

Conservative doses of the solution Histidine-Tryptophan-Ketoglutarate (HTK) for pediatric cardiac surgery with short aortic clamping

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The concept of myocardial preservation, preservative solutions and their doses are still in flux. Cardioplegic solution of Histidine-Tryptophan Ketoglutarate (HTK) has proved to be effective in adult as well as pediatric patients over three decades.

Material and Methods. In 47 children diagnosed with congenital heart disease, with low and medium surgical risk we used HTK cardioplegic solution in a single dose, enough to bring the heart to asystole and cardiac electrical inactivity during surgical repair. Early post reperfusion arrhythmias were recorded and its follow-up to discharge.

Results. Corrective surgical procedure was performed in all patients, using a cardioplegia dosage of 18.18 ml/kg for myocardial preservation. Aortic cross-clamping time was 34.3 minutes in average, and spontaneous defibrillation was 85.1%. All patients had an uneventful postoperative course. Hospital discharge was at 5 days after operation in average.

Conclusions. HTK solution is safe at low doses to maintain myocardial preservation in pediatric cardiac surgery with short aortic cross-clamping time.

Key words: HTK solution; Cardioplegia; Conservative dose.

El concepto de la preservación miocárdica, las soluciones preservadoras y sus dosis continúan en constante cambio. La solución cardioplégica de Histidina-Triptofano-Cetoglutarato (HTK) ha demostrado gran eficiencia, en pacientes adultos y en pacientes pediátricos desde hace tres décadas.

Material y Métodos. En 47 niños con diagnóstico de cardiopatías congénitas de bajo y mediano riesgo se utilizó HTK como solución cardioplégica en una sola dosis, suficiente para llevar al corazón a asistolia y a inactividad eléctrica cardíaca durante la reparación quirúrgica. Se registraron las arritmias tempranas postreperusión y su evolución hasta su egreso.

Resultados. En todos los casos se realizó la corrección quirúrgica propuesta, la dosis de la solución HTK con la cual se consiguió la preservación miocárdica fue de 18.18 ml/kg de peso. El tiempo promedio de pinzamiento aórtico fue de 34.3 minutos y la desfibrilación espontánea fue de 85.1%. Los pacientes tuvieron una evolución satisfactoria y se egresaron 5 días después del procedimiento quirúrgico, sin complicaciones.

Conclusiones. La solución de HTK en dosis bajas es segura para mantener la preservación miocárdica en procedimientos quirúrgicos congénitos de pinzamiento aórtico corto.

Palabras clave: Solución HTK; Cardioplegia; Dosis conservadoras.

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Since the sixties, Bretschneider introduced a crystalloid cardioplegic solution capable of protecting the heart for conventional cardiac surgery and cardiac transplant based on Histidine-Tryptophan-Ketoglutarate and manitol (HTK), with electrolyte components similar to the ones on the intracellular space.

The HTK solution has been used with good results, favoring cellular stability, decreasing edema, capturing free radicals produced by damage from ischemia, producing adenosine triphosphate during reperfusion and acting as a buffer [1,2].

This solution has been used on adult patients with ischemic cardiopathy, aortic and mitral disease, children with congenital heart disease, and cardiac transplantations. Its effectiveness has been proved on patients with adequate and poor ventricular functions, as well as with short aortic cross-clamp-

ping (AC) time procedures, and long AC time procedures for complex surgery.

Proposed doses in order to obtain myocardial protection have been different dependent on the specific working groups. Some of them are as follows: i) The suggested in milliliters of HTK for body weight in one dose (30-60 milliliters/kg); ii) By myocardial tissue gram calculated in only one dose 1ml/min/gram of cardiac weight (0.6% of body weight in children); iii) Standard dose in milliliters per patient and additional doses per each hour after the first two hours of AC [3,5]. However, these calculated volumes have been questioned by reports indicating that lower doses can also be useful on getting asystole and adequate myocardial preservation on adult patients underwent coronary arterial bypass grafting with doses from 10 to 15 ml of HTK/kg.

There are no reports in pediatric cardiac surgery demonstrating the effectiveness of HTK low-dose for procedures with short AC. The main objective in this study was to know the most adequate HTK dose in pediatric cardiac surgery, based on clinical observations achieving asystole, isoelectric line on ECG stopping administration of the HTK cardioplegic solution.

MATERIAL AND METHODS

This study was conducted at Unidad de Alta Especialidad, IMSS No. 71, from 2006 to 2010. Forty-seven patients underwent congenital heart disease correction, all of them with surgical and anesthetic consent. They were managed with invasive monitoring and general balanced anesthesia. Cardiopulmonary bypass (CPB) circuit was filled out with colloid solution (albumin, blood, plasma), with membrane oxygenators, centrifuge pump and hemofilter in all cases. Sternotomy was used, in normothermic extracorporeal circulation, with uni or bicaval cannulation, ascending aortic cannulation and cardioplegia needle, with HTK solution at 4C with 60mm Hg of cardioplegic perfusion pressure, and cold water in the pericardial sac. Once CPB started, the aorta was cross-clamped and the HTK cardioplegic solution administered through ascending aorta, just in one-single dose until achieve asystole, and isoelectric line on the electrocardiogram obtained, stopping inflow right away. Cardioplegia got into into systematic circulation, with no selective aspiration but hemofiltration of the infused volume at the end of CPB. Once the cardioplegic solution was finished, the heart was opened and the surgical procedure as initially planned was carried on corresponding to pathologies of risk 1 to 3 RACHS classification [6]. Finally, the aorta was unclamped, using direct defibrillation with 10 joules when necessary.

Data collected were age, sex, weight, body surface, diagnosis and surgical procedure, AC and CPB time, milliliters of HTK solution, defibrillations, length of stay in the intensive care unit, length of in-hospital stay.

RESULTS

Forty-seven cases were collected, with a mean of 6.27 years. There were 25 female and 22 male patients. Diagnosis

was compounded by 21 atrial septal defects, 19 ventricular septal defects, 2 partial anomalous pulmonary venous connection, 1 double outlet right ventricle, 1 right atrial myxoma, 1 sub aortic membranous, 2 cases of ventricular septal defects plus atrial septal defect plus patent ductus arteriosus, 1 atrial septal defect plus patent ductus arteriosus (**Table 1**).

The weight average was 22.06 kg, with an average of CPB time of 43.06 minutes and AC average time of 34.13 minutes. The length of stay in ICU was 4.20 days. The average dose was 18.18 milliliters per kg of weight of HTK solution. The spontaneous defibrillation was present in 40 out of 47 patients (85.1%) (**Table 2**).

DISCUSSION

The HTK cardioplegic solution has been used over 30 years. Its effectiveness has been demonstrated with numerous reports, most of them on adult patients of conventional cardiac surgery or cardiac transplantation.

The HTK volumes used or proposed for cardiac surgery on adults and children are varied. Doses that go from 1 to 3 liters or more for an adult patient with the same weight. There is not any formal dosage, mainly on patients with bad clinic condition, in whom amount of infused volume is critical, as well as those with renal failure, or children. There are reports about the use of HTK in relation to the calculated weight of the cardiac mass. Nevertheless, this can extremely be variable. Some authors describe HTK doses of 30-50ml/kg or higher on clinical reports, experimental, or for cardiac transplantation, as adequate in order to obtain adequate myocardial preservation [7-11]. On the other hand, conservative HTK doses of 10-15ml/kg on patients with coronary artery disease have shown good outcome. Reports about low HTK doses to keep the heart preserved during a short ischemic time are limited. Contrarily, Pressue has laid out that a reduction of the perfusion rate and infusion time may impair the myocardial equilibrium and additionally the myocardial tolerance to ischemia [11].

In an interinstitutional study in North America, it was shown that most cardiac surgeons use Del Nido cardioplegia (40%) or customized solutions (34%) and less than 5% of the surgeons assigned to the treatment of congenital heart diseases use HTK solution, with induction dose of 30 ml/kg with maintenance dose of 10 -15 ml/kg, a dose higher than than used in this work [12]. Stammer et al. recently compared different types of myocardial preservation solutions such as crystalloid (HTK and Nido) cardioplegias, blood cardioplegia and microplegia showing that the high volume of crystalline solution infused, hemodilution, electrolyte and blood alterations could be a problem compared with blood cardioplegia and microplegia solutions. Hemofiltration might correct this disadvantage [13]. On this study, the Pearson variables (weight/dose) correlation showed no statistical significance regarding the HTK dosage and the patient's weight. In addition, it was demonstrated that in order to achieve the ultimate goal of myocardial preservation in short aortic clamping, it is not necessary to reach the previous described HTK doses, but go

TABLE 1. DIAGNOSIS OF CASES

DIAGNOSIS	N
Atrial septal defect	21
Ventricular septal defect	19
Partial anomalous pulmonary venous connection	2
Double outlet Right ventricle	1
Subaortic stenosis	1
Right atrial myxoma	1
ASD, VSD, Patent ductus arteriosus	1
ASD, Patent ductus arteriosus	1
TOTAL	47

TABLE 2. CASES CHARACTERISTICS

VARIABLE	VALUE
Age (years)	6.27 (1-15)
Weight (kg)	22.06 (8-70)
Gender male	22 (46.8%)
Gender female	25 (53.2%)
Aortic cross-clamping (min)	34.13 ± 25.07
Spontaneous Defibrillation	40/47 (85.1%)
HTK Solution (ml/kg)	18.18 ± 17.65
Pearson correlation weight/dose	0.86

HTK= Histidine-Tryptophan-Ketoglutarate

by the clinical goal to achieve asystole and cardiac electrical inactivity, stopping the administration of HTK when is obtained. The HTK dose administered for pediatric patients on this study was on average 18.18 mml/kg, with aortic clamping around 34.13 minutes. Aslan et al. [10] reported higher dose for adult patients undergoing coronary artery bypass grafting with an aortic cross-clamping time of 36 minutes, on average. This dose (18.18 ml) is less than a half of the HTK dose proposed by Liu in 2008 for pediatric patients of 40 to 50 ml/kg for procedures with an AC prolonged time (172.5 ± 66.4 minutes).

There is no doubt about advantages of using lower doses of cardioplegic HTK solution; namely, less infused volume, fewer complications due to hemodilution, and lower electrolyte disturbances, besides lower costs. From our view, this myocardial preservation method with preservative HTK dose can be applied to the rest of the pathologies within the 1-3 RACHS-1 levels.

Notwithstanding that some authors recommend selective HTK suction, we have figured out all along of more than one decade that no need for aspiration, given the fact this volume goes down, poured into pump-circuit and subsequently hemofiltered. Hemodilution and electrolyte disturbances are fixed on CPB time, without complications. Early arrhythmias by reperfusion are on the accepted range described on the literature, with a spontaneous defibrillation of 85.1%, and the rest required a 10 joules defibrillation, going to normal sinus rhythm [14-15]. Length of stay in ICU was 4 days. Postoperative course was uneventful.

By closing, with all this information showed herein, we can state out that HTK cardioplegic solution is an excellent and safe option on pediatric patients, achieving adequate myocardial protection doses with 18.18 ml/kg with short aortic cross-clamping times.

It is worth highlighting that the decrease of HTK dose is achieved when asystole and the isoelectric line on the electrocardiogram are obtained, discontinuing its infusion. We encourage cardiac surgeons to use this low-dose HTK cardioplegic solution in this kind of pediatric pathologies. Of

course, several longer randomized control trials are needed in order to get better conclusions.

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