014 were included in this study. Patients who did not fulfill these requirements were excluded from the study.

Perioperative Management

In the authors' institution, the first choice of perioperative inotropic medication was milrinone, and epinephrine was added as needed. A calcium agent, mainly calcium chloride, was administered to maintain an iCa >1.20 mmol/L perioperatively according to decisions by cardiac surgeons and anesthesiologists in the operating room or ICU with the aim of providing hemodynamic stability. Other additional management was dependent on cardiac surgeons and anesthesiologists who were responsible for each patient.

Primary and Secondary Outcomes

ICU length of stay (ILOS) was defined as the primary outcome. The period of milrinone administration; use of additional epinephrine; and adverse events, including death, postoperative cardiac arrest and arrhythmia, need for postoperative mechanical ventilation (MV), extracorporeal membrane oxygenation (ECMO), nitric oxide (NO), or peritoneal dialysis (PD) during the ICU stay were defined as secondary outcomes.

Data Sources/Measurement

Data on age, sex, weight, type of surgery based on the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) category,[19] severity of illness based on the Pediatric Index of Mortality (PIM) II,[20] use of CPB, lowest temperature during CPB, and duration of aortic cross-clamp were obtained from the patient database. In addition, data on postoperative events and management in the ICU were obtained and included volume of blood products and inotropic agents for the first 24 hours after surgery; postoperative cardiac arrest; arrhythmia; and the use of MV, ECMO, NO, or PD. Based on the data on inotropic agents, the authors calculated the Vasoactive Inotropic Score (VIS) for each patient.[21]

Ionized Calcium Concentration

iCa in the ICU was measured using an arterial blood gas analyzer (ABL 800; Radiometer Co., Copenhagen, Denmark). The iCa data presented here were corrected to a pH of 7.40 and were stored and retrieved electronically. Blood samples were collected in standard, prepared heparinized blood gas syringes. The analyzer measured whole blood samples at 37°C. The laboratory in the hospital complies with standards of the National Association of Testing Authorities. During the study period, arterial blood gas analyses were performed according to the decision of cardiac surgeons, anesthesiologists, or trained nursing staff.

The highest iCa (iCa_{max}) and lowest iCa (iCa_{min}) within 24 hours after surgery were recorded. The time-weighted average of iCa (iCa_{ave}) was calculated assuming a linear trend between individual measurements and giving a time value to the measurements. For example, 1.20 mmol/L of iCa at 6 AM

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