KLİNİK ÇALIŞMA / CLINICAL RESEARCH

RENAL FUNCTIONAL EFFECTS OF USING N-ACETYL-CYSTEINE (NAC) IN CARDIAC SURGERY

KARDİYAK CERRAHİDE N-ASETİL-SİSTEİN (NAC) KULLANIMININ RENAL FONKSİYON ÜZERİNE ETKİLERİ

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SUMMARY

Objective: *Acute renal failure following cardiac surgery is a very important cause of morbidity and mortality. The risk has been reduced with a variety of some practises. In this study we investigated the effects of two different methods of using N-Acetylcystein (NAC) during cardiac surgery on renal function.*

Method: *60 patients with normal renal function were randomly allocated to three groups. Group I had 50 mg kg^{-1} NAC added to pump priming solution; Group II received 50 mg kg^{-1} NAC i.v. after induction and had an infusion of 20 mg kg^{-1} h^{-1} throughout the operation; Group III was the control group. Demographic and perioperative data, fluid balance, urine output and drainage amounts, haemodynamic data, BUN, creatinine, blood and urine electrolytes, and beta-2 globulin, creatinine clearance and fractional sodium excreation (FeNa) were obtained after induction(T1), before CardioPulmonaryBypass (T2), 30^{th} minutes of CardioPulmonary Bypass (T3), after CardioPulmonaryBypass (T4), at the end of the operation (T5), at postoperative 24^{th} h(T6), and at postoperative 48^{th} h (T7).*

Results: *There were no difference among the demographic and perioperative data, total amount of fluid given, urine outputs and drainage. Urinary albumine/creatinine ratios inceased in Group III at T2 ($p< 0.05$), in Group I at T3, whereas no significant difference was found in Group II. Creatinine values showed a statistically significant increase postoperatively (T6-T7) in all groups ($p< 0.05$). Beta -2 globuline increased in the control group at T6, whereas in Group I and II at T7.*

Conclusion: *Two different regiments of N-Acetylcystein in coronary artery bypass grafting have some benefical effects, but failed to demonstrate preventive effect after 24 hr operation.*

KEY WORDS: *N-Acetylcystein; Renal Function; Cardiac Surgery; Renal Protection*

ÖZET

Amaç: *Kardiak cerrahi sonrası gelişen akut böbrek yetmezliği, çok önemli morbidite ve mortalite nedenlerindendir. Çeşitli uygulamalarla bu risk azaltılmıştır. Bu çalışmada; koroner cerrahi sonrasında 2 farklı yöntem ile N-Asetil-Sistein (NAC) kullanımının renal fonksiyonlar üzerine etkilerini değerlendirilmesi amaçlanmaktadır.*

Method: *Etik kurul onayı alındıktan sonra, normal renal fonksiyona sahip 60 hasta (18-75 yaş), 3 grup olacak şekilde çalışmaya katılmıştır. Grup I'deki hastalarda, 50 mg kg^{-1} NAC pompa priming solüsyonuna eklenmiştir. Grup II'deki hastalarda ise; indüksiyon sonrasında 50 mg kg^{-1} NAC i.v. ve operasyon boyunca ise 20 mg kg^{-1} sa^{-1} infüzyon ile uygulanmıştır. Grup III, kontrol grubu olarak belirlenmiştir. Demografik and perioperatif veriler, sıvı alımı, idrar çıkışı, drenaj miktarları; operasyon sonunda, postoperatif 24. ve 48. saatlerde kaydedilmiştir. Hemodinamik veriler, BUN, kreatinin, kan ve idrar elektrolitleri, beta-2 globulin değerleri ölçülmüştür. Kreatinin klirensi ve fraksiyone Na ekskresyonu (FeNa); indüksiyon öncesinde (T1), pompa öncesinde (T2), pompanın 30. dk'sında (T3), pompa sonrasında (T4), operasyon sonunda (T5), postoperatif 24. (T6) ve 48. (T7) saatlerde hesaplanmıştır.*

Sonuçlar: *Demografik veriler ve klinik bulgular açısından tüm gruplar benzerdi. Total verilen sıvı miktarı, idrar çıkışı ve drenaj açısından gruplar arasında fark yoktu. BUN değerlerinde bir azalma olsa da, tüm gruplar için bu benzerdi. İdrar albümin/kreatinin oranları; pompanın hemen sonrasında Grup III'de (T2) ($p< 0,05$), pompanın 30. dk'sında (T3)ise GrupII'de artmasına rağmen; Grup II'de fark bulunamadı. Kreatinin seviyeleri; postoperatif dönemde (T6-T7), tüm gruplarda belirgin olarak bir artış gösterdi ($p< 0,05$). Beta-2 globulin, kontrol grubunda, postoperatif 24. saatte başlayan bir atış göstermesine rağmen; Grup I and II'de bu artış postoperatif 48. saatte gözlendi.*

Tartışma: *İki farklı N-Asetil-sistein uygulama rejimi de koroner baypas greft cerrahisi olan hastalarda benzer yararlı etkiler göstermiştir; fakat bu koruyucu etkileri operasyondan 24 saat sonra göstermeyi başaramadı.*

ANAHTAR KELİMELER: *N-Asetil-Sistein; Renal Fonksiyon; Kardiyak Cerrahi; Renal Koruma.*

INTRODUCTION

Acute renal injury is common following cardiac operations and can produce serious clinical outcomes in 1-2% of patients, like the need for hemodialysis and even renal transplants. Risk factors such as advanced age, diabetes, chronic obstructive pulmonary disease, preoperative renal impairment, congestive cardiac failure, emergency surgery, re-do surgery, preoperative aortic baloon pump, increased duration of cardiopulmonary pump and low heamatocrit levels increase the likelihood of this complication (1-7). Studies confirms that the morbidity and mortality are increased in coronary surgery patients with slightly elevated preoperative serum creatinine levels and also a better preoperative glomerular filtration rate (GFR) attenuates the effect of postoperative renal function on mortality (3, 8).

Several drugs have been used for renal protection during cardiac operations, e.g. dopamin, mannitol, diuretics, fenoldopam, enalaprilat, dexamethasone, diltiazem etc. (9-15). Antioxidants have also been advocated to decrease oxidative stress after evolving acute myocardial infarction and to decrease ischemia-reperfusion injury during cardiac operations (16).

N-acetylcystein (NAC) is a well-known antidote, as well as non-specific antioxidant, with very few side effects and a large margin of safety. It is also cheap and easily available. Its use has been advocated in patients undergoing radiologic procedures, to protect against contrast induced nephropathy (17-19). In recent years new research targeting the protective effects of N-acetylcysteine in other stress-related and trauma-related areas have been undertaken. Although there are numerous studies, a final conclusion on the efficacy of NAC is yet to be reached. Therefore, in this study, we wanted the demonstrate which method and timing is good practice to protective effects of N-acetylcysteine.

The aim of the present study was to compare the effects of two different methods of NAC administration in patients undergoing CABG using CPB on renal function.

MATERIAL AND METHODS

Study Design and Patients

The institutional ethics committee approved the protocol and informed consent was obtained from each patient. This study was designed as a prospective, controlled, randomized and double blinded study. Sixty consecutive patients with normal renal function (Cr< 1.5 mg dl^{-1}) scheduled for elective coronary artery bypass grafting surgery (CABG) with CPB were included in this study. Exclusion criteria were as follows: patients with end-stage obstructive / restrictive pulmonary disease, renal failure, liver failure, sepsis, multiorgan failure, having previous cardiac surgery and emergency surgery, severe congestive heart failure (left ventricul fraction of ejection <35%), allergy to the drugs. All patients were closely followed for side effects of NAC (Parvolex, Celltech Pharmaceuticals Ltd., Slough, UK) (cuteneous eruptions, wheezing, hemolysis, moderate neutropenia= 2500-3500 μl^{-1}).

All the operations were performed by the same surgical team.

Randomization

These patients were randomly assigned to three groups; either receiving NAC (**GROUP I**, n:20), (**GROUP II**, n:20) or plasebo (**GROUP III**, n:20).

GROUP I (NAC in CPB prime Group, n:20): Patients received 15 ml of 0.9% saline as a loading dose in 15 min right after induction, followed by an infusion 250 ml of 0.9% saline throughout the operation. 50 mg kg^{-1} NAC mixed in 250 ml of 0.9% saline was added to their priming solution for the pump.

GROUP II (Intravenous NAC Group, n:20): NAC was administered in saline 0.9% as a loading dose of 50 mg kg^{-1} iv (15 ml) in 15 min. right after induction, followed by an infusion of 20 mg kg^{-1} hr^{-1} mixed in 250 ml of 0.9% saline throughout the operation. 250 ml of 0.9% saline was added to their priming solution for the pump.

GROUP III (Control Group, n:20): In the control group, patients received 15 ml of 0.9% saline as a loading dose in 15 min right after induction, followed by an infusion 250 ml of 0.9% saline throughout the operation. 250 ml of 0.9% saline was added to their priming solution for the pump.

Randomization assignment of patients to group I, group II, or group III was performed with a list of random numbers that was generated by the random function of computer software. The list contained the natural numerals 1, 2, and 3. These numbers were allocated as follows: 1, Group III; 2, Group I; and 3, Group II administration. The allocation into the treatment or the placebo group and the preparation of the study drug was performed by a person who unrelated to this study. Study personnel, patients, and individual participating in the data collection and data analysis were blinded to the treatment assignment.

Anesthesia Management

The day before surgery, patients were preanesthetically evaluated and premedicated with oral diazepam. In the operating room; electrocardiogram (ECG), pulse oximetry and end-tidal CO_2 and invasive arterial pressure (20-gauge cannula, right radial artery, internal volume 0.2 ml, BD

floSvitch, Faraday road, Swindon, UK) were monitored. After anesthesia induction; a 9,5 F three-lumen central venous catheter (Multicath, Vygon, Ecouen, France) was introduced into the right internal jugular vein. Two peripheral venous lines (18 G and 16 G), a urinary bladder catheter and nasopharyngeal temperature probe were inserted. Arterial blood pressure and central venous pressure (CVP) were monitored during surgery. Anesthesia induction was performed with using 0.2-0.3 mg kg^{-1} etomidate (USAN, INN, BAN) (marketed as **Amidate**), 0.1 mg kg^{-1} vecuronium bromide (Organon, Turkey, marketed as **Norcuron**) 1µg kg^{-1} fentanyl citrate (Janssen - Cilag). Anesthesia was maintained with 2% sevoflurane in a mixture of 50% oxygen and 50% nitrous oxide, except the CPB period during which additional remifentanil was used instead of nitrous oxide. Remifentanil (GlaxoSmithKline and Abbott as Ultiva) infusion was administered to all patients before and after CPB in a dose of 0.025-0.05 mg kg^{-1} min^{-1}. During CPB, remifentanil was infused 0.025 mg kg^{-1} min^{-1} (20). All patients ventilated with positive pressure. Ventilation parameters were adjusted according to keep tidal volume, respiratory rate, acid-base balance and arterial CO_2 levels within physiological limits. All patient received 500 ml Ringer Lactate solution iv before the induction of anestehesia. Thereafter, iv Ringer Lactate solution or hydroxyethyl starch (130/0.4) (Voluven) was infused to keep the CVP between 12 and 14 mmHg. Voluven of the maximum dose was 20 ml kg^{-1} (21).

CPB management

CPB circuit consists of modified coated system and fiber membranous oxygenator (COBE Cardiovascular, Inc., Colorado, USA) (Sarns 9000 Perfusion System, 3M Health Care Group, Michigan, USA). The priming fluid of the CPB circuit contained 1500 ml ringer lactate and 5000 U heparin. All patients received 3mg/kg heparin (Heparine® Leo Pharma, Belgium) before the start of CPB. Activated coagulation time was kept above 450 s throughout the CPB period. Non-pulsatile CPB flow was used 2-2.4 ml/m^2 body surface area and mean perfusion pressure was kept 50-60 mmHg. Hematocrit concentrations were maintained above 22%. Moderate hypothermia (28°C) was induced during CPB. At the end of surgery, normothermia (37°C) was established. After the surgical procedure, reperfusion of the heart, the patients were separated from CPB. In all cardiac surgery patients, anticoagulation was reversed using protamine to achieve a normal activated clotting time. Hemodynamic goals were aimed to maintain mean arterial pressure (MAP) of 70-90 mmHg using dopamine or norepinepherine infusion when required. This drugs and doses of these drugs were recorded. At the end of the surgical procedure, patients admitted to cardiovascular surgery intensive care unit. The patient was weaned from mechanical ventilation at the achievement of normothermia, bleeding control, and hemodynamic stabilization. Postoperative CVP was kept within 10-14 mmHg. The hemoglobin levels were maintained 10 gr dl^{-1}. Postoperative pain treatment was iv morphine patient controlled analgesia (PCA). No patients received non-steroidal antiinflamatory drugs the assessment period.

Data Collection and Definition:

Demographic (age, sex, weight) and perioperative data (duration of operation, duration of CPB, duration of aortic cross clemp, ejection fraction, number of grafts used) as well as fluid balance, urine output and drainage amounts were recorded at the end of operation at 24^{th} and 48^{th} postoperative hours.

Haemodynamic data (MAP, heart rate, CVP), BUN, creatinine, blood and urine electrolytes (Na, K, Cl), and beta-2 microglobulin (indicator of renal tubular injury) were measured, and albumine/creatinine ratio (indicator of glomerular injury), creatinine clearance and fractional sodium excretion (FeNa) were calculated after induction (T1), before CPB (T2), 30^{th} minutes of CPB (T3), after CPB (T4), at the end of operation (T5), at postoperative 24^{th} hour (T6) and at postoperative 48th hour (T7). In this observation, side effects of NAC (rash, wheezing, superficial phlebitis, hemolysis and neutropenia) and the number of patients who required dialysis were recorded.

Statistical evaluation:

All data were evaluated by SPSS 15.0 package program. Kolmogorov-Smirnov test is used to find normal distribution of the variants. The values having no normal distribution were evaluated by Mann Whitney-U test. The values in normal distribution were given as Mean ± SD and the other values were given as Mean. All groups were compared with repeated measures by one-way ANOVA analysis. The cathegorical values were evaluated by Chi-square test. A p value of less than 0.05 was accepted as statistically significant.

RESULTS

Patient Characteristics and Operative Variables

The patient characteristics and operative variables of groups are presented in Table 1. No statistical significant differences among Group I, II, and III were identified with respect to the demographic characteristics and operative variables ($p > 0.05$). There were no differences in the total amount of fluids given, urine outputs and drainage among the three groups (Table 1).

Table 1. Patient Characteristics and Operative Variables

	GROUP I (n=20)	GROUP II (n=20)	GROUP III (n=20)	*P
Age (Years)	58.6±9	65±12.1	59.9±9	2.202
Weight (kg)	80.1±13.2	77.0±8.1	81.6±10.1	0.963
Ejection Fraction (%)	55±15	61±7	60±8	1.513
Number of grafts used (n)	3 (2;4)	3 (1;6)	3 (1;4)	0.583
Operation period (min)	268.7±70.5	256±44.3	267.8±42.8	0.343
ACC period (min)	48±18.4	49.8±11.9	47.1±18.1	0.140
CPB period (min)	76.6±29.3	78.6±20.1	83.5±30.3	0.347
Fluids given to patients during operation (ml)	2757±825.4	3400±530	2959±661.9	4.634
Urine output during operation (ml)	747.5±452	974.5±670.4	1153±706.7	2.149
Postoperative drainage (ml)	368.8±223.9	372.3±231.2	509±2693.2	0.997

*p> 0.05

All data, except number of grafts used, are presented as mean±SD; number of grafts used is shown as median with interquartile rage (25th;75th percentiles).

ACC: Aortic Cross Clamp, CPB: Cardiopulmonary Bypass

None of the patients presented with side effects of NAC (rash, wheezing, superficial phlebitis, hemolysis and neutropenia). No patients required dialysis in the postoperative period.

Creatinine clearance values significantly decreased in the post-CPB period (T4), at the end of operation (T5), postoperative 24th (T6) and 48th (T7) hours when compared with values at after induction period (T1) in Group III. On the other hand, in Group I and II, it decreased at postoperative 24th (T6) and 48th (T7) hours (p< 0.05). When the three groups were compared, post-CPB (T4) values in Group II were found to be lower (p< 0.05) (Table 2).

Values of urinary albumin/creatinine ratio increased before the CPB (T2), 30th minutes of CPB (T3), post-CPB (T4) periods and at the end of the operation (T5) in Group III, when compared with post-induction values (T1). In Group I, urinary albumin/creatinine ratio increased at the 30th minutes of CPB (T3), in post-CPB period (T4), the end of the operation (T5) and at the postoperative 24th (T6) and 48th (T7) hours (p< 0.05), whereas no significant difference was found in Group II (p< 0.05). There was no difference in urinary albumin /creatinine ratios in the three groups of cardiac surgery patients at any time (p< 0.05) (Table 3).

Beta-2 microglobulin values showed significant decrease during CPB (T3) in all groups (p< 0.05). While a significant increase was observed in all groups at the postoperative 48th hour (T7), in only the control group, a significant increase was seen at postoperative 24th hour (T6) when compared with post-induction values (T1) (p< 0.05). There was no difference in beta-2 microglobuline values in the three groups at any time (p< 0.05) (Table 4).

FeNa values increased from before the CPB (T2) to at the end of the operation (T5) in Groups II and III, whereas this increase was seen only in the post-CPB

Table 2. Creatinine Clearance values (ml.min^{-1}) in the Group I, II and III.

Creatinine Clearance (ml.min^{-1})	GROUP I (n:20)	GROUP II (n:20)	GROUP III (n:20)	**p value
T1	107.06±30.5	88.95±25.33	101.51±30.34	0.13
T2	110.00±30.4	88.99±26.84	100.81±27.27	0.06
T3	110.83±23.5	90.74±26.30	100.31±26.58	0.05
T4	106.37±20.11	**85.79±20.26****	**94.37±24.07***	**0.01****
T5	105.67±24.32	87.56±23.39	**95.23±23.7***	0.06
T6	**93.26±22.83***	**77.80±26.72***	**87.26±30.56***	0.19
T7	**93.72±27.92***	**78.68±29.03***	**90.11±33.37***	0.26

All data are presented as mean±SD.

*p< 0.05: When compared to basal values (within group analysis)

**p< 0.05:Among the three groups

Determine T1-T7

Table 3. Values of urinary albumine- to- creatinine ratio (mg.g^{-1}) in the Group I, II and III.

Values of urinary albümine/ creatinine ratio(mg.g^{-1})	GROUP I (n:20)	GROUP II (n:20)	GROUP III (n:20)	***p value*
T1	0.03±0.04	0.35±0.95	0.01±0.01	2.258
T2	0.04±0.05	0.10±0.24	**0.04±0.03***	0.898
T3	**0.06±0.05***	0.28±0.64	**0.08±0.07***	1.989
T4	**0.42±1.39***	0.38±0.79	**0.13±0.13***	0.593
T5	**0.11±0.12***	0.30±0.64	**0.10±0.12***	1.658
T6	**0.11±0.16***	0.16±0.55	0.03±0.02	0.839
T7	**0.07±0.06***	0.14±0.39	0.03±0.03	1.176

All data are presented as mean±SD.

*p< 0.05: When compared to basal values (within group analysis)

**p> 0.05:Among the three groups

Determine T1-T7

Table 4. Beta-2 microglobuline values (µg ml^{-1}) in the Group I, II and III.

Beta-2 microglobuline values (µg ml^{-1})	GROUP I (n:20)	GROUP II (n:20)	GROUP III (n:20)	***p value*
T1	1959.5±644.23	2211.9±597.81	1791.75±667.03	2.205
T2	1899.55±684.58	2218.2±674.89	1753.2±596.52	2.287
T3	**1453.4±429.75***	**1639.5±500.6***	**1446.95±417.32***	1.177
T4	**1744.19±510.96***	**2067.9±618.18***	1807.7±364.62	2.274
T5	1877.35±530.89	2045±607.3	**1684.95±507.88***	2.143
T6	1993.7±462.88	2375.9±1069.01	**2114.15±808.59***	1.139
T7	**2321.4±762.35***	**2651.25±878.59***	**2355.1±872.73***	0.935

All data are presented as mean±SD.

*p< 0.05: When compared to basal values (within group analysis)

**p< 0.05:Among the three groups

Determine T1-T7

period (T4) and at the end of the operation (T5) in Group I when compared with post-induction values (T1) (p< 0.05). In all groups, FeNa values increased at the postoperative 48th hour (T7) (p< 0.05), but these values were in the normal range. FeNa values reached peak levels which were not in the normal range at the end of the operation (T5) in all groups. When the three groups were compared, FeNa values were lower than the other both groups at the 30th minutes of CPB period (T3) in the Group I (p< 0.05) (Table 5).

Although creatinine levels increased in all groups at the postoperative 24th and 48th hours when when compared with post-induction values (T1) (p< 0,05), there was no difference among the groups. During the operation, creatinine levels remained below 1.5 mg dl^{-1} at any time in all groups (Table 6). There were no differences in

Table 5. Fractional sodium excretion (FeNa) values (%) in the Group I, II and III.

Fractional sodium excretion (FeNa) values (%)	GROUP I (n:20)	GROUP II (n:20)	GROUP III (n:20)	***p value*
T1	0.7±0.41	0.75±0.37	0.75±0.48	0.92
T2	0.66±0.31	**0.81±0.4***	**1.05±0.81***	0.09
T3	0.73±0.31	**0.97±0.4***	**1.53±1.17***	**0.003****
T4	**1.66±1.61***	**3.72±4.7***	**2.68±1.98***	0.12
T5	**4.34±5.93***	**6.21±5.55***	**5.46±6.14***	0.6
T6	1.01±0.85	0.8±0.54	0.91±1.83	0.8
T7	**1.99±2.6***	**2.47±3.91***	**1.12±1.25***	0.3

All data are presented as mean±SD.

*p< 0.05: When compared to basal values (within group analysis)

**p< 0.05:Among the three groups

Determine T1-T7

Table 6. Creatinine values (mg.dl^{-1}) in the Group I, II and III.

Creatinine (mg dl^{-1})	GROUP I (n:20)	GROUP II (n:20)	GROUP III (n:20)	**p value
T1	0.84±0.18	0.91±0.15	0.92±0.28	0.838
T2	0.82±0.18	0.92±0.18	0.92±0.26	1.472
T3	0.80±0.16	0.09±0.17	0.91±0.22	2.148
T4	0.83±0.16	0.94±0.15	0.97±0.23	2.940
T5	0.84±0.16	0.93±0.18	0.95±0.22	1.900
T6	**0.96±0.23***	**1.08±0.27***	**1.10±0.36***	1.236
T7	**0.98±0.25***	**1.08±0.31***	**1.06±0.29***	0.775

All data are presented as mean±SD.

*p< 0.05: When compared to basal values (within group analysis)

**p< 0.05:Among the three groups

Determine T1-T7

hemodynamic data, blood electrolytes, urine electrolytes and BUN levels in the three groups of studied cardiac surgery patients (p> 0.05) (Data not shown).

DISCUSSION

Our study demonstrated that these two different regiments of NAC in coronary artery bypass grafting have some beneficial effects, but fail to show preventive effect at early postoperative stage.

Oxidative stress occurs after reperfusion in CPB which may cause renal injury (22). Bypass factors have been manipulated with several strategies and the traditional drugs to reduce the ischemia-reperfusion reaction and its cellular and structural consequences after CABG with CPB. But these may not translate into clinical improvement in renal outcome (10, 23-27). Therefore, several antioxidant agents such as NAC, superoxide dismutase etc. have been tested but found benefical effects on renal function, as some improve function whereas others do not.

NAC is the thiol-modifying agent which promotes glutathione in its reduced form (GSH), which is depleted during ischemia and acts like an oxidant scavenger (28). Recently, NAC has gained wide investigated because of suggesting beneficial effects on oxidative stress related organ injuries in general, and particularly its protective effects on renal function (29,30). NAC have been received with contraversy over the timing and dosage. The dose of NAC (50-150 mg kg^{-1}) and the route of administration of NAC (intravenously, peroral, NAC in CPB prime solution, NAC in cardioplegia solution etc.) were not the same in the different studies about the renal protection (30-37). There was no any concensus a primary objective study which was to indentify the most effective route and dose of administration of NAC associated with significant renal protection in patients undergoing CABG using CPB. Most of studies interested in protective effects on renal function of NAC defined for radiocontrast induced nephropathy (29, 33, 38-41). Kshirsagar et. al. (34) performed metaanalysis of available prospective controlled trials to quantify and compare reported associations of oral N-acetylcysteine with the incidence of nephropathy after exposure to radiocontrast media. In this systematic review, they suggested that there was no significant effect of the use of oral N-acetylcysteine before radiocontrast media reduce the incidence. Studies of NAC to prevent postoperative dysfunction of renal function following cardiac surgery showed contradictory results. Hynninen et. al (21) demonstrated that NAC does not decrease the amount of renal injury occuring in patients with normal preoperative renal function undergoing abdominal aortic surgery and they recommended that NAC should not be used as a prophylactic measure for ARF. Naughton F et. al (37), Ashworth A et. al (42) and Wang et.al (43) performed a systematic review and meta-analysis of utilizing NAC in cardiac surgery requiring CPB. Their analysis showed that NAC was not associated with clinical renal protection in patients undergoing cardiac surgery. In these studies, investigators used different dose of NAC (preoperative 1200 mg and postoperative 600 mg oral bolus, 150 mg kg^{-1} i.v. bolus following 12,5 mg kg^{-1} i.v. infusion over 24 hr or 100 mg kg^{-1} bolus then 20 mg kg^{-1} min^{-1} infusion until 4 hr after CPB etc.). On the other hand, Mahmoud KM et. al (44) demonsrated cardiac protection (but not renal protection) of NAC infusion through scavenging of oxygen free radicals. In our study, we used two different routes of NAC administration in patients undergoing CABG using CPB. In the one of them, 50 mg kg^{-1} NAC was administrated into the CPB prime solution. Fischer UM et.al (45) received either NAC (100 mg kg^{-1} into the cardiopulmonary bypass prime followed by infusion at

20 mg kg^{-1} min^{-1} n= 20) or placebo (n= 20) to their patients undergoing cardiac surgery. Their data suggest that free radical-scavenging using NAC protects renal function in patients subjected to cardiac surgery on cardiopulmonary bypass. Tossios et al. (28) who added NAC the CPB prime followed by infusion till the end of CPB, found that NAC attenuated myocardial oxidative stress in the myocardium of patients subjected to CPB and cardioplegic arrest. But, they did not evaluate renal functions. In our study, except the FeNa levels, there was no difference between the NAC in the prime group and the others on the renal function. FeNa values were lower than the other both groups at the 30th minutes of CPB period (T3) in the NAC in the prime group. Previous studies suggested that ROS (Reactive oxygen species) are present before CPB initiation. Tossios et.al (28) recommended that NAC application should begin before anesthesia induction to reach maximal benefit of its ROS scavenging properties. Also, considering the short half-life of NAC estimated at 2.2 hours (46), NAC should maintaine as a continuous intravenous infusion till the end of CPB. Sucu et al. (47) found that intravenous NAC decreased pump-induced oxidoinflammatory response during CPB, and it could be a novel therapy for assisting in the prevention of CBP-induced oxidoinflammatory damage. Although, in the most of studies, intravenous NAC used from after the anesthesia induction to over 24 hr, observed no clinical or biochemical renal benefit (30, 48-50). In the present study, NAC was administered as a loading dose of 50 mg kg^{-1} i.v. in 15 min. right after induction, followed by an infusion of 20 mg kg^{-1} min^{-1} throughout the operation. Except the creatinine clearance, we did not find any difference between the intravenous NAC group and the others two group (control group and NAC in CPB prime group) on renal function. When the three groups were compared, post-CPB (T4) values in intravenous NAC group and were found to be lower. El-Halafawy YM. (51) showed that NAC administration into the CPB prime or within the cardioplegia resulted in better myocardial protection compared to its intravenous administration and there was no significant change in the clinical outcome and renal function among the three groups.

In the most of studies (52-53) which evaluate the effects of NAC on renal function during cardiac surgery was used primary outcome parameters that evaluated kidney function were serum creatinine concentration greater than 25% above the baseline, BUN, creatinine clearence, urinary albümine/creatinine ratio, change in GFR, FeNa (54), cystatine C (marker of GFR)(21,55), NGAL (neutrophil gelatinase-associated lipocalin), NAG (N-acetyl glucosaminidase) (21,56), beta-2 microglobuline (15, 57-59). Outcome parameters of our study were serum creatinine,

In our study, we found that these two different regiments of NAC in coronary artery bypass grafting have some beneficial effects in early period of the surgery, but fail to demonstrate preventive effect at late fase (24-48 hrs) in these patients. It is a question of continuous intravenous NAC until the postoperative 24^{th} or 48^{th} hrs. Because, NAC was administered only throughout the surgery in our study. Adabag et. al (60) showed with a meta-analysis study that prophylactic administration of NAC in the perioperative period to patients undergoing cardiac surgery does not reduce the incidence of ARI, haemodialysis, death, or lengths of stay. On the other hand, there could be another several possible reasons why we did not observe a treatment effect in the late period. The dose for prevention of CBP-induced nephropathy which we used in this study may be inadequate to counteract the hypoxic-ischemic insults to renal tubular injury. Timing of the initial dose may be important. The last, renal dysfunction observed following CABG surgery is multifactorial. Due to this characteristic of renal dysfunction may not be amenable to the antioxidant and vasodilatory effects of NAC.

In summary, our study demonstrated that administration of NAC intraoperatively failed to produce any beneficial renoproductive effects sustained in the postoperative period in patients with no known preoperative renal injury. Future studies should be designed to include large numbers of patients with similar baseline renal function receiving the alternative dosing and timing regimen of NAC.

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