



Custodial Cardioplegia and Cardiac Preservation during pediatric Cardiac Surgery Procedures: A Narrative Review

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ABSTRACT

Controlled intraoperative cardioplegia is indispensable to pediatric cardiac surgery procedures. Several preservation techniques have been proposed for such purposes, with varying application by different surgeons. The custodial cardioplegia is a recent approach that is considered to be a safe and effective cardiac protector. This narrative review was conducted via searching in four databases, including PubMed, Scopus, Embase, and ScienceDirect. The studies focused on the efficacy and safety of custodial cardioplegia reviewed, especially in pediatric cardiac surgeries and relevant procedures. In total, 21 articles were eligible, and the findings highlighted the controversies regarding the use of various cardioplegic solutions and the variability of their application by surgeons. However, data were inadequate regarding the optimal cardioplegic solutions in this regard. Some of the studies performed on adults suggested that custodial cardioplegia may be equivalent to conventional blood cardioplegia. Most of the reviewed articles showed a consensus on the safety and efficacy of custodial cardioplegia in adult and pediatric cardiac surgeries. It is believed that custodial procedures are not only easily delivered, but they are also convenient and less time-consuming and provide long-lasting motion and bloodless fields for the surgeon to perform the operation. Therefore, use of custodial cardioplegia has been reported to be safe, effective, and cost-efficient compared to conventional cardioplegic solutions. However, different findings have also been denoted in some of the studies in this regard, implying the equal effectiveness of these techniques.

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Introduction

In every cardiac surgery, it is essential to provide a motionless and bloodless field for the surgeon to perform the operation (1). Cardioplegic solutions are considered to be the optimal myocardial preservation methods in cardiac surgery;

these solutions may be indirect or direct to the coronary arteries (2). Myoprotective strategies vary among surgeons, indicating that the optimal cardioplegic strategy has not yet been consolidated (3), and various cardioplegic strategies have

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been proposed to achieve the best possible outcomes.

Crystalloid cardioplegia and blood-based cardioplegia are widely used in pediatric cardiac surgeries (2,4,5). In the United States, use of 167 cardioplegic solutions in heart transplantation has been reported. Therefore, there are numerous cardioplegic solutions available in pediatric cardiac surgery (4). Conventional solutions to induce cardiac arrest are based on hyperkalemic strategies with crystalloid or blood content (6).

In 1970, Bretschneider presented a new cardioplegic solution consisting of histidine, tryptophan, and ketoglutarate, which was referred to as custodiol (7,8). Custodiol is an intracellular crystalloid cardioplegia with low sodium and calcium contents in the form of a solution that buffers intracellular acidosis and provides the precursors required for anaerobic metabolism, as well as sodium depletion due to the hyperpolarized myocyte membrane, which cause cardiac arrest in the diastolic time (9,10). Custodiol has been applied in pediatric cardiac surgeries as an alternative cardioplegic solution with the advantage of single dose administration and relatively equivalent myocardial protection (1).

Compared to custodiol cardioplegia, intact cardiac protection is not achieved with conventional cardioplegic solutions in any type of delivery systems (antegrade versus retrograde or continuous versus intermittent) in all cases, especially in complex cardiac procedures, neonatal and congenital cardiac surgeries, multiple valvular surgery, concomitant coronary artery bypass with valvular surgery, aortic procedures (e.g., Bentall and David procedures), and heart transplantation (11,12). Repeated operative interruptions for cardioplegic administration (every 20 minutes to maintain the protective properties) and occasional direct coronary ostial cannulation are among the setbacks of blood cardioplegia (1,13).

Custodiol cardioplegia is cost-efficient, less time-consuming, and convenient, while it is also easily delivered and causes minimal systemic electrolyte imbalance. Furthermore, it could be administered as a single dose and is beneficial for lengthy cardiac surgeries (up to 3-4 hours); as a result, there are few interruptions in the lengthy cardiac surgeries performed based on this method (6,14-16).

Although various cardioplegic techniques with variable advantages and disadvantages have been used in adults, the differences between the immature heart of pediatric patients compared to the mature heart of adults must be taken into account. In newborns, only 30% of the myocardial mass comprises the contractile tissue, while this

rate is estimated at 60% in the myocardium of adults. Moreover, it has lower ventricular capacity, preload reserve, oxidative capacity, and isotropic reserve and fewer mitochondria. Low cardiac output syndrome (LCOS) is more often detected in pediatric patients (4).

Literature Review

In this narrative review, we searched via databases such as PubMed, Scopus, Embase, and ScienceDirect using keyword combination, including 'histidine-tryptophan-ketoglutarate' or 'custodiol' or 'cardioplegic solutions' or 'custodiol solution' or 'cardiac arrest' with mesh and entree headings. In addition, manual search was performed in order to identify the studies that could not be retrieved in the initial literature search.

The published articles on custodiol cardioplegia and its efficacy and safety were selected and reviewed (n=21). Afterwards, the studies that compared custodial cardioplegia with conventional cardioplegic strategies were identified, especially those in the field of pediatric cardiac surgeries and heart transplantation. Due to the wide variety of the articles in the field of cardiomyocyte protection and preservation, we mainly focused on the independent investigation of custodiol solutions to briefly mention the advantages and disadvantages of the common methods used in this regard. It was challenging to decide on the most effective myocardial protection technique in some cases. For instance, lengthy and complex operations with recurrent cardioplegic delivery from the open aortic root are required in the newborns and patients with damaged myocardium.

According to the current review, propositions and explanations vary regarding the preference of cardioplegic methods. In a study, Michal Sobieraj et al. (2) have suggested that cardio protection along with other factors, such as prolonged cardiopulmonary bypass duration, low body surface area in the patient, urgency of surgical operation, and complex cardiac surgeries (e.g., coronary heart disease [CHD]), may influence postoperative clinical outcomes, leading to conditions such as LCOS and overall complications in the patients with CHD. According to the mentioned research, crystalloid cardioplegic solutions have significant adverse effects on the postoperative course in the children with CHD. In contrast, blood cardioplegia has no adverse effects on these outcomes, and its application could exert protective effects by reducing the incidence of LCOS and its complications.

A prospective randomized study by Garbade J. et al. (2013) reported an association between spontaneous ventricular fibrillation in the opera-

tion room and higher incidence of postoperative arrhythmias with custodiol (17). On the other hand, Gaudino et al. (18) suggested that lower right ventricular (RV) ejection fraction, cardiac indices, and longer inotropic duration were associated with poor preoperative RV function in the patients receiving custodiol cardioplegia.

Another randomized clinical trial in this regard compared single-dose custodiol with multiple-dose blood cardioplegia in 80 patients undergoing mitral valve repair surgery using Troponin-T and CK-MB as the markers of myocardial ischemia based on the assumption that custodiol provides insufficient protection and preservation (19). In two other studies conducted on adults with thoracic aorta repair, the findings indicated that the incidence of LCOS and inotropic use were similar in the patients receiving custodiol and blood cardioplegia (1,13).

In some studies, use of custodiol cardioplegia has been recommended in more complex surgeries due to its single-dose efficacy and long-lasting cardioplegia. For instance, Qulisy et al. (1) have suggested that in the children undergoing cardiac surgery, custodiol cardioplegia may be associated with the lower effectiveness of myocardial preservation and increased adverse outcomes compared to blood cardioplegia. Furthermore, Scrascia et al. (19) stated that custodiol cardioplegia improved cardiac protection in longer ischemia compared to blood cardioplegia.

In general, blood cardioplegia is more physiological and considered superior compared to the crystalloid solution for the ischemia durations of more than one hour. In blood cardioplegia, hemoglobin is used for oxygen transportation and contains metabolic substrates, thereby causing lower hem dilution. It also contains oxygen free radical scavengers (4).

In this regard, Yasuhiro Kotani et al. (3) surveyed a population including 122 members of the Congenital Heart Surgeons' Society, focusing on cardioplegic formulations, dosage, and administration and perfusion methods in four targeted groups of neonates, infants, children, and adolescents. The analysis of the responses suggested that blood-based cardioplegic methods were widely applied, with approximately 90% of the surgeons using some variations of blood-based cardioplegia. Moreover, the researchers denoted that despite the acceptance of blood-based cardioplegia by almost 90% of surgeons in the survey, there were still controversies regarding the experimental clues to support the administration of blood-based cardioplegia in the immature myocardium.

Fabiano F. Viana et al. (11) performed a pro-

spectively compiled single-center database review, suggesting that custodiol solutions are convenient and as safe as blood-based cardioplegia, which results in the preference of surgeons and health centers for employing custodial or blood-based cardioplegia.

In some studies focusing on congenital heart surgeries, the age-dependent variations in normal myocardial metabolism and response to cardioplegic arrest have implied that the optimal method may differ in neonates, infants, children, and adults (20,21).

Conclusion

According to this review, medical centers must decide on the myocardial protection method used in cardiac surgeries. The foremost factors in this regard are clinical outcomes and the experience of surgeons. In addition, the main factors affecting the selection of such methods include effectiveness, simplicity, cost-efficiency, and acceptance by surgeons.

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Conflict of Interest

The authors declare no conflict of interest.

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