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Use of Histidine-Tryptophan Ketoglutarate and St. Thomas Cardioplegia solutions in cardiac surgery: A narrative review

Bisar Amac[1], Sukran Amac[2], Nazim Kankilic[3]

1. Harran University, Faculty of Health Sciences, Department of Perfusion, Sanliurfa, Turkey
2. University of Health Sciences, Hamidiye Health Sciences Institute, Pharmaceutical Technology (PhD Candidate), Istanbul, Turkey
3. University of Health Sciences, Sanliurfa Mehmet Akif Inan Training and Research Hospital, Department of Cardiovascular Surgery, Sanliurfa, Turkey.

Correspondence
Bisar Amac, Harran University, Faculty of Health Sciences, Department of Perfusion, Sanliurfa, Turkey.

e-mail
amacbisar@gmail.com

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ORCID ID of the author(s):
BA: 0000-0003-0320-4239
SA: 0000-0003-2106-4807
NK: 0000-0001-7111-7503

Abstract

Cardioplegia is the mainstay of myocardial protection in cardiac surgery with cardiopulmonary bypass. Historically, cardioplegia emerged in the late 19th century when scientists discovered that high concentrations of potassium could stop the heart in diastole and that this could be used as an approach in open heart surgery. The most important finding in cardioplegia is that the heart restores its function after cardiac arrest without myocardial damage. In this article, the myocardial protective effects of St Thomas cardioplegia and histidine-tryptophan-ketoglutarate cardioplegia solutions were evaluated in adult cardiac surgery. Both cardioplegia solutions continue to be useful and important in cardiac surgery, but their superiority over each other remains controversial. We also believe that cardiovascular surgeons and perfusionists should focus mainly on the myocardial protective effect in the selection of different cardioplegia solutions. In conclusion, whatever the preferred cardioplegia solution, it should provide basic cardioplegia properties such as preservation of energy stores, rapid diastolic cardiac arrest, reversibility and minimal toxicity.

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Introduction

Cardioplegia is the mainstay of myocardial protection in cardiac surgery with cardiopulmonary bypass (CPB). Because CPB may cause myocardial ischaemia and reperfusion injury in cardiac surgery, leading to impaired cardiac function. Therefore, cardioplegia is the most commonly used method to protect the myocardium. Cardioplegia is a pharmacological cardiac arrest solution administered intentionally and temporarily to stop the heart. Historically, cardioplegia emerged in the late 19th century when scientists discovered that high concentrations of potassium (K+) could stop the heart in diastole and that this could be used as an approach in open heart surgery. The most important finding in cardioplegia is that the heart restores its function after cardiac arrest without myocardial damage (1).

Cardioplegia can reduce myocardial metabolic demand. Cardioplegia is divided into two main categories. These are crystalloid-based and blood-based solutions. Cold crystalloid cardioplegia was the cornerstone of cardiac surgical practice and was also later added to blood to increase the oxygen carrying capacity of crystalloid cardioplegia, maintainoncotic pressure and scavenge free radicals. Over time, many advanced cardioplegic solutions have emerged in cardiac surgery, including St. Thomas cardioplegia (STC) and histidine-tryptophan-ketoglutarate (HTK) solution or Bretschneider cardioplegia (2). Common cardioplegia solutions containing crystalloid materials include STC and HTK cardioplegia solutions. STC cardioplegia solution contains an extracellular solution, while HTK contains an intracellular solution. HTK is commonly used in heart and organ transplant surgery to preserve organs. Blood cardioplegia (BC) and DN cardioplegia solutions contain mixtures of crystalloids and blood products. The original BC solution is usually made using a 1:4 mixture of blood and crystalloid. DN cardioplegia solution containing a 4:1 mixture has recently entered clinical use. Originally used for paediatric cardiac surgery, it is now frequently used for adult cardiac surgery (3). Another important point about cardioplegia used in myocardial protection is single dose and multidose cardioplegia solutions (4).

Regardless of the preferred cardioplegia solution, all types of agents must meet certain conditions listed below (5,6):

- Preserve energy stores to meet the metabolic needs of the heart during aortic cross clamping (5,6).
- Provide rapid diastolic cardiac arrest (5,6).
- Exhibit rheological properties for proper distribution throughout the myocardium (5,6).
- It should increase osmolarity to prevent myocardial oedema due to ischaemia (5,6).
- It should have a buffer effect to prevent secondary acidosis (5,6).
- It must have reversibility (5,6).
- It should have no or minimal side effects.
- Provide induction of hypothermic state for specific cardioprotective solutions (5,6).

In the selection of different cardioplegia solutions, perfusionists mainly focus on myocardial protective effect and cost. However, there is no uniform standard for cardioplegia types or dosages (7). In this article, we evaluated the myocardial protective effects of STC and HTK cardioplegia solutions in adult cardiac surgery.

Histidine-Tryptophan Ketoglutarate Cardioplegia solution

Developed by German physiologist Hans Jürgen Bretschneider and his group at the University of Göttingen in the early 1970s, HTK solution is an intracellular crystalloid solution formulated for use in cardiac surgery. HTK solution is also called Bretschneider cardioplegia solution. This solution was introduced into clinical practice in 1977 and modified in the 1980s. Although HTK solution was primarily intended for use in cardiac surgery, it has also found a place in the preservation of other organs such as the liver, pancreas and kidneys. The HTK solution was marketed under the brand name Custodiol® (Essential Pharmaceuticals, Durham, NC, United States of America) and is now widely applied as a cardioplegic strategy for myocardial protection. In the following years, additional research was conducted leading to the development of various cardioplegic solutions that differed in the composition of the solution used, the method of administration and the temperature. HTK has been proposed as a replacement for blood agents and other conventional cardioplegia, providing up to three hours of myocardial protection with hypothermia. This cardioplegia saves surgeons time by reducing the total application time of cardioplegia in large operations. However, despite this advantage, the use of HTK was ignored for a period. This was due to the difficulty in understanding the complex biochemical mechanisms involved in inducing cardiac arrest and the general disinterest of the cardiac surgical community in time for cardioplegia. Since the 1980s,

HTK or Bretschneider solution has been used in heart transplantation due to its long-term cardioprotective properties. Recent studies confirm the benefits of using Custodiol® for allotransplant preservation. In terms of haemodynamic parameters, cardiac enzyme release and 30-day mortality, HTK solution provides similar results compared to cold blood cardioplegia with built-in advantages in terms of technicality and shortening ischaemic times (1,5).

HTK solution is an intracellular cardioplegia solution that was first used as a cardioplegia solution in cardiac surgery operations, and as mentioned above, it has been widely used in transplantation surgery due to its organ protective properties. The solution, which is administered as a single dose and lasts for 6 to 8 minutes, provides myocardial protection for up to 180 minutes. A single dose is sufficient in almost all complex cardiac operations. It is administered as 20 to 25 mL/kg in adult cases. It can be administered antegrade or retrograde. Custodiol® solution containing low concentrations of sodium (Na+) and calcium (Ca+) deprives the myocardium of ions for exchange across ion channels to generate an action potential and cause cardiac arrest. Tryptophan is a cell membrane stabilising agent, ketoglutarate increases energy production during reperfusion and mannitol osmotically regulates the cell membrane. Histidine is added as a buffer to increase the efficiency of anaerobic glycolysis (8-10).

HTK or Bretschneider (Custodiol®) cardioplegia solution: 15 µmol/L Na+, 9 µmol/L K+, 4 µmol/L magnesium (Mg+), 0.02 µmol/L Ca+, 198 µmol/L histidine, 2 µmol/L tryptophan, 1 µmol/L ketoglutarate and 30 µmol/L mannitol and has a pH value between 7.02-7.20 (8.10).

- Sodium and calcium: Provides the concentration of buffer systems. It prolongs the duration of ischaemia-induced glycolysis and prevents intracellular overload and irregular activities (8-10).
- Histidine/Histidine Hydrochloride (HCl) (pH buffer): Provides to increase the efficiency of anaerobic glycolysis. It provides normal osmolarity and membrane protection of the buffer system. It also prevents metabolic acidosis (8-10).
- Tryptophan (Membrane potential stabiliser): Protects the cell membrane and supports membrane integrity. In short, it acts as a membrane potential stabiliser (8-10).
- Alpha Ketoglutarate (Nicotinamide adenine dinucleotide (NAD) precursor, important in ATP synthesis): It helps to stabilise the myocardial cell membrane and is a substrate for anaerobic metabolism; it is an intermediate in the Krebs cycle and is also a precursor of NAD. It also provides ATP production during reperfusion and inhibits glucose and lactate production (8-10).
- Mannitol Mannitol maintains physiological osmolarity and prevents intracellular osmotic pressure to reduce cellular oedema. Mannitol also acts as a free radical scavenger (8-10).

St Thomas Cardioplegia solution

The late 1960s and early 1970s were associated with the return of a solution of high to moderate K+ concentration as an attractive strategy for inducing cardioprotection. In fact, in 1975, STC solution No. 1 was introduced by Hearse and Braimbridge in open-heart surgery in London. The formulation of the solution was based on the desire to deviate as little as possible from the normal extracellular ionic composition and, in particular, to minimise the amount of K+ traditionally used to achieve rapid and complete arrest. The solution was prepared by adding 16 mmol/L potassium chloride (KCl), 16 mmol/L magnesium chloride (MgCl2) and 1 mmol/L procaine to 1 L Ringer's solution. This solution subsequently came into widespread clinical use worldwide. After the clinical introduction of STC solution No.1, experimental work was continued to improve its efficacy. This involved conducting detailed dose-response studies aimed at optimising the concentration of each ingredient and looking for new ingredients or procedures that could provide additional protection. As a result of these studies, STC solution No. 2 was introduced in 1981. Although both types of solution contained increased Mg+ (16 mmol/L) and normal calcium ion concentrations, they differed in K+ ion concentrations. The first STC solution contained K+ ions at a concentration of 20 mmol/L, whereas the second contained a lower content, 16 mmol/L. The mechanism responsible for the effects of these solutions is based on diastolic arrest through membrane depolarisation. STC solution No. 2 was introduced commercially in the United States in 1982 under the name Plegisol® (Abbott Laboratories, North Chicago, Ill.). The solution was designed to function as a base solution to which various additives such as lidocaine, nifedipine and creatine phosphate could be added to meet the individual requirements of surgeons (1,11).

STC No 2 solution: 110 mmol/L Na+, 16 mmol/L K+, 16 mmol/L Mg2+, 1.2 mmol/L Ca2+ and 10 mmol/L

sodium bicarbonate (NaHCO3-) (12).

STC solution (Plegisol®) is the most popular extracellular crystalloid cardioplegia solution. It is a K+ based solution used as crystalloid solution only or combined with blood (4:1 blood:crystalloid). It has an optimal extracellular K+ concentration. Many centres usually add extra K+ to the cardioplegia solution and combine it with blood, typically at a ratio of 4:1 (blood:crystalloid). It is typically repeated every 20 minutes to maintain arrest and myocardial protection during aortic cross clamp (9,10,13).

Possible Plegisol® content in the market is as follows: The solution contains 6.43 mg sodium chloride, 0.176 mg calcium chloride dihydrate, 3.253 mg magnesium chloride hexahydrate (MgCl2) and 1.193 mg KCl granules as active substance in 1000 mL solution in a PVC bag in a plastic casing ready for use at +4 oC. In clinical use, 20 mL of sodium bicarbonate with a ratio of 8.4% is added. In addition, the initial cardioplegia dose is 15 ml/kg (full dose) and maintenance doses are administered as half dose (1/2) every 20 minutes.

However, single dose applications have also been performed using modified STC solution. There are several studies on single dose STC solution. Mork et al. (14) compared the myocardial protective effect of a single dose of STC solution and Bretschneider solution in minimally invasive mitral valve surgery and found that the postoperative myocardial protective effect was similar between them; however, the postoperative troponin T level was significantly lower in the STC solution group. Hiraoka et al. (15) compared glucose-insulin-K+ and STC solutions in isolated aortic valve replacement at intervals of approximately 40 minutes and 60 minutes, respectively, and reported that postoperative CK-MB levels were significantly lower in the STC solution group. These findings suggest that long intermittent dosing using STC solution can be administered safely (14-16).

Data from clinical studies

In CPB-guided cardiac surgery, various cardioplegia solutions are used to protect both an immobilised heart and myocardium. HTK and STC solutions are among the cardioplegia solutions used in cardiac arrest and myocardial protection. There are many studies in the literature on the use of these two cardioplegies (14,17-20). Aarsaether E, et al. (17) conducted a porcine experimental study comparing these two cardioplegies. In their study, they compared mechanoenergetic function (preservation of left ventricular mechanoenergetics) and troponin T release after cardioplegic arrest induced by repeated administration of STC solution and single dose of HTK cardioplegia solution. Fourteen pigs were infused with 30 mL/kg HTK cardioplegia (n=7) or 500 mL STC (n=7) followed by 200 mL STC cardioplegia 20 and 40 min later. After one hour of aortic cross-clamping, pigs were weaned from CPB and pig hearts were reperfused for 4 hours. Stroke status was determined by a conduction catheter placed in the left ventricle. Myocardial oxygen consumption was measured in relation to coronary blood flow and arterial-coronary sinus oxygen saturation difference. Troponin T was sampled from the coronary sinus. The slope of the stroke status-myocardial oxygen consumption relationship increased by 1.09 (+/-0.53) in the HTK group and 0.33 (+/-0.70) in the STC group following the 4th hour of ischaemia and reperfusion. Troponin T was significantly higher in the HTK group compared with the STC group. Repeated administration of STC resulted in better preservation of mechanoenergetic function and lower troponin T release after ischaemia compared with a single dose of HTK cardioplegia, indicating improved cardioprotection with STC (17).

Wang ZH, et al. (18) investigated HTK and STC cardioplegia in paediatric cardiac surgery and investigated the myocardial protective effect of these two solutions in cardiac surgery for tetrology of fallot (TOF). In their study, they examined seventy-seven paediatric TOF patients who underwent total surgical repair between January 2014 and October 2015. They divided the patients into HTK group (n = 35) and STC group (n = 33). They evaluated the perioperative values of the groups in the study. They analysed the primary endpoints, including spontaneous cardiac re-beat time, intensive care unit (ICU) length of stay, total hospital stay, postoperative mechanical ventilation time, postoperative hospital stay and perioperative echocardiographic results. They found that the duration of spontaneous cardiac restart was significantly shorter in the HTK group compared to the STC group (0.26 min ± 0.56 vs. 1.33 ± 1.02, $p < 0.001$). They reported that there was no significant difference between the two groups in terms of intensive care unit length of stay ($p = 0.29$), postoperative mechanical ventilation time ($p = 0.84$) and overall length of stay (0.73); and the mortality rates of the two groups were similar (2.9% - 3.0%). In conclusion, they stated that they thought that the modified STC solution was as safe as the HTK solution (18).

A study investigating combined STC and HTK cardioplegia for myocardial protection in heart transplant patients was conducted by Lee KC, et al. (19) The study included 31 heart transplant patients between June 2008 and March 2010. During heart procurement, they initially infused 1,000 mL of cold STC solution to induce cardiac arrest. After procurement, a further 2,000 mL of cold STC solution

was infused at low perfusion pressure. A further 1,000 mL of cold STC solution was perfused before donor heart implantation. Donor age, preoperative characteristics of the recipient, duration of ischaemia, duration of hospital stay, postoperative graft function, major cardiac events and transplant vasculopathy were studied. As a result of their study, they reported that the combination of STC and low pressure perfusion with HTK solution was safe for donor heart preservation and provided short-term survival similar to other approaches (19).

Mork C, et al. (14) compared the use of HTK (Bretschneider (Custodiol®)) and STC 2 cardioplegia solution in mitral valve repair via anterolateral right thoracotomy. The study included 184 patients undergoing isolated mitral valve procedures from May 2012 to February 2019 who underwent mitral valve repair via anterolateral right thoracotomy. Of the patients in the study, 123 received Bretschneider (Custodiol®) cardioplegia and 61 received STC. The primary efficacy endpoint was peak postoperative high-sensitivity cardiac troponin (hs-cTnT) during hospitalisation. Secondary endpoints were peak creatine kinase-muscle brain type (CK-MB) and creatine kinase (CK) and safety outcomes. They used the inverse probability of treatment weighting to correct for confounding by indication. They concluded that STC 2 cardioplegia was associated with lower postoperative peak levels of all cardiac markers reflecting cardiac ischaemia such as hs-cTnT, CK and CK-MB in the propensity-weighted treatment groups compared with Bretschneider (Custodiol®). They also reported that there was no difference in postoperative complications between the treatment groups (14).

Regarding single dose administration of STC solution, Barbero C, et al. (20) compared single dose STC with Custodiol® cardioplegia in right mini-thoracotomy mitral valve surgery. The primary endpoint of their prospective observational study was cardiac troponin T levels at different postoperative time points. In their study, they compared thirty-nine patients receiving STC solution with 25 patients receiving Custodiol® cardioplegia. They reported that there was no difference in postoperative markers of myocardial damage. They noted that ventricular fibrillation with resumption of electrical activity was more frequent after Custodiol® cardioplegia. In conclusion, they stated that in selected patients undergoing right mini-thoracotomy mitral valve surgery, effective myocardial protection exceeding one-hour ischaemic arrest can be achieved with a single dose of STC (20).

Conclusions

In CPB-guided cardiac surgery, various cardioplegia solutions are used to protect both an immobilised heart and myocardium. HTK and STC solutions are among the cardioplegia solutions used in cardiac arrest and myocardial protection. The usability and importance of both cardioplegia solutions in cardiac surgery are undisputed, but there is an ongoing debate about their superiority over each other. However, in the selection of different cardioplegia solutions, cardiovascular surgeons and perfusion specialists should mainly focus on myocardial protective effect and cost. Consequently, whatever the preferred cardioplegia solution, it should provide basic cardioplegia properties such as preservation of energy stores, rapid diastolic cardiac arrest, reversibility and minimal toxicity, etc.

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Data analysis and interpretation: BA, SA, NK

Collection and/or assembly of data: BA, SA, NK

Writing the article: BA, SA, NK

Critical revision of the article: BA, SA, NK

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