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CASE SERIES

Evaluation of serum troponin I following the use of a modified-cardioplegia chemical composition for myocardial protection: a case series

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Heart failure (HF) is a major complication of cardiac surgery. To reduce the incidence of HF, del Nido cardioplegia, a calcium-free hyperkalaemic solution, was developed to reduce intracellular calcium influx that affects the heart following hyperkalaemic arrest. The absence of PlasmaLyte A, a base solution for del Nido cardioplegia, has led to the adoption of Ringerfundin as a substitute. This case series examines the myocardial protection provided by Ringerfundin using postoperative troponin I values. We describe 27 patients who received modified del Nido cardioplegic solutions, finding no significant increment in postoperative troponin I (troponin I value < 6 ng/ml) at 0, 12 and 24 hours and on the third day of blood sampling. Postoperative troponin I values at 24 hours and on the third day fell to near the preoperative values. The modified Ringerfundin-del Nido cardioplegic combination can be a safe alternative during cardiac surgery requiring continuous antegrade cardioplegia.

Keywords: cardioplegia, myocardial protection, del Nido solution, Ringerfundin, troponin I

Case series

All patients who underwent open-heart surgery between 2018 and 2022 were retrospectively reviewed. A total of 27 patients who received a continuous solution of modified del Nido antegrade cardioplegia, including atrio-septal, ventriculo-septal and heart valve defects, were identified. Patient characteristics included age, gender, body surface area and preoperative comorbidities (Table I). Approximately 500–750 ml modified del Nido antegrade cardioplegia solution was administered using mild systemic hypothermia (32–34 °C) after the aorta was cross-clamped (500–1 000 ml). The modified del Nido cardioplegia was the only cardioplegic solution used in this study and was administered at 4 °C. For the initial antegrade dose, the solution was administered as a blood to crystalloid ratio of 1:4 that consisted of 13 mEq Na^+, 26 mEq K^+, 10 ml $MgSO_4$ 20%, 6.0 ml lidocaine 2%, and 17 ml mannitol 20% (Table II). When ventricular fibrillation was achieved (usually about 1 L), cardioplegia was switched to continuous antegrade using a blood to crystalloid ratio of 4:1 to prevent haemodilution. Ventricular fibrillation is an abnormal rhythm that occurs a few seconds before asystole and leads to cardiac arrest. This sequence occurred after the administration of cardioplegia. After the heart stopped beating, open-heart surgery was performed.

General anaesthesia (GA) was used in 27 patients. GA was induced intravenously with midazolam 0.1 mg/kg, fentanyl 3–4 mcg/kg and atracurium 0.5–0.6 mg/kg. Datex-Ohmeda Avance CS2 (North America, USA) was used, and sevoflurane at a minimum alveolar concentration (MAC) of 2% was used for maintenance. Atracurium 0.5 mg/kg was administered intravenously every 30 minutes.

Hypothermia (32 °C) was induced during the surgery in all 27 patients. Patients were connected to a cardiac bypass machine with an oxygenator Terumo 25 FX (Bagshot, Surrey, UK). The activated clotting time was maintained above 480 s with the administration of heparin at 300–400 IU/kg. The bypass machine was primed with 1 200 ml of a solution containing Ringerfundin crystalloid 500 ml, gelofusine colloid, heparin 5 000 IU, mannitol

Table I: Patient demographics

Variable	Mean ± SD or median (IQR 25–75)
Age (mean)	33 ± 1.2
Male gender	11
BMI (kg/m^2)	23.3 ± 0.7
BSA (m^2)	1.8 ± 0.8
ASD closure (*n*)	12
VSD closure (*n*)	1
Heart valve replacement (*n*)	11
Repair of aorta + left atrial myxoma (*n*)	3

BMI – body mass index, BSA – body surface area, ASD – atrial septal defect, VSD – ventricular septal defect

Table II: Comparison of Ringerfundin with PlasmaLyte A

	Ringerfundin	PlasmaLyte A
Na^+ (mmol/L)	130	140
K^+ (mmol/L)	4	5
Ca^{2+} (mmol/L)	2.7	0
Mg^{2+} (mmol/L)	0	3.0
Cl^- (mmol/L)	109	98
Accetate (mmol/L)	0	27
Malate (mmol/L)	0	0
Gluconate (mmol/L)	0	23
Osmolarity (mosmol/L)	278	295
Approximate pH	5.5	7.4

Table III: Intraoperative observation data

Variable	Mean ± SD
The average length of aortic cross-clamping (minutes)	70.1 ± 6.7
The average length of CPB (minutes)	98.5 ± 5.2
Lowest mean temperature (celsius)	31.6 ± 0.02
Number of patients requiring defibrillation (%)	55.5

CPB – cardiopulmonary bypass

Table IV: Postoperative troponin I levels

Condition	Troponin I level (ng/ml) mean ± SD
Preoperative	0.04 ± 1.02
0 hours after surgery	2.24 ± 1.38
12 hours after surgery	4.23 ± 1.07
24 hours after surgery	0.81 ± 0.90
Third day after surgery	0.39 ± 0.82

20% 160 ml, albumin 5% 10 ml and sodium bicarbonate (NaHCO3 8.4%/Meylon 84 by Otsuka [Jakarta, Indonesia], each ml solution contained 84 mg of sodium bicarbonate) 30 ml.

During cardiopulmonary bypass, the flow rate was 2.0–2.5 L/min/m^2. The mean arterial pressure was maintained between 60 and 80 mmHg. The partial pressures of oxygen and carbon dioxide were maintained at 180–200 mmHg and 35–45 mmHg, respectively, through regular blood gas analysis. The patient's body temperature was lowered by an average of 1 °C per minute during the cooling period and increased by an average of 1 °C per 3 minutes during the rewarming period. An antegrade cardioplegic cannula was inserted in the ascending aorta, followed by aortic cross-clamping, and continued with 1 000 ml of modified del Nido cardioplegia with a mean temperature of 4 °C. If needed, the del Nido cardioplegia solution was administered after 90 minutes of ischaemia.

Baseline serum cardiac troponin I levels were measured preoperatively, and serial serum troponin I measurements were taken at 0, 12 and 24 hours postoperatively. Other laboratory examinations were performed according to standard operating procedures and postoperative care.

The mean (standard deviation [SD]) durations of the cardiopulmonary bypass and aortic cross-clamping were 98.5 and 70.1 minutes, respectively, without any complications related to administering the cardioplegia solution (Table III). The total volume of cardioplegic solution administered was approximately 1 000 ml. Ventricular fibrillation occurred in almost all patients, and 55.5% of patients who developed ventricular fibrillation were electrically cardioverted once or twice with 10–20 J.

Increased serum troponin levels during the postoperative period may be associated with myocardial damage resulting from cardiac arrest during cardiac bypass surgery. In this case series, we assessed serial increases in serum troponin I levels (Table IV).

We monitored serum troponin I levels in patients who received Ringerfundin as the base solution for del Nido cardioplegia. The objective of this study was to examine the potential myocardial preservation properties of Ringerfundin by reviewing the levels of intraoperative and postoperative troponin I in patients undergoing adult open-heart surgery.

Discussion

In the procedures examined in this study, Ringerfundin was used as a substitute for the calcium-free PlasmaLyte A (Deerfield, USA). Both solutions are balanced crystalloids, thus containing potassium, chloride and sodium at levels closer to the extracellular fluid than saline solutions.[1] The crystalloid solutions differ, however, with Ringerfundin having approximately 2.5 mmol/L calcium and PlasmaLyte A having no calcium. Ringerfundin is associated with reduced plasma osmolarity when used in large quantities.[2] Hadimioglu et al.[3] found that Ringerfundin and PlasmaLyte A could be used for uncomplicated kidney transplants despite PlasmaLyte A delivering the best metabolic profile. Zadák et al.[4] also found that Ringerfundin was well tolerated, with no undesirable side effects. It showed stable metabolic effects without the need for an increase in oxygen consumption or total energy requirement, without any calcium depletion. It did not cause an electrolyte imbalance or affect serum osmolality when 2 000 ml was administered over 4 hours.[4] These findings provide the basis for our consideration of using Ringerfundin as a substitute for PlasmaLyte A. Table I compares the contents of PlasmaLyte A and Ringerfundin.

Our data demonstrate the effectiveness of myocardial protection using continuous antegrade administration. Our data also show the absence of perioperative myocardial infarction, good left ventricle (LV) and right ventricle (RV) functions, usage of low doses of vasoactive drugs after cardiac shunt, and no need for additional mechanical circulatory support. The return of cardiac rhythm was spontaneous in more than half of the patients (54%). The rest of the patients (55.5%) required electrical cardioversion after aortic cross-clamp removal before the return of an organised cardiac rhythm. Thus, del Nido's previous strategy of administering cardioplegia provided sufficient protection to complete the surgery without significant hindrance. The incidence of ventricular fibrillation was the highest in our case series. Studies reported by Auer et al.[5] and Gunaydin et al.[6] found that using a cardiopulmonary bypass machine often leads to other adverse cardiovascular effects; one common problem is that the heart develops atrial fibrillation, which occurs in 40–50% of patients. The proposed reason is that an inflammatory response irritates the myocardium because the heart is being operated on, manipulated, often frozen, and changed. It also includes damage to the conduction system due to manipulation of nerve fibres during surgery and surgical injuries to the heart muscles.[5,6]

The composition of the del Nido solution is critical and offers myocardial protection. The del Nido cardioplegia solution increased the intracellular potassium concentration. As a result, diastolic cardiac arrest occurs electromechanically, aiming to create a more precise operating field for the surgeon to

work optimally and protect the myocardium from ischaemic injury that may arise in this phase.[7] The calcium ion content is 2.7 mmol/L in Ringerfundin while calcium is absent in PlasmaLyte A. The implications of calcium in the modified del Nido solution were examined by Takemoto et al.[8] Researchers have identified a characteristic calcium paradox that is related to heart contraction. At concentrations of 0.1 mmol/L calcium, ventricular fibrillation is not induced, and no myocardial contraction is observed. At concentrations above 0.6 mmol/L, excellent cardioprotective effects are observed. The current study's findings were consistent with those of the animal model by Takemoto et al.[8]

Current evidence shows that the use of del Nido cardioplegia offers several advantages. These include uninterrupted surgery, stabilisation of calcium regulation throughout the ischaemic period, lower need for systemic cooling and, eventually, lower total volumes of cardioplegia. Additional evidence of the reduced risk of myocardial damage may be the basis for using Ringerfundin as a base for del Nido cardioplegia. Despite having calcium, Ringerfundin does not cause calcium overload, as stated by Zadák et al.[4] Thus, it can be considered a comparable solution to those with no or low calcium concentrations.

The del Nido cardioplegia solution was administered repeatedly after 90 minutes. Some previous case studies have suggested repeating administration every 60 minutes under certain clinical conditions. In this case series, almost all surgeries were of short duration. Consequently, only one dose of del Nido cardioplegia was administered.[9] In their study, Kim et al.[9] provided a single dose of del Nido cardioplegia and the reported serum troponin I levels as 0.01 ng/ml preoperatively (range 0.01–0.47 ng/ml), 4.3 ng/ml immediately (range 0.1–43.7 ng/ml) and 1.5 ng/ml after 3 days (range 0.1–33.5 ng/ml). These figures are comparable to this case series using the modified del Nido findings, as shown in Table IV.

Compared to the administration of blood cardioplegia, which is repeated every 20 minutes and has an interruption during the operation, the del Nido cardioplegia solution can reduce the interruption time. Repeated administration of blood cardioplegia can also increase fluid intake in patients undergoing cardiac bypass. In a study conducted by Ucak et al.,[10] patients who underwent cardiopulmonary bypass, who were administered a solution of del Nido cardioplegia and blood cardioplegia, had a shorter duration of aortic cross-clamping and cardiac bypass, as well as requiring a smaller volume of cardioplegia solution compared to blood cardioplegia.

A meta-analysis conducted by Guru et al.,[11] indicated that patients with blood cardioplegia showed a lower incidence of low cardiac output syndrome and decreased cardiac enzyme levels than patients receiving crystalloid cardioplegia solutions. However, another analytical study by Sá et al.[12] indicated that there was no significant difference between the administration of crystalloid and blood cardioplegia solutions in the incidence of low cardiac output syndrome.

Although not fully understood, ischaemia-reperfusion injury is caused by increased intracellular calcium concentrations in myocytes postischaemia.[13] An increase in Ca^{2+} is associated with an increase in Na^{+} during periods of ischaemia, leading to calcium influx via $Na^{+}/Ca2^{+}$ channels. As a result of high intracellular Ca^{2+}, myocytes contract more rapidly, which causes irreversible damage and even death of myocardial cells. Consequently, del Nido cardioplegia provides a theoretical advantage over other cardioplegia solutions because it is calcium-free and contains lidocaine as a Na^{+} channel blocker and magnesium as a physiological calcium competitor. All these components seem to limit calcium influx in the postreperfusion phase. The effectiveness of this mechanism has been demonstrated in the hearts of animals and children. In the heart of rats, del Nido cardioplegia resulted in significantly lower intracellular calcium levels than in hearts with continuous blood cardioplegia. Adult patients receiving del Nido solution experienced a decrease in troponin I levels after surgery compared to patients receiving a blood cardioplegia solution.

The increase in troponin levels during the postoperative period reflects myocardial damage when the patient is in cardiac arrest while the cardiac bypass machine is running. This case series showed no significant increase in troponin I levels (troponin I value < 6 ng/ml). On the third day postoperatively, troponin I values fell to near the preoperative values. Ucak et al.[10] compared troponin I levels in patients undergoing coronary bypass surgery and found no significant difference between the del Nido cardioplegia solution and blood cardioplegia.

Conclusion

We suggest that intermittent cold blood cardioplegia and the del Nido cardioplegia solution can be considered safe alternatives in cardiac surgery that requires continuous antegrade cardioplegia in certain clinical conditions. When used in some clinical conditions, durations and types of surgery, Ringerfundin may demonstrate effectiveness and can be considered as a choice for the basis of crystalloid cardioplegia solution. Further studies on specific cardiac conditions should be conducted to evaluate the safety, clinical outcomes and effectiveness of this solution as the base solution for crystalloid cardioplegia.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This case report was carried out under the permission and approval obtained from Health Research Ethics Committee Dr. Moewardi General Hospital with Ethical Clearance Reference Number 159/II/HREC/2018.

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