COMPARATIVE STUDY BETWEEN THE EFFECTIVENESS OF N-ACETYLCYSTEINE AND BICARBONATE IN RENAL PROTECTION AFTER CARDIAC BYPASS SURGERY

Galal A. El Kady, Sherif G. Anis, Amr A. Kasem, Mostafa M. Serry and Alia M. Mohamed`

Department of Anesthesia & Intensive Care and Pain Management, Faculty of Medicine - Ain Shams University, Cairo, Egypt

Corresponding :

Alia M. Mohamed

Mobile: 01282003853

E mail:

aliamohamed1987@hotmail.com

Received: 18/7/2019
Accepted: 21/8/2019

ABSTRACT:

Background: *Cardiac surgery-associated acute kidney injury is a common and serious postoperative complication of cardiac surgery that employs cardiopulmonary bypass. Acute renal failure occurs in up to 30% of patients who undergo cardiac surgery.*

Aim of the Work: *to compare between the effectiveness of acetylcysteine and bicarbonate in prevention of acute kidney injury in patients undergoing elective cardiac bypass surgeries.*

Patients and Methods: *This interventional prospective comparative randomized single blinded study was conducted on 120 cardiac patients, hypertensive, diabetic with normal preoperative kidney functions, of either sex, aging >40 years old, scheduled for elective cardiac bypass surgery at Cardiothoracic Surgery Department of Ain Shams University hospitals. Study started June 2017 and ended December 2018; after the approval of the ethical medical committee and obtaining a written informed consent from the patient.*

Results: *The current study showed nonsignificant correlation between usage of NAC and bicarbonate and renal protection after cardiac bypass surgeries. Also the current study showed the more the time of aortic clamping, time of CPB and the lower the MAP during CPB, the more the rise in serum creatinine after 24 hours.*

Conclusion: *The current study shows that perioperative intravenous administration of NAC with or without sodium bicarbonate may not have a role in prevention of acute kidney injury in patients undergoing elective cardiac bypass surgeries as detected by serum creatinine and creatinine clearance.*

Key words: *N-acetylcysteine, Bicarbonate, Renal Protection, Cardiac Bypass Surgery*

INTRODUCTION:

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common and serious postoperative complication of cardiac surgery that requires cardiopulmonary bypass (CPB)[(1)].

Due to the difference in surgery type, the range of incidence is between 8.9 and 39%. Isolated CABG has the lowest incidence of AKI, followed by valvular surgery and combined CABG with valvular surgery in series[(2,3)].

Risk factors associated with the development of CSA-AKI have been well established. Preoperative risk factors include advanced age, female gender, reduced left ventricular function or congestive heart failure, diabetes mellitus, peripheral vascular disease, emergent surgery, and preoperative elevated serum creatinine[(4)].

CSA-AKI is caused by a variety of factors including metabolic abnormalities, ischemia and reperfusion injury, neurohormonal activation, inflammation, and oxidative stress[5].

Also during the perioperative period, the volume status of the patients is of importance. Other factor of major importance is low cardiac output, before, during, or after surgery, that is directly related to AKI risk[6].

Additional factors include aortic cross-clamping and declamping techniques, blood transfusion, hypothermia and hemolysis[2].

Identification of patients before surgery who are at high risk for developing CSA-AKI should permit the efficient application of prophylactic and therapeutic measures[7].

Sodium bicarbonate causes urinary alkalinization that may protect renal tissues from injury induced by oxidant substances, complement activation, and hemoglobin-induced pigment nephropathy[8].

N-acetylcysteine (NAC) reduces pro-inflammatory cytokines, oxygen free-radical production, and ameliorates ischemia reperfusion injury; therefore, it may theoretically reduce postoperative complications in cardiac surgery[9].

AIM OF THE WORK:

The aim of this study is to compare between the effectiveness of acetyl cysteine and bicarbonate in prevention of acute kidney injury in patients undergoing elective cardiac bypass surgeries.

PATIENTS AND METHODS:

One hundred and twenty cardiac patients, hypertensive, diabetic with normal preoperative kidney functions, of either sex, aging >40 years old, were scheduled for elective cardiac bypass surgery at Cardiothoracic Surgery Department of Ain Shams University hospitals. Study started June 2017 and ended December 2018. It was an interventional prospective comparative randomized single blinded study after the approval of the ethical medical committee and obtaining a written informed consent from the patient.

Exclusion criteria:

Patients with the following criteria were excluded from the study, emergency operation, patients who had allergy to NAC, or prior adverse reaction to NAC (e.g generalized rash, urticarial, bronchospasm, hypotension), patients scheduled for off pump surgery or extracardiac procedure e.g. pericardictomy, patients who required chronic dialysis, patient unable to give informed consent (e.g dementia), patients with preoperative serum creatinine more than 1.5mg/dl.

Preoperative evaluation:

All patients were subjected to the following: clinical examination, ECG, Routine laboratory investigations including complete blood count (CBC), random blood sugar (RBS), liver function test (LFT), kidney function test (KFT), prothrombin time (PT) and partial thromboplastin time (PTT), Echocardiography examination with full study and measurement of cardiac volume, and function.

Anesthetic technique:

All patients were premedicated with oral diazepam (5mg) at the morning of the operation. A peripheral intravenous cannula was inserted. The left radial artery was cannulated.

Anesthesia was induced with propofol (2mg/kg), cisatracurium (0.15mg/kg), and fentanyl (5microgram/kg), intravenously. Anesthesia was maintained with isoflurane, increments of fentanyl, morphine and incremental doses of cisatracurium (0.03mg/kg) as needed. Central venous line

was inserted under complete aseptic conditions.

Mechanical ventilation was maintained until the start of the CPB.

Immediately after the induction of anesthesia, before the first surgical incision, group A received NAC at an intravenous dose of 150mg/kg in 250ml of 5% glucose over 15min, followed by a continuous intravenous infusion of 50mg/kg in 250ml of 5% glucose over 4h and then 100mg/kg in 250ml of 5% glucose over 20h (total dose=300mg/kg body weight over 24h). Group B received sodium bicarbonate 8.4% (90ml of bicarbonate added on glucose 5% infused at rate of 3ml/kg/hour immediately after induction of anesthesia, prior to the first surgical incision, followed by 1 mL/kg/hour for 24 hours. Group C received combination of bicarbonate and NAC in equivalent previos doses and volumes over the same period. Group D received 750ml of glucose 5% over the same period.

Cardiopulmonary bypass technique after heparin administration at a dose of 3–5mg/kg, aortic and right heart cannulation was performed. CPB was established once the activated clotting time was greater than 450s, CPB was instituted with a non pulsatile heart-lung machine, with the blood flow maintained at 2–2.4l/ min/m2. The prime volume comprised of mannitol, crystalloid solutions and heparin. The target was to keep hematocrit at about 24% after initiation of CPB. The body temperature during bypass was maintained between 28 and 30C. After removal of the ACC, and the reperfusion at normothermic CPB, weaning off bypass was done, where Adrenaline (40-400 ng/kg/min.) was the first choice if inotropes were needed, while Nitroglycerine(0.5-10 microgram/kg/min.) was the first choice if vasodilators were needed.

Measurements:

Preoperative measurements:

HR, MAP, temperature, CVP, hemoglobin level, EF%, serum urea, serum electrolytes, PH and HCO3 of arterial blood gas sampling, serum creatinine and creatinine clearance were recorded.

Intraoperative measurements:

RBS, CVP and UOP were recorded every hour all through operation.

Invasive mean arterial blood pressure were continuously monitored and recorded for the sake of the study at the following intervals (5min after induction, before going on bypass, the lowest reading during bypass).

Time of operation and time of aortic clamping were documented.

Postoperative measurements:

Serum urea, serum creatinine, creatinine clearance, electrolytes (Na, K), PH and HCO3 of arterial blood gas sampling, UOP, RBS and vital data were recorded at the following intervals; immediately post-operative and every 6 hours for 24 hours starting from end of operation.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

- Probability (P-value)

– P-value < 0.05 was considered significant.

– P-value < 0.001 was considered as highly significant.

– P-value > 0.05 was considered insignificant.

RESULTS:

One hundred and twenty patients were subjected to the current study,15 patients were excluded from that study. five patients died, six patients developed postoperative bleeding and reopened and four patients developed allergy from acetylcysteine.

Table (1): Comparison between groups according to serum creatinine (mg/dl)

Serum creatinine	Group A *(n=28)*	Group B *(n=26)*	Group C *(n=26)*	Group D *(n=25)*	ANOVA	p-value
Baseline	0.79±0.12	0.79±0.14	0.78±0.20	0.77±0.18	1.492	0.540
Immediately postoperative	0.74±0.11	0.77±0.14	0.77±0.20	0.78±0.18	1.865	0.092
6 hrs. postoperative	0.68±0.10	0.74±0.14	0.75±0.20	0.69±0.18	1.574	0.274
12 hrs. postoperative	0.86±0.15	0.85±0.20	0.81±0.20	0.88±0.19	0.989	0.608
18 hrs. postoperative	0.94±0.13	0.91±0.23	0.94±0.39	1.04±0.19	1.460	0.229
24 hrs. postoperative	1.03±0.20	0.98±0.28	1.04±0.55	1.15±0.31	1.181	0.320

F- One Way ANOVA; p-value >0.05 NS;

This table shows no statistically significant difference between groups according to serum creatinine (mg/dl).

Table (2): Comparison between groups according to serum sodium (mmol/l)

Serum sodium	Group A *(n=28)*	Group B *(n=26)*	Group C *(n=26)*	Group D *(n=25)*	ANOVA	p-value
Baseline	138.20±1.63	137.30±1.82	137.90±1.60	137.60±1.83	1.513	0.215
Immediately postoperative	138.20±1.63	139.90±1.95	138.70±1.58	137.80±1.75	1.922	0.118
6 hrs. postoperative	138.90±1.84	145.30±1.70†	146.20±1.49†	138.60±1.83$^{\#\#}$	16.267	<0.001**
12 hrs. postoperative	139.20±1.63	146.60±2.81†	148.10±1.24†	138.60±1.83$^{\#\#}$	18.303	<0.001**
18 hrs. postoperative	139.90±1.84	148.70±2.81†	150±1.20†	139.10±1.84$^{\#\#}$	23.527	<0.001**
24 hrs. postoperative	140.20±1.63	150.60±2.85†	152.20±1.63†	139.60±1.83$^{\#\#}$	19.143	<0.001**

*F- One Way ANOVA; p-value >0.05 NS; **p-value <0.001 HS*

Post Hoc:
†: Significant difference with group A (p-value <0.05 S)
‡: Significant difference with group B (p-value <0.05 S)
#: Significant difference with group C (p-value <0.05 S)

This table shows statistically significant difference between groups according to serum sodium samples obtained at 6,12,18 and 24 hours after end of surgery. Values are higher in group B and C.

Table (3): Comparison between groups according to serum potassium (mmol/l)

Serum potassium	Group A *(n=28)*	Group B *(n=26)*	Group C *(n=26)*	Group D *(n=25)*	ANOVA	p-value
Baseline	3.82±0.19	3.79±0.16	3.81±0.20	3.77±0.16	0.469	0.704
Immediately postoperative	4.06±0.24	3.91±0.37	4.03±0.37	4.11±0.31	1.023	0.115
6 hrs. postoperative	4.37±0.18	4.09±0.33	4.13±0.37	4.26±0.26	0.516	0.774
12 hrs. postoperative	4.40±0.22	4.07±0.29	4.18±0.48	4.29±0.34	1.125	0.127
18 hrs. postoperative	4.44±0.16	4.14±0.24	4.25±0.45	4.36±0.26	0.567	0.852
24 hrs. postoperative	4.38±0.11	4.21±0.19	4.29±0.32	4.42±0.17	1.238	0.139

F- One Way ANOVA; p-value >0.05 NS;

This table shows no statistically significant difference between groups according to serum potassium (mmol/l).

Table (4): Comparison between groups according to creatinine clearance (ml/min.)

Creatinine clearance	Group A *(n=28)*	Group B *(n=26)*	Group C *(n=26)*	Group D *(n=25)*	ANOVA	p-value
Baseline	116.21±16.45	118.26±12.23	118.17±19.27	115.43±22.03	1.125	0.127
Immediately postoperative	118.84±18.89	121.93±13.09	117.01±19.30	116.24±22.53	0.567	0.852
6 hrs. postoperative	116.54±22.59	115.73±14.19	118.80±20.96	119.11±23.44	1.238	0.139
12 hrs. postoperative	111.16±16.59	112.76±15.88	113.21±17.82	109.77±21.31	0.624	0.613
18 hrs. postoperative	96.55±36.01	96.36±16.38	103.39±23.36	106.35±20.43	1.188	0.317
24 hrs. postoperative	98.65±19.67	90.74±19.03	97.86±25.85	98.73±23.62	0.903	0.442

F- One Way ANOVA; p-value >0.05 NS;

This table shows no statistically significant difference between groups according to creatinine clearance (ml/min.).

Table (5): Comparison between groups according to (pH) of arterial blood gas samling

Arterial blood gas (pH)	Group A *(n=28)*	Group B *(n=26)*	Group C *(n=26)*	Group D *(n=25)*	ANOVA	p-value
Baseline	7.39±0.03	7.37±0.03	7.37±0.02	7.38±0.02	1.063	0.310
Immediately postoperative	7.36±0.05	7.38±0.02	7.37±0.03	7.36±0.02	1.369	0.247
6 hrs. postoperative	7.34±0.03	7.44±0.02†	7.40±0.05†	7.34±0.02‡#	7.866	<0.001**
12 hrs. postoperative	7.33±0.02	7.44±0.03†	7.41±0.06†	7.35±0.02‡#	7.971	<0.001**
18 hrs. postoperative	7.34±0.02	7.45±0.04†	7.42±0.05†	7.34±0.02‡#	6.393	<0.001**
24 hrs. postoperative	7.35±0.02	7.47±0.04†	7.44±0.05†	7.35±0.02‡#	8.564	<0.001**

*F- One Way ANOVA; p-value >0.05 NS; **p-value <0.001 HS*
Post Hoc:
†: Significant difference with group A (p-value <0.05 S)
‡: Significant difference with group B (p-value <0.05 S)
#: Significant difference with group C (p-value <0.05 S)

This table shows statistically significant difference between groups according to (pH) of arterial blood gas samples obtained at 6, 12,18 and 24 hours postoperative starting from end of operation. Values are higher in group B and C.

Table (6): Comparison between groups according to (HCO_3) of arterial blood gas sampling (mmol/l)

Arterial blood gas (HCO3)	Group A *(n=28)*	Group B *(n=26)*	Group C *(n=26)*	Group D *(n=25)*	ANOVA	p-value
Baseline	23.65±1.06	23.41±0.92	23.50±1.16	23.47±1.19	0.264	0.851
Immediately postoperative	23.17±1.73	24.01±0.92	23.10±2.12	22.97±1.19	1.894	0.211
6 hrs. postoperative	21.93±1.18	24.91±0.92†	26.25±2.51†	22.16±1.32‡#	52.133	<0.001**
12 hrs. postoperative	22.53±1.07	26.20±1.02†	27.40±2.80†	22.66±1.32‡#	62.596	<0.001**
18 hrs. postoperative	23.08±1	27.65±0.97†	27.80±1.12†	23.16±1.32‡#	172.579	<0.001**
24 hrs. postoperative	23.43±0.96	29.78±1.04†	29.85±1.25†	23.46±1.32‡#	307.507	<0.001**

*F- One Way ANOVA; p-value >0.05 NS; **p-value <0.001 HS*
Post Hoc:
†: Significant difference with group A (p-value <0.05 S)
‡: Significant difference with group B (p-value <0.05 S)
#: Significant difference with group C (p-value <0.05 S)

This table shows statistically significant difference between groups according to HCO_3 (mmol/l) of arterial blood gas samples obtained at 6, 12,18 and 24 hours postoperative starting from end of operation.

Table (7): Comparison between groups according to outcome evaluation of patients postoperatively

Outcome	Group A *(n=30)*	Group B *(n=30)*	Group C *(n=30)*	Group D *(n=30)*	ANOVA	p-value
Duration of mechanical ventilation (hrs)						
Mean ± SD	15.20±1.56	14.60±1.94	14.10±1.54	14.10±2.01	1.603	0.155
Range	13-18	12-18	12-17	12-18		
Length of stay in ICU(hrs)						
Mean ± SD	26.60±4.82	28.80±8.10	30±8.19	26.40±4.88	2.038	0.112
Range	24-36	24-48	24-48	24-36		
Length of Stay in Hospital (days)						
Mean ± SD	7.80±1.19	7.80±1.42	8±1.58	7.70±1.21	0.258	0.856
Range	7-10	7-11	7-11	7-10		

F- One Way ANOVA; p-value >0.05 NS;

This table shows no statistically significant difference between groups according to outcome evaluation of patients postoperatively

Table (8): Correlation between bypass time, aortic cross clamping time, lowest MAP on bypass ,outcome evaluation of patient after surgery and development of kidney injury as indicated by elevation in serum creatinine and decrease in creatinine clearance, using Pearson Correlation Coefficient in group A.

Group A	Serum creat after 24hrs		Creat clearance after 24hrs	
	r	p-value	r	p-value
Serum creat after 24hrs			-0.751	<0.001**
Creat clearance after 24hrs	-0.751	<0.001**		
Bypass time (min)	0.102	0.593	-0.249	0.185
Time of aortic clamping (min)	0.588	<0.001**	-0.584	<0.001**
Lowest reading during bypass	-0.414	0.023*	0.693	<0.001**
Duration of mechanical ventilation (hrs)	0.736	<0.001**	-0.892	<0.001**
Length of stay in ICU(hrs)	0.775	<0.001**	-0.820	<0.001**
Length of Stay in Hospital (days)	0.743	<0.001**	-0.687	<0.001**

r-Pearson Correlation Coefficient
*p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

The table showed that in group (A) the more the time of bypass and time of aortic cross clamping and the lower MAP during bypass, the more the liability to develop kidney injury, as indicated by increased serum creatinine and decrease creatinine clearance.

Also the table showed the more the rise in serum creatinine, the more the duration of mechanical ventilation, more ICU stay and more hospital stay.

Table (9): Correlation between bypass time, aortic cross clamping time, lowest MAP on bypass ,outcome evaluation of patient after surgery and development of kidney injury as indicated by elevation in serum creatinine and decrease in creatinine clearance, using Pearson Correlation Coefficient in group B.

Group B	Serum creat after 24hrs		Creat clearance after 24hrs	
	r	p-value	r	p-value
Serum creat after 24hrs			-0.859	<0.001**
Creat clearance after 24hrs	-0.859	<0.001**		
Bypass time (min)	0.602	<0.001**	-0.750	<0.001**
Time of aortic clamping (min)	0.359	0.049*	-0.599	<0.001**
Lowest reading during bypass	-0.507	0.004*	0.566	<0.001**
Duration of mechanical ventilation (hrs)	0.597	<0.001**	-0.788	<0.001**
Length of stay in ICU(hrs)	-0.428	0.018*	0.219	0.244
Length of Stay in Hospital (days)	0.816	<0.001**	-0.916	<0.001**

r-Pearson Correlation Coefficient
*p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

The table showed that in group (B) the more the time of bypass and time of aortic cross clamping and the lower MAP during bypass, the more the liability to develop kidney injury, as indicated by increased serum creatinine and decrease creatinine clearance.

Also the table showed the more the rise in serum creatinine, the more the duration of mechanical ventilation, more ICU stay and more hospital stay.

Table (10): Correlation between bypass time, aortic cross clamping time, lowest MAP on bypass ,outcome evaluation of patient after surgery and development of kidney injury as indicated by elevation in serum creatinine and decrease in creatinine clearance, using Pearson Correlation Coefficient in group C.

Group C	Serum creat after 24hrs		Creat clearance after 24hrs	
	r	p-value	r	p-value
Serum creat after 24hrs			-0.891	<0.001**
Creat clearance after 24hrs	-0.891	<0.001**		
Bypass time (min)	0.442	0.014*	-0.576	<0.001**
Time of aortic clamping (min)	0.742	<0.001**	-0.784	<0.001**
Lowest reading during bypass	-0.828	<0.001**	0.778	<0.001**
Duration of mechanical ventilation (hrs)	-0.163	0.390	-0.095	0.618
Length of stay in ICU(hrs)	-0.156	0.411	-0.200	0.289
Length of Stay in Hospital (days)	-0.110	0.564	-0.169	0.373

r-Pearson Correlation Coefficient
*p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

The table showed that in group (C) the more the time of bypass and time of aortic cross clamping and the lower MAP during bypass, the more the liability to develop kidney injury, as indicated by increased serum creatinine and decrease creatinine clearance.

Also the table showed no signifiacant correlation between the rise in serum creatinine and the duration of mechanical ventilation, ICU stay and hospital stay.

Table (11): Correlation between bypass time, aortic cross clamping time, lowest MAP on bypass, outcome evaluation of patient after surgery and development of kidney injury as indicated by elevation in serum creatinine and decrease in creatinine clearance, using Pearson Correlation Coefficient in group D.

Group D	Serum creat after 24hrs		Creat clearance after 24hrs	
	r	p-value	r	p-value
Serum creat after 24hrs			-0.935	<0.001**
Creat clearance after 24hrs	-0.935	<0.001**		
Bypass time (min)	0.834	<0.001**	-0.795	<0.001**
Time of aortic clamping (min)	0.625	<0.001**	-0.509	0.004*
Lowest reading during bypass	-0.392	0.032*	0.273	0.144
Duration of mechanical ventilation (hrs)	0.685	<0.001**	-0.504	0.004*
Length of stay in ICU(hrs)	0.831	<0.001**	-0.732	<0.001**
Length of Stay in Hospital (days)	0.840	<0.001**	-0.751	<0.001**

r-Pearson Correlation Coefficient
*p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

The table showed that in group (D) the more the time of bypass and time of aortic cross clamping and the lower MAP during bypass, the more the liability to develop kidney injury, as indicated by increased serum creatinine and decrease creatinine clearance.

Also the table showed the more the rise in serum creatinine, the more the duration of mechanical ventilation, more ICU stay and more hospital stay.

DISCUSSION:

The current study was designed to evaluate the possibility that NAC and bicarbonate could serve as a potential renal protector against reperfusion injury during cardiac bypass surgeries. It's a interventional, prospective, comparative, randomized, single blinded study placebo – controlled study including four groups of patients. It was conducted in the Cardiothoracic Surgery Department of Ain Shams University hospitals, Cairo, Egypt. Study started June 2017 and ended December 2018.

AKI is not only a frequent complication in cardiac surgical patients, but has also been shown to be independently associated with morbidity and mortality. Unfortunately, little progress has been made within the last years in the development of strategies to reduce the incidence and improve the prognosis of this complication[(10)].

In the current study , serum creatinine and creatinine clearance were used for diagnosis of perioperative acute kidney injury (AKI).

The current study showed non significant correlation between usage of NAC and bicarbonate and renal protection after cardiac bypass surgeries.

Brown et al., showed that combination prophylaxis with NAC and NaHCO3 substantially reduce the occurrence of contrast induced AKI, but not dialysis dependent[(11)].

Thayssen et al.,[(12)] showed that combined treatment with NAC and NaHCO3 didn't reduce the rate of CIN, but that combination may reduce the risk of renal dysfunction after 30 days.

The current study showed non-significant correlation between rise in serum creatinine, increased time of mechanical ventilation, increase length of stay in ICU and increase length of stay in hospital.

The current study showed that usage of sodium bicarbonate led to metabolic alkalosis and hypernatremia.

Also the current study showed that the more the time of aortic clamping, time of CPB and the lower the MAP during CPB, the more the rise in serum creatinine after 24 hours.

Some studies were against this study and showed that NAC has a renoprotective role against oxidative stress during CPB. The role of NAC as an antioxidant in reducing the oxidative stress caused by the CPB had been investigated for a long time. In 2004, Sucu and his colleagues[13] conducted a study to investigate the effect of NAC on preventing pump-induced oxido-inflammatory response during cardiopulmonary bypass, which was done on Fourty patients undergoing CABG who were randomly divided into a study group receiving NAC and control group, samples were collected for measurement of myeloperoxidase (MPO), malondialdehyde (MDA), interleukin-6, α1-acid glycoprotein (AAGP), and C-reactive protein (CRP) during surgery and postoperatively as oxido-inflamatory markers. The study showed that NAC pretreatment reduced the CPB induced oxido-inflammatory response, possibly by preventing the oxido-inflammatory cascade activation, as indicated by the marked attenuation of the markers.

Savluk et al., demonstrated that in patients with preexisting mild renal failure undergoing CABG surgery, intravenous NAC had a renoprotective effect, whereas continued low-dose dopamine (renal dose) had no protective effect. NAC caused a statistically significant increase in GFR, increased creatinine clearance and a decrease in creatinine **[15]**.

Fischer et al.**,** showed that NAC reduced serum creatinine compared with the control group in their study. Moreover, Wijeysundera et al.,[17] found that there was preservation of postoperative GFR in patients with preexisting moderate renal dysfunction undergoing cardiac surgery and a significant reduction in mortality with NAC.

Sisillo et al.,[19] demonstrated a reduction in the incidence of the serum creatinine concentration with the usage of NAC in cardiac surgery. However, this reduction did not reach statistical significance.

Furthermore, Ayhan et al.,[17] found that two different regimens of NAC in CABG had some beneficial effects in the early the period of the surgery, but failed to demonstrate preventive effects in patients in the late phase.

Santana et al., showed that the incidence of kidney injury was reduced with NAC in CABG. They investigated two independent markers of kidney injury, namely cystatin C and neutrophil gelatinase associated lipocalin (NGAL). In the current study, the criteria used to characterize AKI were serum creatinine and creatinine clearance calculated by Cockcroft–Gault equation**[18]**.

It has been illustrated that NAC can reduce the risk of contrast nephropathy in humans, while the renoprotective effect of NAC on CPB remains controversial[19].

Other studies agreed with the current study and showed that NAC usage wasn't significantly associated with reduction in serum creatinine and prevention of post-operative AKI.

Adabag et al.,[20] found that NAC was not significantly associated with decrease in serum creatinine levels, the incidence of AKI, hemodialysis requirements, operative mortality, intensive care, or length of hospital stay in patients undergoing cardiac surgery. These patients received oral NAC 600 mg twice daily preoperatively, but the researchers administered NAC orally, and such administration may reduce its effectiveness.

Tossios et al.,[21] suggested that NAC application should begin before anesthesia induction to yield maximal benefit of its reactive oxygen species (ROS)-scavenging properties. Considering that the NAC is estimated to have a short half-life, at 2.2 hours, in the current study, 50 mg/kg of NAC was administered as the loading dose in 100 cc of 0.9% NaCl for 15 minutes; following this 20 mg/kg/h of NAC was given as an infusion in 100 cc of 0.9% NaCl during the operation.

In the current study, NAC was started immediately after the induction of anesthesia, before the first surgical incision, intravenous dose of 150mg/kg in 250ml of 5% glucose over 15min, followed by a continuous intravenous infusion of 50mg/kg in 250ml of 5% glucose over 4h and then 100mg/kg in 250ml of 5% glucose over 20h.

Hyninen et al.,[22] demonstrated that NAC does not decrease the amount of kidney injury occurring in patients with normal preoperative renal function undergoing abdominal aortic surgery.

In addition, Sucu et al.,[13] found that intravenous NAC decreased the pump-induced oxido-inflammatory response during CPB. In aortic surgery, it may result in kidney injury, and this may have different mechanisms, with the exception oxido-inflammatory damage[13].

Haase et al.,[8] concluded that a high dose (300 mg/kg intravenously) of NAC was no more effective than a placebo in attenuating CPB-related acute renal failure in high-risk cardiac surgery patients. Theoretically, high-dose NAC may have been excessive, and paradoxically, it may have diminished the level of radical oxygen species, thereby attenuating their potentially positive role in the regulation of intracellular signaling.

There has been no consensus on the identification of the most effective route and dose of NAC administration associated with significant renal protection in patients undergoing CABG. However, NAC is an inexpensive, relatively safe, well-tolerated, and widely used drug[14].

Recently, Haase and coworkers have elegantly delineated a pathophysiological line of evidence that the severity of the renal insult induced by on-pump cardiac surgery may, at least in part, be related to the degree of hemoglobinuria: the histological features of CSA-AKI resemble the pigment nephropathy typically observed during rhabdomyolysis. Since alkalization of the urine is among the established measures to treat rhabdomyolysis, they used this concept successfully as a strategy for the prevention of CSA-AKI in a small pilot trial, the results of that prospective observational cohort study showed that perioperative treatment with bicarbonate does not reduce the incidence of CSA-AKI as measured by postoperative changes in creatinine, and the need for dialysis. Moreover, it is associated with clearly unwarranted effects like a decrease in arterial blood pressure (during the bolus application of bicarbonate an increased need for fluids and vasopressors, and an increased hospitalization time[8,16].

The result of that study agreed with the current study that there was no statistically significant correlation between the usage of bicarbonate, decrease in serum creatinine and prevention of postoperative AKI.

Thus it is rather likely that the observed adverse effects in the intervention period were indeed related to the use of bicarbonate infusion, that is, alkalization, despite only achieving minimal changes in maximal plasma pH. Data show that bicarbonate is frequently used in cardiac surgical patients to treat acidosis, especially during cardio-pulmonary bypass. Despite this, few data are available on the short- and long-term hemodynamic effects of bicarbonate. Tripathi and coworkers observed a biphasic response after the infusion of bicarbonate 1 mmol /Kg BW during steady state conditions during

CPB with an immediate venous pooling (leading to a decrease in the CPB reservoir volume), followed by a moderate increase in MAP. In contrast, observations in patients with end-stage renal disease show that higher dialysate bicarbonate concentrations lead to a decrease in arterial blood pressure during dialysis, an effect that may be explained by an increase in endothelial nitric oxide production[18].

Since the differences in maximal pH between the study groups were rather small (0.1 pH difference) despite being statistically significant, one may assume that the lack of a nephroprotective effect of bicarbonate infusion may be related to the fact that no adequate alkalization was achieved[20].

Haase and his colleagues tested a novel pathophysiological concept considering acute kidney injury being a potential sideropathy with oxidoinflammatory stress as a common unifying pathway causing cell injury aggravated by labile iron compounds [22].

They found that bicarbonate infusion achieved plasma and urinary alkalinization, but did not reduce kidney function deterioration indicated by serum creatinine concentration and urinary output. The current study demonstrated that there was no reduction of acute kidney injury or tubular protection after open heart surgery in patients who were administered sodium bicarbonate despite achieving adequate plasma and urinary alkalinization [26].

Also causal association of systemically administered sodium bicarbonate and mortality appeared to be possible. Given that findings, they didn't recommend the routine prophylactic use of sodium bicarbonate infusion for that purpose[23,24].

Haase et al, conducted a pilot double-blinded, randomized control trial of 100 cardiac surgery patients. The patients underwent treatment to see if postoperative serum bicarbonate infusion can attenuate postoperative increases in serum creatinine. Their primary outcome was reaching a serum creatinine of >25% above baseline within the first five postoperative days. They found a statistical significance using bicarbonate in patients with creatinine increases >25% however there was no difference in patients with creatinine increases of either >50% and >100%. There was no statistical significance found when acute kidney injury was defined by the AKIN criteria. No mortality benefit was seen in patients receiving postoperative serum bicarbonate infusion[21].

Furthermore, other large RCT studies looking at n-acetylcysteine, fenoldopam and statins failed to show a clear benefit in postoperative renal protection[8,25].

Mehta and colleagues showed that no difference was found between postoperative serum bicarbonate infusion and normal saline groups seen in the prospective pilot study [27,28].

Conclusion

This study shows that perioperative intravenous administration of NAC with or without bicarbonate may not have a role in prevention of acute kidney injury in patients undergoing elective cardiac bypass surgeries as detected by serum creatinine and creatinine clearance.

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