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Original study

Postoperative sodium concentrations after cardiac surgery using histidine-tryptophan-ketoglutarate cardioplegia and cardiopulmonary bypass – a retrospective study

Y. Devrieze[1], P. Mertens[1], N. Mintjens[1], V. Saldien[1]

[1]*Antwerp University Hospital, Department of Anesthesiology, Edegem, Belgium.*

Corresponding author: Devrieze Y., MD, UZA, Drie Eikenstraat 655, 2650 Edegem, Belgium. Tel: +32478268666
E-mail: ylonkadevrieze@hotmail.com

Unstructured abstract

Introduction: **Histidine-tryptophan-ketoglutarate (HTK) cardioplegia is used to induce cardiac arrest during cardiopulmonary bypass (CPB) in cardiac surgery. HTK cardioplegia is hyponatremic (15 mmol/L) and slightly hyperosmolar (310 mOsm/kg) and can induce hyponatremia when it enters systemic circulation. The purpose of this study is to investigate the effect of HTK cardioplegia, cannulation strategy and intraoperative correction of sodium levels on postoperative sodium concentration. Secondly, the effect of the sodium concentrations on postoperative agitation is evaluated.**
Methods: **Patients who underwent cardiac surgery using CPB and HTK cardioplegia were included in this retrospective study. Sodium concentrations of arterial blood gases (ABG) and laboratory blood samples were analyzed at multiple points in time. It was recorded if the perfusionist corrected intraoperative hyponatremia with hypertonic saline or sodium bicarbonate 8.4%. Characteristics of the patients, intraoperative data and the patient's Richmond Agitation-Sedation Scale (RASS) score were collected.**
Results: **The median sodium concentration on ABG [IQR] decreased from 139 mmol/L [138-140] to 125.5 mmol/L [122-130] (p < 0.001) after the administration of HTK cardioplegia. The median sodium concentration after the administration of HTK cardioplegia was significantly lower in the group with single cannulation than with double cannulation (123 mmol/L [121-125] vs. 130 mmol/L [128-133]; p<0.001). The median sodium concentration increased to 134 mmol/L [133-136] (p=0.007) at T6. There was no significant difference in postoperative sodium concentration between patients who received correction intraoperatively and those who did not, or between patients who had agitation and those who had not.**
Conclusions: **The administration of HTK cardioplegia induced acute hyponatremia during cardiac surgery mainly in patients with single venous cannulation. Postoperatively, a normalization of sodium concentrations can be observed. No difference in postoperative sodium concentration was observed with or without intraoperative correction of sodium. Intraoperative correction of hyponatremia shows no benefit or harm on postoperative sodium concentrations. Hyponatremia could be avoided or at least diminished by using double venous cannulation.**

Keywords: **Histidine-tryptophan-ketoglutarate solution, hyponatremia, hypertonic saline solution, cardiopulmonary bypass.**

Introduction

At the moment, there are no clear treatment guidelines in the Antwerp University Hospital (UZA) whether or not to correct acute hyponatremia after the administration of Histidine-tryptophan-ketoglutarate (HTK) cardioplegia during cardiac surgery with cardiopulmonary bypass (CPB). In practice, hypertonic saline and sodium bicarbonate are frequently administered. HTK cardioplegia is widely used to induce cardiac arrest during CPB[1]. The advantages of HTK cardioplegia are that it

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is given in a single dose, it allows uninterrupted workflow, and it offers myocardial protection for more than two hours[1-3]. HTK cardioplegia is an intracellular crystalloid cardioplegic solution and it is hyponatremic compared to blood (15 mmol/L vs. 135-145 mmol/L)[3,4]. Rapid administration of the required volumes of HTK cardioplegia can induce acute hyponatremia in patients when the solution mixes with the patient's blood1. Rapid development of hyponatremia can lead to cerebral swelling and is associated with postoperative seizures in pediatric cardiac patients[5]. Most studies on HTK cardioplegia investigate the aspects of myocardial protection, but only few focus on acute hyponatremia and its clinical relevance[2,6]. Some studies suggest correcting acute hyponatremia with hypertonic saline, but others recommend that acute correction of HTK-induced hyponatremia should be avoided[1,5-7]. HTK cardioplegia is slightly hyperosmolar (310 mOsm/kg) compared to the osmolality of human blood (275-300 mOsm/kg). As such, correction of isotonic hyponatremia with hypertonic saline could be harmful as it can induce a hyperosmolar state with associated cerebral shrinking[1]. Correcting hyponatremia in general can result in osmotic demyelination syndrome if done too rapidly[8,9].

The primary objective of this study is to evaluate the effect of HTK cardioplegia on postoperative sodium concentrations on arrival in the intensive care unit (ICU). Our secondary objectives are to investigate the impact of the type of cannulation or intraoperative sodium correction on postoperative sodium concentrations in time and the effect of the sodium concentrations on postoperative agitation.

Methods

Ethical statements

This retrospective study was approved by the ethics committee of UZA and the University of Antwerp (UA) by prof. dr. Michielsen P. on the 28th of November 2022, project ID 3899 – EDGE 2809. Informed consent was waved as the reviewed medical data were already collected as part of routine clinical care.

Collected data

In this retrospective observational study, the medical records of all patients aged 18 years and older who underwent open cardiac surgery using CPB with HTK cardioplegia between January 1st, 2019 and June 30th, 2019 at UZA were reviewed. Patients who had abnormal preoperative blood sodium levels (Na <135 mmol/L or Na > 145 mmol/L), required emergency cardiac surgery, had more than one CPB-run during the same operation, had a delayed postoperative extubation beyond 24 hours were excluded. Patients were also excluded if the perfusion report was missing.

Sodium levels at specific time points were retrospectively collected. Intraoperatively, arterial blood gases (ABG) were measured before CPB (baseline), after administration of HTK cardioplegia and after weaning from CPB (T1). During the procedure, ABG were measured on a case-by-case basis. A blood sample was routinely measured the day before the operation (baseline). An ABG (T2) and blood sample (T3) were taken on arrival of the patient in the ICU. During their stay in the ICU, ABGs and blood samples were regularly obtained. Sodium values on ABG and blood samples were systematically measured after 6 hours (T4-T5), 12 hours (T6-T7) and 24 hours (T8-T9) of arrival. The change in sodium concentration from baseline (ΔNa) was calculated for each point in time. Hyponatremia is defined as a serum sodium concentration of less than 135 mmol/L. Moderate hyponatremia is when the sodium concentration is between 125 and 134 mmol/L and severe hyponatremia is a sodium concentration less than 125 mmol/L[5].

All data were collected retrospectively from the electronic health records. Characteristics of the patients, including age, gender, weight, height and preoperative laboratory results were obtained. Intraoperative data such as the type of surgery, duration of surgery, choice of cannulation for CPB, CPB duration, aortic cross clamping (ACC) duration, HTK cardioplegia volume and volume of intraoperative fluids (Plasmalyte, Volulyte 6%, Geloplasma 3% and Glucion 5%) were gathered. A double venous cannulation is used during most open-cardiac surgeries. The cannulae are placed in the superior and inferior vena cava. A single two-stage venous cannula is used during closed-cardiac surgeries. In this type of surgery, the cannula is placed in the groin and advanced to the right atrium. Aortic valve surgery and aorta surgery can be performed with a single two-stage venous cannula. The choice of cannulation is made multidisciplinary with a leading role for the surgeon. A possible reason why surgeons would place a single two-stage cannula is because it is time saving. A single peripheral venous cannula is used during minimally invasive surgery. Ultrafiltration during CPB was performed on indication and the hemofiltrated volume was recorded. Indications of ultrafiltration are volume overload, hyperkalemia or hyponatremia. It was noted if the perfusionist, in collaboration with the anesthesiologist, corrected hyponatremia with hypertonic saline or sodium bicarbonate 8.4%.

In the ICU, the Richmond Agitation-Sedation Scale (RASS) was used to indicate whether patients were alert and calm or agitated[10].

Group inclusion

When a two-stage cannula or a peripheral cannula was used during CPB, the patient was included in the group "single cannulation". The patient was included in the group "double cannulation" if a double cannulation was used during CPB.

In a second subgroup analysis, patients who received hypertonic saline or sodium bicarbonate 8.4% were included in the group with intraoperative correction of sodium ("corrected group"). Patients who did not receive hypertonic saline or sodium bicarbonate were included in the "uncorrected group".

In a third subgroup analysis, patients were included in the agitation group when the RASS score indicated that the patient was agitated after extubating.

Standards of care

Anesthetic management was standardized. General anesthesia was induced using propofol target-controlled infusion (TCI) with a 1-1.5 µg/mL target after one minute and sufentanil 2 µg/kg. Anesthesia was maintained with a combination of continuous infusion of propofol TCI and sevoflurane. Neuromuscular relaxation was achieved with rocuronium 1 mg/kg. Hemodynamic monitoring was performed with 5-lead electrocardiography, pulse oximetry and continuous arterial blood pressure monitoring. Cerebral monitoring was performed with cerebral oximetry and bilateral electroencephalography (EEG) to monitor brain function (NeuroWave®, Systems inc., Neurosense). CPB was started after heparinization, targeting an Activated Clotting Time (ACT) above 480 seconds. Depending on renal function, the CPB was primed with 1500ml volulyte 6% or geloplasma 3%. Cardiac arrest was achieved using two liters of HTK cardioplegia. Additional HTK cardioplegia was administered in case of prolonged surgery or the occurrence of cardiac electrical activity.

Postoperatively, patients were transferred to the ICU. An infusion of glucose 5% 1000ml with 2g magnesium in 24 hours was administered routinely. Depending on hemodynamics and transfusion requirements plasmalyte, geloplasma 3%, albumin 20% or 5%, packed cells, fresh frozen plasma and thrombocytes were administered postoperatively. When the patients were hemodynamically and respiratory stable, they were weaned and eventually extubated depending on the RASS score.

Statistical analysis

IBM SPSS Statistics 28.0.1.1 software was used for the statistical analysis of the data.

Data was checked for normality using the Shapiro-Wilk test. If the value of significance was below 0.05, the data were considered not normally distributed. Depending on normality, continuous data are presented as mean (with standard deviation) or median (with interquartile range). Differences in postoperative sodium concentrations between patients with single or double cannulation, with and without intraoperative correction of sodium and with and without agitation were analyzed using the Mann-Whitney U test. This test is also used to compare ΔNa between the group with and without intraoperative correction of sodium. Other characteristics and intraoperative details between groups were compared using the Mann-Whitney U test for non-normal distribution or T-test for normal distribution. Categorical variables are presented as numbers and percentages and analyzed by Chi-squared analysis. The differences between two time points were tested by the Wilcoxon signed-rank test. For all analyses, a value of $p < 0.05$ was considered significant.

Results

During the study period, 144 patients underwent cardiac surgery at UZA using CPB and HTK cardioplegia. Fifteen patients were excluded because cardiac surgery was urgent. Six patients were excluded because they had more than one CPB-run during the operation. Fourteen patients were excluded because they had a delayed postoperative extubation beyond 24 hours and five patients were excluded because the perfusion report was missing. After applying the exclusion criteria, 108 patients were included. The main characteristics of the patients and intraoperative details are listed in Table I.

Arterial blood gas

Before CPB (baseline) the median sodium value was 139 mmol/L [138-140] on ABG. After administration of HTK cardioplegia, the sodium level was lower than before CPB with a median value of 125.5 mmol/L [122-130] ($p < 0.001$). Hyponatremia occurred in 101 of 108 patients (93.5%). A total of 46 patients (42.6%) had severe hyponatremia. 41 of 46 patients (89.1%) with acute severe hyponatremia underwent cardiac surgery using one venous cannula. After weaning from CPB (T1), the sodium level increased compared to the level after the administration of HTK cardioplegia with a median value of 132 mmol/L [130-133] ($p<0.001$) and 96 patients were hyponatremic (88.9%). One

Table I. — Characteristics of patients and intraoperative details (n=108).

Age	Mean (SD)	66.85 (11.61)
Male sex	n (%)	69 (63.9)
Weight	Median [IQR]	76 [68.25-86]
BMI	Median [IQR]	26.48 [23.90-28.71]
BSA	Median [IQR]	1.91 [1.74-2.02]
eGFR	Median [IQR]	81.5 [69.25-90.75]
Creatinine	Median [IQR]	0.87 [0.76-1.03]
Intraoperative details		
Operation - Aortic valve surgery - Mitral valve surgery - Aorta surgery - Redo surgery - Valve surgery and CABG - Valve and aorta surgery - Multiple valves surgery - Other (Myxoom, …)	n= 108 32 16 3 6 29 10 8 4	% 29.6 14.8 2.8 5.6 26.9 9.3 7.4 3.7
Duration of surgery, min	Median [IQR]	180 [180-240]
CPB time, min	Median [IQR]	114.5 [93.5-149]
ACC time, min	Median [IQR]	86 [69-110]
HTK cardioplegia volume, mL	Median [IQR]	2000 [2000-2500]
HTK cardioplegia volume, mL/kg	Median [IQR]	28.60 [25-34.84]
Cannulation - Single cannulation - Two-stage cannula - Peripheral cannula - Double cannulae	N=108 61 50 11 47	% 56.5 46.3 10.2 43.5
Ultrafiltration	n (%)	72 (66.7)
Ultrafiltration, mL	Median [IQR]	800 [0-1500]
Intraoperative fluids (colloids and crystalloids), mL	Median [IQR]	1739 [1319-2319]

BMI: body mass index; BSA: body surface area; eGFR= estimated glomerular filtration rate; CPB= cardiopulmonary bypass; ACC= aortic cross clamping; HTK= Histidine-tryptophan-ketoglutarate.

Table II. — Median sodium concentrations on ABG between single and double cannulation at different time stages: baseline (pre-CPB), after administration of HTK cardioplegia, after weaning from CPB (T1), on arrival in the ICU (T2), 6 hours (T4), 12 hours (T6) and 24 hours (T8) after arrival in the ICU.

	Single cannulation (n=61)	Double cannulation (n=47)	
Baseline sodium, median [IQR], mmol/L	139 [138-140]	139 [137-140]	p=0.368
After HTK cardioplegia, median [IQR], mmol/L	123 [121-125]	130 [128-133]	p<0.001
Severe hyponatremia after HTK cardioplegia, n (%)	41 (67.2)	5 (10.6)	p<0.001
T1, median [IQR], mmol/L	131 [130-133]	132 [131-134]	p=0.013
T2, median [IQR], mmol/L	132 [131-134]	133 [132-136]	p=0.007
T4, median [IQR], mmol/L	134 [132-135]	134 [132-136]	p=0.590
T6, median [IQR], mmol/L	134 [133-136]	134 [133-136]	p=0.675
T8, median [IQR], mmol/L	133 [132-134]	133 [132-134]	p=0.436
Sodium correction, n (%)	37 (60.7)	9 (19.1)	p<0.001
Ultrafiltration, n (%)	56 (91.8)	16 (34)	p<0.001

HTK= Histidine-tryptophan-ketoglutarate.

patient had severe hyponatremia (0.9%) and 95 patients had moderate hyponatremia (88%). On arrival in the ICU (T2), the sodium concentration increased compared to T1 with a median value of 133 mmol/L [131-134.75] ($p<0.001$). 81 patients (75%) had moderate hyponatremia. There was no severe hyponatremia at this time point. The sodium concentration after 6 hours (T4) and 12 hours (T6) in the ICU increased with a median value of 134 mmol/L [132-135] ($p<0.001$) and 134 mmol/L [133-136] ($p=0.007$), respectively. 62 patients (57.4%) had moderate hyponatremia at T4 and 60 patients (55.6%) at T6. After 24 hours (T8), the sodium concentration decreased compared to T6 with a median value of 133 mmol/L [132-134] ($p<0.001$). 87 patients (81.3%) had moderate hyponatremia after 24 hours in the ICU.

Laboratory blood samples

Before CPB (baseline), the median sodium value was 141 mmol/L [139-142] on laboratory results. On arrival in the ICU (T3), the sodium concentration decreased compared to baseline with a median value of 140 mmol/L [138-142] ($p=0.076$). One patient (0.9%) had moderate hyponatremia. Sodium concentrations after 6 hours (T5) and after 12 hours (T7) in the ICU increased with a median value of 141 mmol/L [139-143] ($p=0.001$) and 141 mmol/L [140-143] ($p=0.150$), respectively. At these time points, hyponatremia did not occur. After 24 hours (T9), the sodium concentration decreased compared to T7 with a median value of 139 mmol/L [138-140] ($p<0.001$) and two patients (2%) had moderate hyponatremia.

Table III. — Characteristics of patient and intraoperative details between patients with and without sodium correction. Median sodium concentrations at different time stages: after HTK cardioplegia, after weaning from CPB (T1), on arrival in the ICU (T2-T3), 6 hours (T4-T5), 12 hours (T6-T7) and 24 hours (T8-T9) after arrival in the ICU.

	Uncorrected group (n=62)	Corrected group (n=46)	p=
Age, median [IQR], year	70 [62-75]	66.5 [59-77]	0.657
Male sex, n (%)	38 (61.3)	31 (67.4)	0.671
Weight, median [IQR], kg	75 [67.75-85.25]	77.5 [69.75-87.50]	0.604
BMI, median [IQR], kg/m²	26.23 [23.98-29.31]	26.76 [23.68-28.36]	0.941
BSA, median [IQR], m²	1.89 [1.72-2.01]	1.91 [1.74-2.04]	0.595
eGFR	81 [70-90.25]	82.5 [67.25-91.25]	0.862
Creatinine, median [IQR], mmol/L	0.84 [0.76-1.03]	0.88 [0.75-1.04]	0.840
Duration of surgery, median [IQR], min	180 [180-240]	180 [180-240]	0.637
CPB time, median [IQR], min	113.5 [95.25-146.00]	115.50 [92-165]	0.608
ACC time, median [IQR], min	84 [66.50-109]	86.5 [70.75-115.75]	0.396
HTK cardioplegia volume, median [IQR], mL	2000 [2000-2312.5]	2000 [2000-2760.75]	0.027
HTK cardioplegia volume, median [IQR], mL/kg	27.97 [25.23-33.39]	29.09 [25-37.53]	0.396
Cannulation, n (%)	- Single cannulation 24 (38.7) - Double cannulation 38 (61.3)	- Single cannulation 37 (80.4) - Double cannulation 9 (19.6)	<0.001
After HTK cardioplegia (ABG), median [IQR], mmol/L	129 [126-133]	122 [120-124]	<0.001
Severe hyponatremia after cardioplegia, n (%)	11 (17.7)	35 (76.1)	<0.001
T1, median [IQR], mmol/L	132 [131-134]	131 [130-133]	0.209
T2, median [IQR], mmol/L	133 [132-135]	132 [131-134]	0.239
T3, median [IQR], mmol/L	140 [138-142]	140 [138-142]	0.621
T4, median [IQR], mmol/L	134 [132-135]	135 [132-136]	0.393
T5, median [IQR], mmol/L	141 [139-143]	141 [139-142]	0.924
T6, median [IQR], mmol/L	134 [133-136]	134 [134-136]	0.138
T7, median [IQR], mmol/L	141 [140-143]	141 [140-142]	0.815
T8, median [IQR], mmol/L	133 [131-134]	133 [132-134]	0.820
T9, median [IQR], mmol/L	139 [137-140]	139 [138-140]	0.545

BMI: body mass index; BSA: body surface area; eGFR= estimated glomerular filtration rate; CPB= cardiopulmonary bypass; ACC= aortic cross clamping; HTK= Histidine-tryptophan-ketoglutarate.

Cannulation

In a subgroup analysis, we examined the effect of single (61 patients) vs. double cannulation (47 patients) (Table II). The median sodium concentrations on ABG after HTK cardioplegia (123 mmol/L [121-125] vs. 130 mmol/L [128-133]; p<0.001), after weaning from CPB (T1) (131 mmol/L [130-133] vs. 132 mmol/L [131-134]; p=0.013) and on arrival in the ICU (T2) (132 mmol/L [131-134] vs. 133 mmol/L [132-136]; p=0.007) were significantly lower in the group with single cannulation, but clinically negligeable. 41 of 61 patients (67.2%) with single cannulation and 5 of 47 patients (10.6%) with double cannulation had severe hyponatremia after the administration of HTK cardioplegia (p<0.001). There was a significant difference between the two groups in tendency of intraoperative sodium correction (60.7% vs. 19.1%; p<0.001). Ultrafiltration was performed in 56 of 61 patients (91.8%) in the group with single cannulation and in 16 of 47 patients (34%) in the group with double cannulation (p<0.001).

Sodium correction

In 46 patients (42.6%) the sodium concentration was corrected during cardiac surgery. Of these patients, 20 (43.5%) received 3g of hypertonic saline and 12 (26.1%) received 6g of hypertonic saline. One patient (2.2%) received 50 mL of sodium bicarbonate 8.4%, 2 (4.3%) received 100 mL of sodium bicarbonate 8.4% and 11 (23.9%) received a combination of hypertonic saline and sodium bicarbonate 8.4%. The median sodium concentration before intervention in the group with correction was 122 mmol/L [120-124].

The impact of intraoperative sodium correction on postoperative sodium concentrations was examined in a subgroup analysis. The group of 46 patients who received hypertonic saline or sodium bicarbonate intraoperatively (corrected group) was compared with the group of 62 patients who did not receive hypertonic saline or sodium bicarbonate (uncorrected group). The characteristics of the patients and intraoperative details between the two groups are shown in Table III.

The median sodium concentrations of the uncorrected and the corrected group are shown in Figure 1 (ABG) and Figure 2 (laboratory blood samples). The median sodium concentrations at baseline ABG (139 mmol/L [137-140] vs. 139 mmol/L [138-141]; p= 0.043) and laboratory sample (140 mmol/L [139-142] vs. 141 mmol/L [140-143]; p=0.007) are significantly lower in the corrected group. The median sodium concentration on ABG after the administration of HTK cardioplegia is significantly lower in the group with correction than without correction (122 mmol/l [120-124] vs. 129 mmol/L [126-133], p<0.001). At the other time points, the postoperative median sodium concentrations did not differ significantly between the two groups (Table III). 11 of 62 patients (17.7%) of the uncorrected group and 35 of 46 patients (76.1%) of the corrected group had severe hyponatremia after the administration of HTK cardioplegia (p<0.001).

The median ΔNa after administration of HTK cardioplegia was significantly higher in the group with intraoperative correction (17 mmol/L [13-20]) than in the uncorrected group (10 mmol/L [7-14]) (p<0.001). The median ΔNa at both T1 (7.5 mmol/L [5-8.25] vs. 7 mmol/L [6-8.25]; p=0.718) and T2 (6 mmol/L [4-6] vs. 6 mmol/L [5-8]; p=0.700) did not differ in the corrected group compared to the uncorrected group. At T4, the median ΔNa is significantly smaller in the corrected group (4

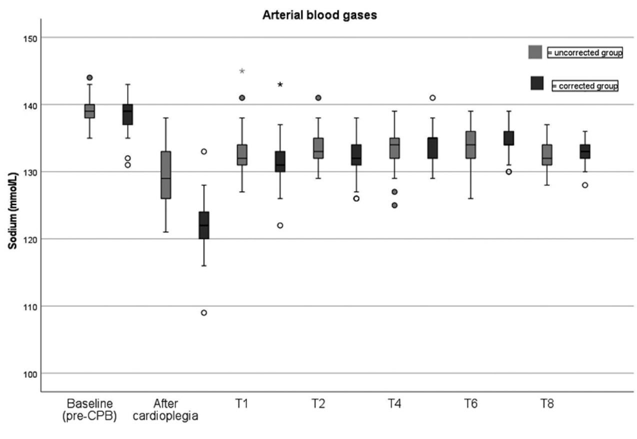

Fig. 1 — Median sodium concentrations (thick line) of the uncorrected and the corrected group on ABG presented as a box (first and third quartile) at different time stages: baseline (pre-CPB), after administration of HTK cardioplegia, after weaning from CPB (T1), on arrival in the ICU (T2), 6 hours (T4), 12 hours (T6) and 24 hours (T8) after arrival in the ICU.

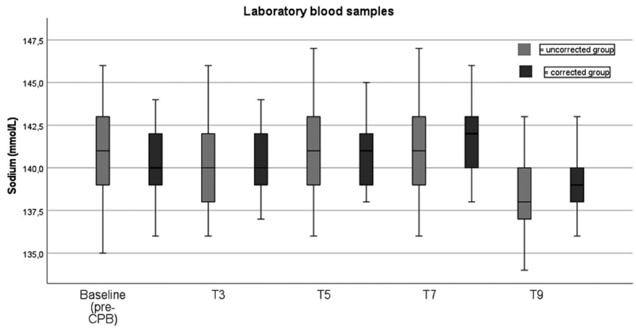

Fig. 2 — Median sodium concentrations (thick line) of the uncorrected and the corrected group on laboratory blood samples presented as a box (first and third quartile) at different time stages: baseline (pre-CPB), on arrival in the ICU (T3), 6 hours (T5), 12 hours (T7) and 24 hours (T9) after arrival in the ICU.

Table IV. — Characteristics of patient and intraoperative details between patients with and without agitation. Median sodium concentrations on ABG at different time stages: baseline (pre-CPB), after administration of HTK cardioplegia, after weaning from CPB (T1), on arrival in the ICU (T2), 6 hours (T4), 12 hours (T6) and 24 hours (T8) after arrival in the ICU.

	Alert and calm (n=96)	Agitation (n=12)	p=
Age, median [IQR], year	68.5 [60.25-75]	71 [67-78.75]	0.220
Male sex, n (%)	62 (64.6)	7 (58.3)	0.671
Weight, median [IQR], kg	76.5 [68.25-86]	75.5 [68.25-82.75]	0.799
BMI, median [IQR], kg/m²	26.39 [23.90-28.98]	27.14 [24.13-27.60]	0.922
BSA, median [IQR], m²	1.91 [1.74-2.02]	1.85 [1.70-1.99]	0.788
eGFR	82 [67.50-92]	81 [71.75-87.5]	0.475
Creatinine, median [IQR], mmol/L	0.86 [0.75-1.06]	0.90 [0.82-1.01]	0.460
Operation time, median [IQR], min	180 [180-240]	240 [185-240]	0.098
CPB time, median [IQR], min	114.5 [93.5-145.75]	122.5 [95-159.75]	0.528
ACC time, median [IQR], min	86 [69-109.5]	92.5 [74-120.75]	0.295
Lowest sodium during CPB, median [IQR], mmol/L	125 [122.25-129]	126 [119.5-128.5]	0.295
Baseline sodium, median [IQR], mmol/L	139 [138-140]	138 [136-139]	0.026
After HTK cardioplegia, median [IQR], mmol/L	125 [122-131]	126 [120-129]	0.246
Severe hyponatremia after HTK cardioplegia, n (%)	41 (42.7)	5 (41.7)	0.945
T1, median [IQR], mmol/L	132 [130-133]	131 [128-133]	0.125
T2, median [IQR], mmol/L	133 [132-135]	132 [130-135]	0.121
T4, median [IQR], mmol/L	134 [133-135]	132 [130-135]	0.067
T6, median [IQR], mmol/L	134 [133-136]	134 [132-137]	0.635
T8, median [IQR], mmol/L	133 [132-134]	132 [130-135]	0.214
HTK cardioplegia volume, median [IQR], mL	2000 [2000-2500]	2250 [2000-2725]	0.294
HTK cardioplegia volume, median [IQR], mL/kg	27.97 [25-34.66]	31.00 [25.48-39.32]	0.466

BMI: body mass index; BSA: body surface area; eGFR= estimated glomerular filtration rate; CPB= cardiopulmonary bypass; ACC= aortic cross clamping; HTK= Histidine-tryptophan-ketoglutarate.

mmol/L [2-7]) compared to the uncorrected group (5 mmol/L [4-7]) (p=0.020). The ΔNa at T6 (3.5 mmol/L [2-6] vs. 5 mmol/L [4-7]; p=0.005) and T8 (6 mmol/L [3.5-7.5] vs. 6 mmol/L [5-8]; p= 0.034) were also significantly smaller in the group with the intraoperative correction than the group without correction.

The median difference between the sodium concentration after administration of HTK cardioplegia and at T1 in the uncorrected group was 2.5 mmol/L [0.75-5] and in the corrected group 10 mmol/L [6-12]. There was a significant difference in the increase of sodium concentration at T1 between the two groups (p < 0.001).

Agitation

Agitation occurred in 12 of 108 patients (11.1%). The characteristics of patients with and without agitation and the intraoperative details are listed in

Table IV. The lowest median sodium concentrations during CPB are equal in the two groups (alert and calm vs. agitation: 125mmol/L [122-129] vs 126 mmol/L [120-129]; p=0.295). Overall, there are no statistically significant differences in intraoperative and postoperative sodium concentrations between the two groups (Table IV).

Of the 12 patients with postoperative agitation, 6 patients received intraoperative correction of their sodium concentration. There was no statistically significant correlation between postoperative agitation and intraoperative correction of sodium (p=0.582).

Discussion

In this retrospective observational study, we observed acute hyponatremia after the administration of HTK cardioplegia during open cardiac surgery using CPB. This observation is consistent with the findings of Van Houte et al., Kim et al. and Lindner et al[1, 5, 7]. In our retrospective study osmolality was not investigated, because osmolality is not routinely determined in our center. The osmolality of HTK cardioplegia is slightly hyperosmolar compared to plasma[1,7]. Retrospective and prospective studies have shown that the administration of HTK cardioplegia results in acute hyponatremia without a decrease in osmolality[1,7]. Therefore, some authors advise against correction of hyponatremia, as it can result in a hypertonic state[1,7].

Acute severe hyponatremia after administration of HTK cardioplegia occurred mainly in patients with a single venous cannulation in which the HTK cardioplegia enters the systemic circulation. The entry of HTK cardioplegia into the systemic circulation with a single cannula can cause volume overload, hemodilution, hyperkalemia and hyponatremia. This explains why ultrafiltration is performed more in single cannulation compared with double cannulation. The median sodium concentrations were significantly lower in the group with single cannulation than in the group with double cannulation until arrival in the ICU. After 6 hours in the ICU, no differences in postoperative sodium concentrations were observed. As other studies have shown, a double cannulation strategy in which the HTK cardioplegia is aspirated from the coronary sinus is preferable to prevent hemodilution and acute severe hyponatremia during CPB[1,11.]

In our study HTK cardioplegia induced hyponatremia was corrected in 46 patients (42.6%) during open cardiac surgery. This study has shown a relation between single cannulation in which the HTK cardioplegia enters the systemic circulation and the tendency of intraoperative correction of sodium. In a subgroup analysis, no differences in postoperative sodium concentration between the groups with and without intraoperative correction of sodium were seen. In the group with intraoperative correction of sodium, a higher fluctuation (ΔNa) was observed after the administration of HTK cardioplegia compared to the group without correction. Also, the median increase of sodium was significantly higher during the time after administration of HTK cardioplegia to T1 in the group with intraoperative correction of sodium. After 6 hours in the ICU, a smaller difference of median ΔNa was observed in the corrected group than in the uncorrected group.

Postoperatively, the sodium concentration on ABG increased in the first 12 hours after arrival in the ICU. In contrast to other studies, moderate hyponatremia still occurred on ABG after 12 hours[1,7]. Hyponatremia did not occur on laboratory blood samples 6 and 12 hours after arrival in the ICU. There was a difference in sodium concentration between ABG and laboratory blood samples. Gupta et al. and Bo Zhang et al. have reported that laboratory measured sodium is statistically higher compared to ABG-measured sodium[12,13]. The difference between laboratory and ABG results was linked with serum protein and albumin. Because of this difference, test results cannot be used interchangeably[12-14]. ABG are not a standardized procedure and the accuracy is not guaranteed. Factors such as hemodilution, sample acquisition, etc. could affect this error. Due to lack of intraoperative laboratory blood samples, ABGs were used to evaluate the intraoperative sodium concentrations.

This study shows a significant decrease of the sodium concentration on ABG and laboratory blood samples after 24 hours in the ICU. Because the decrease in sodium occurs 24 hours after arrival, it is unlikely to be solely related to the cardiac surgery, CPB and the administration of HTK cardioplegia. Postoperative factors such as the administration of fluids, transfusion, fluid shift and antidiuretic hormone activity may play a role in the onset of postoperative hyponatremia[15].

In a subgroup analysis, a group of patients with postoperative agitation was compared with a group of patients without agitation. Kim et al. described postoperative seizures in pediatric patients who underwent cardiac surgery because of fluctuations of sodium[5]. The clinical relevance of intraoperative acute hyponatremia after the administration of HTK cardioplegia in adult patients has not yet been described in other studies. In this study, there was no statistically significant difference in sodium concentration between the group with and without agitation. Factors such as general anesthesia, hypothermia and postoperative pain can also cause postoperative agitation.

This study is limited by its retrospective design. Osmolality could not be examined because it is not routinely determined in our center, which is a weakness of this study. Another limitation is the rather small study population. Other causes of intraoperative hyponatremia (hemodilution because of priming volume of CPB and intraoperative fluids, etc.) were not included in this study. Furthermore, the statistical analysis does not correct for repeated measurements (e.g. repetitive samples in same patients). This could lead to a type I error and could explain the statistical significance of clinically negligeable differences in sodium concentrations. The RASS score was used as an indication of whether patients were agitated. This scale is not the best objective measurement to evaluate neurological outcomes in hyponatremia. Moreover, there was no correction for confounders (e.g. hypothermia, pain, etc.).

In future prospective research, standardized intraoperative laboratory blood samples should be used for measuring intraoperative sodium concentrations. Further, the effect of hypertonic sodium and sodium bicarbonate 8.4% on osmolality should be investigated. The effect of ultrafiltration on sodium concentration and osmolality should also be investigated. Further prospective research is necessary to investigate the decrease of sodium concentration after 24 hours in the ICU.

In conclusion, the administration of HTK cardioplegia induces acute hyponatremia during cardiac surgery using CPB mainly in patients with single venous cannulation. Postoperatively, a normalization of sodium concentrations can be observed with a decrease after 24 hours. No correlation was found between postoperative sodium concentration and intraoperative correction of sodium or between postoperative sodium concentration and postoperative agitation. Intraoperative correction of hyponatremia shows no benefit or harm on postoperative sodium concentrations. Hyponatremia could be avoided or at least diminished by using double venous cannulation.

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