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RESEARCH ARTICLE

Comparison of Bretschneider's Histidine–tryptophan–ketoglutarate Cardioplegia Solution and Conventional Blood Cardioplegia Solution in Terms of Postoperative Acute Kidney Injury and Outcome Parameters

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ABSTRACT

Objectives: This study aimed to compare Bretschneider's histidine–tryptophan–ketoglutarate (BHTK) and blood cardioplegia in terms of postoperative acute kidney injury (AKI) and outcome parameters in patients who underwent open-heart valve surgery.

Methods: A total of 94 patients who underwent open-heart valve surgery between January 2016 and November 2021 were retrospectively evaluated. According to the administration of BHTK and blood cardioplegia, patients were stratified into two groups. Postoperative Kidney Disease Improving Global Outcomes was compared in terms of development of AKI and outcomes according to staging.

Results: A total of 31 patients in the BHTK group and 63 patients in the blood cardioplegia group were evaluated. No statistical difference was found between the groups in terms of postoperative AKI ($p>0.05$). Postoperative 24 and 48 h blood urea nitrogen (BUN) was higher in the BHTK group ($p=0.007$ and $p=0.023$). This difference equalized on the 7th day. No statistical difference was found in the mechanical ventilation time, intensive care unit and hospital stay, and 30-day mortality.

Conclusion: Literature evaluating the systemic effects of BHTK solution is limited. In our study, although no difference was found between BHTK and blood cardioplegia in terms of AKI development, the increase in BUN in the BHTK group was remarkable. Further studies exploring the clinical impact of this finding are warranted.

Keywords: Acute kidney injury, blood cardioplegia, blood urea nitrogen, bretschneider's histidine-tryptophan-ketoglutarate, myocardial protection

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Introduction

Cardioplegia solutions are formulations that induce diastolic arrest in the heart to maintain cardiac immobility and a blood-free surgical field during open-heart surgery. Through preserving myocardial energy reserves, preventing osmotic and electrolyte imbalances, and buffering acidosis, these solutions basically increase tolerance to ischemia and reperfusion injury.[1] Bretschneider's histidine–tryptophan–ketoglutarate (BHTK or Custodiol) solution is an intracellular crystalloid cardioplegia solution that also contains histidine–tryptophan–ketoglutarate with trace amounts of calcium (Ca) to hamper low sodium (Na) and calcium paradox.[2]

Blood cardioplegia content can vary. It is usually acquired by mixing the autologous blood extracted from the extracorporeal circulation with the crystalloid solution (contain-

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ing sodium bicarbonate [NaHCO3], magnesium [Mg], and potassium chloride [KCl], among others) in different proportions when the patient is in cardiopulmonary bypass (CPB) and is used in repeated doses.[1]

The development and use of a BHTK cardioplegia solution remarkably improves myocardial protection during open-heart surgery. However, a few clinical studies[3] have reported on the metabolic changes caused by this crystalloid cardioplegia solution, which enters the systemic circulation in large volumes, and its influence on end organs such as the kidney.

The most prevalent complication following cardiac surgery is acute kidney injury (AKI), with reported incidence rates ranging from 5%–43%.[4] AKI is a clinical condition associated with substantial mortality and morbidity, independent of other variables.[5] A mortality rate of 60% was observed in patients who develop postoperative AKI. The mortality rate following open-heart surgery ranges from 2%–8% and reaches 60% in patients who develop postoperative AKI.[6,7]

This study aimed to compare BHTK cardioplegia solution and conventional blood cardioplegia solution in terms of development of postoperative AKI and outcomes in patients who underwent open-heart valve surgery.

Methods

After the ethics committee approval was obtained with the decision number 586 dated 12.23.2021, 94 patients who underwent open-heart surgery for aortic valve replacement (AVR), mitral valve replacement (MVR), and AVR + MVR between January 2016 and November 2021 in Izmir Katip Çelebi University Atatürk Training and Research Hospital Cardiovascular Surgery clinic were retrospectively reviewed. From the archives, the hospital information operating system and file records were used. Patients with a known acute renal failure, chronic renal failure, total circulatory arrest, and cerebral perfusion during CPB were excluded from the study. Patients were stratified into two groups based on the administration of BHTK and blood cardioplegia. Demographic data such as comorbidities, history of contrast agent use within the last week, history of cardiac surgery, revision surgery, preoperative ECG rhythm, and nephrotoxic agent use were extracted.

Creatinine clearance (CC) was determined using the Cockcroft–Gault formula (CC [mL/min]=(140-age [years]×weight [kg]×[0.85 if female]/[72×serum creatinine [mg/dL]). The inotrope score (IS) was determined using the formula IS=dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min)+100×epinephrine dose (mcg/kg/min).

Moreover, the preoperative results of the complete blood count, biochemistry, coagulation parameters, and transthoracic echocardiography were recorded. Also, whether the case was an emergency or elective surgery, surgery type, cross-clamp duration, CPB duration, surgery duration, intraoperative IS, amount of ultrafiltration during CPB, amount of intraoperative fluid administered, amount of intraoperative diuresis and diuretic use, intraoperative defibrillation requirement, and intra-aortic balloon pump (IABP) use were recorded. In addition to these, such data as postoperative IS, amount of drainage in the first 24 h, extubation time, length of intensive care unit stay, length of hospital stay, arrhythmia, new-onset atrial fibrillation (AF), IABP administration, need for renal replacement therapy, 30-day mortality, AKI (according to Kidney Disease Improving Global Outcomes [KDIGO] grading scale), and postoperative complications (respiratory, neurological, gastrointestinal, bleeding, and infection complications) were also recorded. This study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

Cardioplegia Administration

A blood cardioplegia solution was prepared using 3 mmol Mg, 30 mmol potassium (K), and 10 mmol NaHCO3 into 1 L of isothermic blood content to achieve cardiac arrest in patients receiving blood cardioplegia as a standard. The BHTK solution composition is shown in Table 1.

To maintain cardiac arrest, cardioplegia was repeated every 20 min in patients receiving antegrade blood cardioplegia. In cases where both antegrade and retrograde cardioplegia were used, retrograde cardioplegic solution was continuously administered 20 min after antegrade cardioplegia. Conversely, in cases where the BHTK solution was administered, it was repeated 90 min later if warranted.

Statistical Methods

All statistical analyses were conducted using SPSS 22 program. Descriptive statistics was expressed using mean and standard deviation for continuous variables and numbers

Table 1. BHTK (custodiol) solution components

Components	Concentration (mmol/L)
Na	15
K	9
Mg	4
Ca	0.02
Histidin	198
Triptofan	2
α-ketoglutarat	1
Mannitol	30
pH	7.02–7.20
Osmolarite	290 mosmol/kg

BHTK: Bretschneider histidine tryptophan ketoglutarate.

Table 2. Sociodemographic characteristics and preoperative clinical findings of the patients

Variables	Blood cardioplegia (n=63)		BHTK cardioplegia (n=31)		p
	n	%	n	%	
Age	56.22±13.07		50.03±14.74		0.041*
EuroSCORE II	1.48±1.03		2.23±1.34		0.001*
STS risk of death	1.23±0.86		1.65±1.12		0.043*
STS kidney damage	1.13±0.90		1.47±1.09		0.122
STS mortality/morbidity	8.60±4.02		10.79±4.64		0.045
Sex (male)	33	52.4	15	48.4	0.716
Smoking	24	38.1	14	45.2	0.512
Hypertension	28	44.4	13	41.9	0.818
Diabetes	6	9.5	7	22.6	0.085
Coronary artery disease	20	31.7	10	32.3	0.960
Myocardial infarction	0	0	1	3.2	0.330
Heart failure	4	6.3	5	16.1	0.128
Decreased LVEF (<35%)	1	1.6	4	12.9	0.039*
Dyslipidemia	9	14.3	4	12.9	0.855
Carotid artery stenosis	2	3.2	0	0	0.447
Peripheral artery disease	0	0	1	3.2	0.330
COPD	10	15.9	2	6.5	0.198
Asthma	3	4.8	2	6.5	0.536
Stroke	9	14.3	4	12.9	0.855
Contrast history within 1 week	23	36.5	7	22.6	0.173
Cardiac surgery history	9	14.3	12	38.7	0.008*
Redo case	9	14.3	10	32.3	0.041*
Pre-op atrial fibrillation	24	38.1	15	48.4	0.341
Pre-op atrial flutter	1	1.6	0	0	0.670
Drug use	63	100	31	100	–
Insülin	2	3.2	3	9.7	0.199
Beta blocker	43	68.3	26	83.9	0.107
Statin	6	9.5	3	9.7	0.623
Aspirin	51	81	23	74.2	0.452
Diuretic	39	61.9	24	77.4	0.133
Steroid	1	1.6	1	3.2	0.553
Nephrotoxic drug use	10	15.9	9	29	0.135
ACEI/ARB	10	15.9	6	19.4	0.673
Aminoglycoside	0	0	1	3.2	0.330
Amphotericin B	0	0	0	0	–
Cyclosporine/tacrolimus	0	0	0	0	–
NSAID	0	0	3	9.7	0.034*
Vancomycin	0	0	1	3.2	0.330

*: p<0.05 was considered statistically significant. Values are expressed as frequency (%), mean±SD and n. BHTK: Bretschneider histidine tryptophan ketoglutarate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; STS: Society of thoracic surgeons; LVEF: Left ventricular ejection fraction; COPD: Chronic obstructive pulmonary disease; ACEI: angiotensin converting enzyme inhibitor; ARB: Angiotensin-2 rejeptor blocker; NSAID: non-steroidal anti-inflammatory drug.

and percentages for categorical variables. Prior to analysis, conformation of data to the normal distribution was evaluated using skewness and kurtosis values, normality tests, and histogram graphics. To determine the differences in the mean values between the groups, the independent variables T test or dependent variables T test was used for the variables that conformed to the normal distribution. The Mann–Whitney U test or Wilcoxon test was used for the variables

Table 3. Comparison of the surgery types and intraoperative data of the patients

Variables	Blood cardioplegia (n=63)		BHTK cardioplegia (n=31)		p
	n	%	n	%	
Total amount of antegrade cardioplegia (mL)	1128.57±457.61		1277.41±431.82		0.064
Total amount of retrograde cardioplegia (mL)	1941.26±1478.84		0±0		–
Cross clamp time (min)	68.88±24.15		85.09±28.66		0.009*
CPB duration (min)	101.44±31.46		120.09±28.72		0.007*
Operation time (min)	211.26±48.04		250.41±53.88		0.001*
Intraoperative inotrope score	24.52±36.44		33.23±35.76		0.049*
Ultrafiltration amount (mL)	122.22±318.99		567.74±672.12		0.0001*
Preoperative CVP	10.77±4.08		11.87±4.25		0.232
Total amount of fluid given (mL)	4099.84±953.29		3887.09±1199.02		0.353
Total amount of diuresis (mL)	1861.58±867.36		2170.96±855.15		0.106
Type of surgery					
AVR	25	39.7	9	29	0.512
MVR	30	47.6	16	51.6	
AVR+MVR	8	12.7	6	19.4	
Urgency of surgery	1	1.6	0	0	0.670
Defibrillation need	19	30.2	9	29	0.911
IABP use	0	0	2	6.5	0.106
Intra operative diuretic use	28	44.4	18	58.1	0.214
Intra op ERT (unit)					
0	37	58.7	15	48.4	0.514
1	12	19	9	29	
≥2	14	22.2	7	22.6	
Intra op FFP (unit)					
0	42	66.7	18	58.1	0.318
1	11	17.5	4	12.9	
≥2	10	15.9	9	29	

*: p<0.05 was considered statistically significant. Values are expressed as frequency (%), mean±SD and n. BHTK: Bretschneider histidine tryptophan ketoglutarate; CPB: Cardiopulmonary bypass; CVP: Central venous pressure; AVR: Aortic valve replacement; MVR: Mitral valve replacement; IABP: Intra-aortic balloon pump; ERT: Erythrocyte suspension; FFP: Fresh frozen plasma.

that did not fit the normal distribution. To determine the differences in the categorical variables between groups, a Ki-square test or Fischer's exact test was used. The difference in the values between the means of repeated measurements in the groups were evaluated using the Mann–Whitney U test. Furthermore, in cases of more than two time zones, the evaluation of time, groups, and joint effect was conducted using the two-way analysis of variance test on repeated measures. Post hoc analyses were performed using the Bonferroni test. In all analyses, statistical significance was set at p<0.05.

Results

Of the 94 patients (mean age 54.18±13.88 years, 48 males and 46 females), 31 were in the BHTK group and 63 in the blood cardioplegia group. The demographic characteristics and preoperative findings of the patients are shown in Table 2. In the BHTK group, the left ventricular ejection fraction was lower, while the number of patients with a history of repeated surgery and cardiac surgery was greater, including the cross-clamp time, CPB time, operation time, and intraoperative IS, each being greater. No significant difference was found between the two groups regarding IABP use, the need for intraoperative defibrillation, postoperative arrhythmia, new-onset AF, or the need for a pacemaker. Table 3 presents the surgical procedures, intraoperative data, and a comparison of cardioplegia varieties and number of patients.

No difference was found between the two groups in terms of postoperative AKI development, 30-day mortality, new-onset AF, and other complications (Table 4).

Comparing the blood urea nitrogen (BUN) value according to time and cardioplegia type and determining the common effect, a significant difference was found in both cardioplegia groups according to time (p<0.05). Postoperative

Table 4. Comparison of patients in terms of postoperative complications, AKI, and mortality

Variables	Blood cardioplegia (n=63)		BHTK cardioplegia (n=31)		p
	n	%	n	%	
30 day mortality	2	3.2	2	6.5	0.401
AKI	21	33.3	12	38.7	0.650
KDIGO (if AKI+; n=33)					
1	18	85	9	75	0.830
2 or 3	3	15	3	25	
Postoperative RRT	1	1.6	2	6.5	0.252
Highest creatinine day					
1–2	50	79.4	27	87.1	0.522
3–4	7	11.1	3	9.7	
5–7	6	9.5	1	3.2	
Arrhythmia	1	1.6	1	3.2	0.553
AF	13	20.6	9	29	0.366
Newly onset AF	4	6.3	3	9.7	0.421
Reoperation	7	11.1	3	9.7	0.832
Infection	12	19	3	9.7	0.243
Respiratory dysfunction	6	9.5	2	6.5	0.616
Neurological complication	0	0	1	3.2	0.330
Temporary pacemaker	28	44.4	20	64.5	0.067
Bleeding	46	73	20	64.5	0.397
Gastrointestinal complication	2	3.2	0	0	0.447

Values are expressed as frequency (%), mean±SD and n. AKI: Acute kidney injury; BHTK: Bretschneider histidine tryptophan ketoglutarate; KDIGO: Kidney disease improving global organization; RRT: renal replacement therapy; AF: Atrial fibrillation.

24 and 48 h BUN values were found to be significantly higher in the BHTK cardioplegia group than the blood cardioplegia group (p=0.007 and p=0.023). This difference was equalized on the 7th day. It was determined that the time and cardioplegia type showed a remarkable joint effect on the BUN value (p<0.05) (Table 5). The blood BUN value changes according to time in groups are shown in Figure 1.

In terms of postoperative mechanical ventilation time, length of intensive care unit and hospitalization stay, and extubation time, no significant difference was found (Table 6).

Discussion

In this study, we compared BHTK and blood cardioplegia in terms of postoperative AKI and outcome parameters in patients who underwent open-heart valve surgery. In terms of postoperative AKI development in the study, no statistically significant difference was observed between the two cardioplegia methods.

One of the most common and serious complications in the postoperative period following open-heart surgery is AKI, which has been associated with a prolonged intensive care and hospital stay and increased mortality.[8]

In a study involving 1900 patients, Viana et al.[1] compared blood cardioplegia with BHTK cardioplegia. Although severe left ventricular dysfunction, EuroSCORE 2, cross-clamp, and CPB duration parameters were higher in the BHTK group, no difference was found in the study in terms of postoperative kidney damage,[1] which corroborates with our results.

In another study, BHTK and blood cardioplegia were compared for AVR surgery in 1650 patients with propensity score matching, and no difference was found between the two groups in terms of kidney damage requiring dialysis.[9]

BHTK is an intracellular solution that was used in the 1970s for cardioplegic arrest. Its effects are demonstrated through the induction of hyperpolarization. Histidine buffers ischemia-induced acidosis, while tryptophan stabilizes the cell membrane. Alpha ketoglutarate is the main component of the Krebs cycle in the cell. The mannitol in the solution contributes to the maintenance of cellular osmolarity.[10]

The cardiac effects of the BHTK solution have been extensively studied in the literature; however, the number of studies systematically investigating the metabolic changes induced by these solutions in other vital organs remains limited.

Table 5. Comparison of blood urea nitrogen (BUN) by time and cardioplegia type and determining the common effect

Variables	1. BUN value before the operation	2. BUN value 24 hours after the operation	3. BUN value 48th hour after the operation	4. BUN value 7th day after the operation
Blood cardioplegia	18.67±5.68	20.51±6.96	24.24±9.33	17.45±9.69
BHTK cardioplegia	20.80±8.70	25.43±8.81	28.53±12.59	17.83±9.82
		Wilks' Lambda	**F**	**p**
Time		0.489	30.671	0.0001**
Time*group		0.907	3.024	0.034**
Group		–	3.590	0.061
		***Post-hoc* bonferonni**		
Time (Blood cardioplegia)		1<2; 1<3; 1=4; 2<3; 2>4; 3>4		
Time (BHTK cardioplegia)		1<2; 1<3; 1=4; 2=3; 2>4; 3>4		

*: Two-way repeated measures Analysis of Variace (ANOVA); **: Data expressed as Mean±SD and n, %. BHTK: Bretschneider histidine tryptophan ketoglutarate.

A study evaluating amino acid and nitrogen metabolism changes caused by histidine degradation contained in BHTK has exhibited that large amounts of histidine pass into the systemic circulation due to the application of BHTK in higher volumes compared to blood cardioplegia. Furthermore, it has been demonstrated that nitrogen atom metabolites in the imidazole ring structure are converted to either ammonium ions or urea.[11] In a study using urine samples from 100 patients undergoing open-heart surgery, to investigate the metabolic changes caused by the BHTK solution, dysregulation of glutamine/glutamate, purine/pyrimidine, vitamin B6, and histidine metabolism was explored. The researchers of this study highlighted the need for further study into the fundamental processes underlying both its possible detrimental effects and its organ-protecting properties.[3]

In a trial comparing BKTK solution and BKTK-N solution employed during CPB, it was revealed that BHTK causes proximal tubule swelling and cytochrome-C release in porcine kidney, which may be associated with AKI.[12]

Our study revealed that the BHTK group showed significantly higher BUN values during the 24 and 48 h postoperatively. On day 7, it was also observed that the elevation spontaneously resolved. In the statistical analysis of BUN, creatinine, glomerular filtration rate, and CC, only the BUN value was found to be affected by time and cardioplegia type, which can be explained by the fact that BHTK produces a large quantity of urea and ammonium, which are histidine metabolites. However, we failed to find any clinical studies in parallel with that conclusion. To better understand the practical implications of this finding, we recommend conducting a larger randomized controlled trial, emphasizing the need to explore regarding the impact of this finding on renal effects in tissue culture.

One of the major concerns accompanying cardiac surgery is myocardial injury, which is associated with the development of arrhythmia, major cardiac and renal morbidities, prolonged intensive care unit and hospital stay, and high mortality risk.[13]

In our clinic, selecting the cardioplegia solution is a joint decision of the cardiac surgeon, anesthesiologist, and

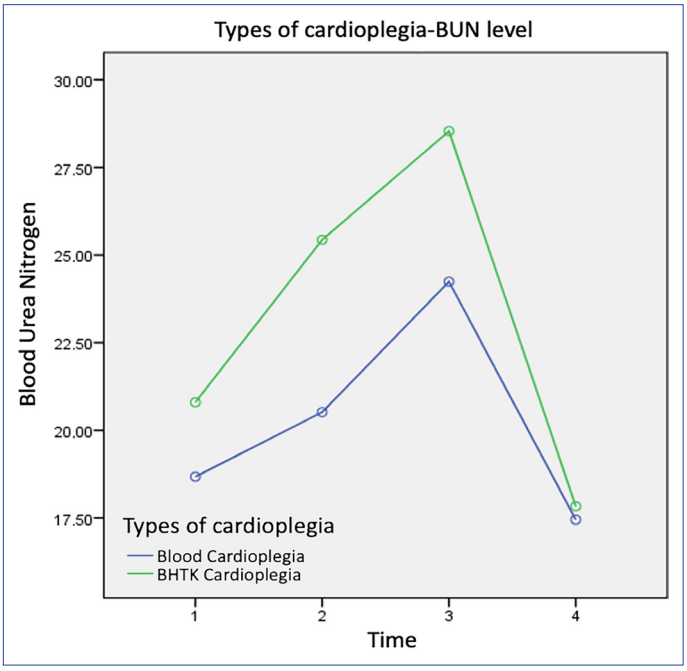

Figure 1. Change of blood urea nitrogen value according to time and groups.
BHTK: Bretschneider histidine tryptophan ketoglutarate.

Table 6. Comparison of the postoperative data of the patients

Variables	Blood cardioplegia (n=63)		BHTK cardioplegia (n=31)		p
	n	%	n	%	
Postoperative CVP	9.84±3.28		11.06±3.47		0.099
Postoperative inotrope score	23.26±39.76		36.53±38.10		0.010*
Drainage amount (mL) in the first 24 hours	461.11±236.48		546.12±516.00		0.505
Extubation time (hour)	14.97±13.81		16.51±19.96		0.456
Length of stay in intensive care (day)	3.85±4.15		4.03±2.19		0.109
Length of stay in hospital (day)	10.36±9.53		11.61±8.28		0.151
Post operative atrial fibrillation	10	15.9	9	29	0.135
Post operative IABP	0	0	1	3.2	0.330
Postoperative ERT (unit)					
0	42	66.7	16	51.6	0.359
1	12	19	8	25.8	
≥2	9	14.3	7	22.6	
Postoperative FFP (unit)					
0	36	57.1	13	41.9	0.305
1	10	15.9	5	16.1	
≥2	17	27	13	41.9	

*: p<0.05 was considered statistically significant. Values are expressed as frequency (%), mean±SD and n. BHTK: Bretschneider histidine tryptophan ketoglutarate; CVP: Central venous pressure; IABP: Intraaortic balloon pump; ERT: Erythrocyte suspension; FDP: Fresh frozen plasma.

perfusionist. We prefer the BHTK solution for valve operations with worse cardiac performance in cases where we foresee a prolonged operation time and where an uninterrupted view of the field could be required in terms of surgical technique. Obviously, this is the rationale for the difference in cross-clamp, CPB, and operation times between the two groups in our study.

Based on the results of a recent large meta-analysis comparing BHTK and blood cardioplegia for myocardial protection, BHTK solution was found to have the same efficacy and safety as other cardioplegic solutions in most clinical parameters.[10]

IS or the need for inotropes, IABP use, arrhythmia incidence, and cardiac biomarkers are the parameters evaluated while detecting myocardial damage in an open-heart surgery.[9,14–16]

In a prospective randomized study comparing blood and BHTK cardioplegia with a total of 345 patients undergoing AVR, no significant difference was found between the two groups in terms of spontaneous sinus rhythm, inotropic agent use, AF development, mechanical ventilation duration, perioperative myocardial ischemia, and mortality after opening the aortic cross-clamp.[17] Except for the use of inotropes, these findings are also consistent with our study. We also found that IS during and after surgery was higher in the BHTK cardioplegia group. However, any difference was not observed between both groups in terms of ejection fraction (EF) values in the preoperative and postoperative repeated measurements.

In our study, no difference was found between the groups in terms of preoperative and postoperative AF incidence, the need for defibrillation during surgery, new-onset AF, the need for temporary/permanent pacemaker, and IABP. Our study findings corroborate with the literature.[18,19]

Edelman et al.[20] reported that no difference was found for mortality similar to our results in their systematic review comparing BHTK and conventional cardioplegia, based on the meta-analysis results including 14 studies. Additionally, in terms of postoperative complications, bleeding, reoperation, mechanical ventilation time, and intensive care unit stay and hospital stay, no difference was found between the two groups.

Limitations

One of the study limitations was the single-center and retrospective nature of the study. Thus, the findings should be confirmed through multicenter and prospective studies. Moreover, the patient sample was small, and plasma and urine biomarkers neutrophil gelatinase-associated lipocalin, interleukin-18 (NGAL, IL-18, cystatin C, kidney injury molecule-1) were not investigated to identify cardiac biomarkers and AKI earlier.

Conclusion

Based on our data, we can conclude that BHTK solution provides effective myocardial protection and improves clinical outcomes during open-heart valve surgery. Additionally, we would like to highlight that this result should be supported by cardiac biomarkers. No difference was found between the two groups in terms of AKI development according to the KDIGO grading scale. However, BUN elevation, which is the histidine metabolite, is remarkable in the BHTK group.

Disclosures

Ethics Committee Approval: The study was approved by The İzmir Katip Çelebi University Non-interventional Clinical Research Ethics Committee (Date: 23/12/2021, No: 586).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – E.G.D., S.G.; Design – A.S.T., B.E.G.; Supervision – M.A., A.G.; Materials – A.S.T.; Data collection &/or processing – E.G.D., A.S.T.; Analysis and/or interpretation – S.G., B.E.G.; Literature search – M.A., A.S.T.; Writing – S.G., E.G.D.; Critical review – N.K., A.G.

References

1. Viana FF, Shi WY, Hayward PA, Larobina ME, Liskaser F, Matalanis G. Custodiol versus blood cardioplegia in complex cardiac operations: An Australian experience. Eur J Cardiothorac Surg 2013;43:526–31.
2. Preusse CJ. Custodiol cardioplegia: A single-dose hyperpolarizing solution. J Extra Corpor Technol 2016;48:P15–20.
3. Lee CC, Hsieh YJ, Chen SW, Fu SH, Hsu CW, Wu CC, et al Bretschneider solution-induced alterations in the urine metabolome in cardiac surgery patients. Sci Rep 2018;8:17774.
4. Nadim MK, Forni LG, Bihorac A, Hobson C, Koyner JL, Shaw A, et al. Cardiac and vascular surgery-associated acute kidney injury: The 20th International Consensus Conference of the ADQI (Acute Disease Quality Initiative) Group. J Am Heart Assoc 2018;7:e008834.
5. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006;1:19–32.
6. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005;16:162–8.
7. Lagny MG, Jouret F, Koch JN, Blaffart F, Donneau AF, Albert A, et al. Incidence and outcomes of acute kidney injury after cardiac surgery using either criteria of the RIFLE classification. BMC Nephrol 2015;16:76.
8. Thiele RH, Isbell JM, Rosner MH. AKI associated with cardiac surgery. Clin J Am Soc Nephrol 2015;10:500–14.
9. Hoyer A, Lehmann S, Mende M, Noack T, Kiefer P, Misfeld M, et al. Custodiol versus cold Calafiore for elective cardiac arrest in isolated aortic valve replacement: A propensity-matched analysis of 7263 patients. Eur J Cardiothorac Surg 2017;52:303–9.
10. Albadrani M. Histidine–tryptophan–ketoglutarate solution versus multidose cardioplegia for myocardial protection in cardiac surgeries: A systematic review and meta-analysis. J Cardiothorac Surg 2022;17:133.
11. Teloh JK, Dohle DS, Petersen M, Verhaegh R, Waack IN, Roehrborn F, et al. Histidine and other amino acids in blood and urine after administration of Bretschneider solution (HTK) for cardioplegic arrest in patients: Effects on N-metabolism. Amino Acids 2016;48:1423–32.
12. Feirer N, Dieterlen MT, Klaeske K, Kiefer P, Oßmann S, Salameh A, et al. Impact of Custodiol-N cardioplegia on acute kidney injury after cardiopulmonary bypass. Clin Exp Pharmacol Physiol 2020;47:640–9.
13. Mentzer RM Jr. Myocardial protection in heart surgery. J Cardiovasc Pharmacol Ther 2011;16:290–7.
14. Gaudino M, Pragliola C, Anselmi A, Pieroni M, De Paulis S, Leone A, et al. Randomized trial of HTK versus warm blood cardioplegia for right ventricular protection in mitral surgery. Scand Cardiovasc J 2013;47:359–67.
15. Guru V, Omura J, Alghamdi AA, Weisel R, Fremes SE. Is blood superior to crystalloid cardioplegia? A meta-analysis of randomized clinical trials. Circulation 2006;114(Suppl 1):I331–8.
16. Hummel BW, Buss RW, DiGiorgi PL, Laviano BN, Yaeger NA, Lucas ML, et al. Myocardial protection and financial considerations of custodiol cardioplegia in minimally ınvasive and open valve surgery. Innovations (Phila) 2016;11:420–4.
17. Øvrum E, Tangen G, Tølløfsrud S, Øystese R, Ringdal MA, Istad R. Cold blood versus cold crystalloid cardioplegia: A prospective randomised study of 345 aortic valve patients. Eur J Cardiothorac Surg 2010;38:745–9.
18. Buckberg GD, Beyersdorf F, Allen BS, Robertson JM. Integrated myocardial management: Background and initial application. J Card Surg 1995;10:68–89.
19. Whittaker A, Aboughdir M, Mahbub S, Ahmed A, Harky A. Myocardial protection in cardiac surgery: How limited are the options? A comprehensive literature review. Perfusion 2021;36:338–51.
20. Edelman JJ, Seco M, Dunne B, Matzelle SJ, Murphy M, Joshi P, et al. Custodiol for myocardial protection and preservation: A systematic review. Ann Cardiothorac Surg 2013;2:717–28.