The effects of low dose N-acetylcysteine (NAC) as an adjunct to cardioplegia in coronary artery bypass surgery

Koroner arter baypas cerrahisinde kardiyoplejiye eklenen düşük doz N-asetilsisteinin (NAC) etkileri

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ABSTRACT

Objective: We aimed to evaluate the efficacy of low dose N-acetylcysteine (NAC) against myocardial ischemia-reperfusion damage in coronary artery bypass surgery accompanied by cardiopulmonary bypass (CPB).

Methods: Thirty patients operated due to triple coronary artery disease were enrolled into this prospective randomized study (control group- n=15 and NAC group - n=15). N-acetylcysteine was added to induction cardioplegia solution in dose of 4 mmol/l and in dose of 2 mmol/l to maintenance cardioplegia solution in the NAC group. Hemodynamic measurements were performed before and after anesthesia with different intervals. Creatine kinase-MB (CK-MB) levels were analyzed during 24 hours postoperatively. Blood samples were obtained from coronary sinus before CPB (T_1), just before the cross-clamp removed (T_2) and 30 minutes later (T_3). Malondialdehyde (MDA), glutathione peroxidase (GSH-Px), nitric oxide (NO) levels and neutrophil percentage were determined. Statistical analysis was performed using student's t test, Chi-square and two-way ANOVA tests.

Results: There were no significant differences between the two groups with regard to the hemodynamic parameters, and CK-MB levels. The MDA levels were significantly lower in NAC group than in control group during reperfusion period (0.75 nmol/l vs 0.88 nmol/l, p<0.05). Neutrophil percentage in coronary sinus blood was significantly lower in NAC group than in control group during the reperfusion period (77.6% vs 82.7%, p<0.05). The GSH-Px and NO levels were also not statistically different between groups.

Conclusion: Low dose NAC as an adjunct to cardioplegic solutions effectively reduces myocardial oxidative stress in coronary bypass surgery with cardiopulmonary bypass, but may not restore the myocardial injury. *(Anadolu Kardiyol Derg 2008; 8: 437-43)*

Key words: N-acetylcysteine, coronary artery bypass surgery, ischemia-reperfusion, cardioplegia

ÖZET

Amaç: Kardiyopulmoner baypas eşliğinde yapılan koroner arter baypas cerrahisinde miyokard iskemi-reperfüzyon hasarına karşı düşük doz N-asetilsisteinin (NAC) etkisini değerlendirmeyi amaçladık.

Yöntemler: Üç damar hastalığına bağlı opere edilen 30 hasta bu ileriye dönük randomize çalışmaya alındı (kontrol grubu - n=15 ve NAC grubu - n=15). Çalışma grubunda, indüksiyon kardiyopleji solüsyonuna - 4 mmol/l, idame kardiyopleji solüsyonuna her birine 2 mmol/l NAC eklendi. Hemodinamik ölçümler anestezi öncesi ve sonrasında farklı sürelerde yapıldı. Kreatin kinaz- MB (CK-MB) seviyeleri postoperatif 24. saate kadar ölçüldü. Kan örnekleri kardiyopulmoner baypastan önce (T_1), kros klemp kaldırılmadan hemen önce (T_2) ve 30 dakika sonra (T_3) koroner sinüs- ten alındı. Malondialdehid (MDA), glütatyon peroksidaz (GSH-Px), nitrik oksit (NO) seviyeleri ve nötrofil yüzdesi ölçüldü. İstatistiksel analiz için eşleştirilmemiş t, Ki-kare ve iki-yönlü ANOVA testleri kullanıldı.

Bulgular: İki grup arasında hemodinamik ölçümlerde anlamlı farklılık yoktu. Gruplar arasında CK-MB seviyelerinde de farklılık bulunmadı. Re- perfüzyon döneminde ise MDA seviyeleri, çalışma grubunda, kontrol grubuna göre anlamlı olarak düşük bulundu (0.75 nmol/l'e karşı 0.88 nmol/l, p<0.05). Koroner sinüs kanındaki nötrofil yüzdesi yine reperfüzyon periyodunda, kontrol grubuna göre anlamlı olarak düşük bulundu (%77.6'ya karşı %82.7, p<0.05). Glütatyon peroksidaz ve NO seviyeleri ise istatistiksel olarak gruplar arasında farklı değildi.

Sonuç: Kardiyopulmoner baypas eşliğinde yapılan koroner arter baypas cerrahisinde, kardiyopleji solüsyonlarına eklenen düşük doz NAC, mi- yokardiyal oksidatif stresi azaltır, fakat miyokardiyal hasarı düzeltemeyebilir. *(Anadolu Kardiyol Derg 2008; 8: 437-43)*

Anahtar kelimeler: N-Asetilsistein, koroner arter baypas cerrahisi, iskemi-reperfüzyon, kardiyopleji

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Introduction

The systemic inflammatory response syndrome (SIRS) during cardiopulmonary bypass can be caused by contact of blood with the artificial surface of cardiopulmonary bypass (CPB) circuit, development of ischemia-reperfusion injury and operative trauma. The SIRS can lead to postoperative complications such as respiratory failure, renal dysfunction and myocardial damage (1). In the ischemic myocardium, reperfusion is necessary for the salvage of cardiac cells; however, reperfusion itself also causes injury. Ischemia reperfusion (I/R) damage is a multifactorial entity. Both cardiac myocytes and coronary endothelial cells are effected from nitric oxide (NO) deprivation, neutrophil activation, and release of free oxygen radicals (FOR) (2). Potential sources of free radicals during I/R are myocytes, vascular endothelium and leucocytes (3). The FOR-dependent lipid peroxidation causes changes in structure, proteins and permeability of the cell membrane. Myocardial I/R damage increases morbidity and mortality in open-heart surgery by leading to reperfusion arrhythmias, microvascular damage, myocardial stunning and cell death (4).

The ischemia-reperfusion injury can be caused by endothelial dysfunction and microvascular injury, oxidative stress and Ca^{+2} overload. Oxidative stress is associated with increased formation of FORs (3). The alterations in membrane permeability, configuration, and cellular proteins due to the radicals have been suggested as a main cause for I/R injury. The I/R injury causes arrhythmias, microvascular damage, myocardial stunning and cell death (4). The imbalance between oxidant productions as malondialdehyde (MDA) during I/R and endogenous antioxidants as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) is the determinant of the structural changes (3).

Several agents like thiol containing compounds, beta-blockers, angiotensin-converting enzyme inhibitors and calcium antagonists have been used to protect the myocardium and minimize the damage in CPB. N-acetylcysteine (NAC), which is used in clinical practice as a mucolytic drug, is among these agents. Ascribed to its sulphydryl (SH) group it has antioxidative properties, and it increases the radical scavenging capacity of glutathione (5). The effectiveness of NAC as antioxidant in CPB patients has been previously tested (6-9). However, they have used relatively high doses of NAC.

In the present study the effects of low dose NAC added in cardioplegic solution in coronary artery bypass grafting (CABG) patients on myocardial I/R damage were investigated.

Methods

Patient selection

The study (prospective, randomized and controlled) was approved by Medical Ethics Committee of the institution and informed consent was obtained from each patient.

This 6-months prospective study evaluated 30 patients with 3-vessel disease undergoing elective CABG without concomitant procedures. Patients with diabetes mellitus, renal or liver diseases were not included.

Patients admitting during this period were randomly (envelope method) allocated in two groups: the control group (n=15) and the NAC group (n=15). The control group received crystalloid/blood cardioplegia, the NAC group received NAC as adjunct to crystalloid/blood cardioplegia.

Anesthesia and surgical procedure

Standard median sternotomy incision was used for the exposure of the heart. Anesthesia was induced with 20-40 mcg/kg fentanyl citrate and 0.1 mg/kg midazolam, and maintained with 0.3 mcg/kg/min fentanyl and 0.8 mg/kg/min midazolam infusions. Before cannulation, patients had received heparin at a dose 3 mg/kg of body weight. Cardiopulmonary bypass was performed with a roller pump (Stockert Instrument, Germany) by maintaining the flow rate above 2-2.4 lt/m^2, and a membrane oxygenator (Dideco, Italy) was used. The patients were cooled to 30-32^{0}C and re-warmed to 37°C before CPB was discontinued. Cardiac arrest was obtained by an initial bolus of 500 ml antegrade blood cardioplegia followed by a bolus of 500 ml of retrograde blood cardioplegia. Thereafter, cold blood cardioplegia was administered in retrograde and continuous fashion at a rate of 50 ml/min. A hot shot final cardioplegia was delivered antegradely just before removal of the cross clamp. A commercial cardioplegia set (Dideco, Italy) was used to mix the crystalloid solution and blood in a proportion of 1:4 at 20°C. The solution was delivered through a catheter (DLP, Medtronic Inc, USA) inserted into the coronary sinus and cannula with additional venting (DLP, Medtronic Inc, USA) in aortic root. Topical ice slush was applied in patients. In the NAC group, initial cardioplegic solution containing 4 mmol/L of NAC (Asist, Husnu Arsan, Turkey) was delivered. The NAC content of subsequent cardioplegic solutions was reduced to 2 mmol /L.

Hemodynamic measurements

Radial artery was cannulated and a pulmonary artery catheter (Edwards Lifesciences, USA) for monitoring of hemodynamic measurement was introduced. Thermodilution cardiac output was measured using a CO computer (Spectramed Hemopro, USA). The following hemodynamic data were obtained: mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), stroke volume (SV), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). The hemodynamic measurements were repeated in 6 periods (T_1-T_6) as follows: before anesthesia induction, post-operative 1st, 6th, 12th, 24th and 48th hours.

Myocardial injury assessment

Blood samples were also collected from central venous line before anesthetic induction, and at 1st, 12th, and 24th hours postoperatively and were analyzed for creatine kinase MB (CK-MB) isoenzyme activity.

Myocardial oxidative stress assessment

Coronary sinus blood samples were obtained before CPB (T_1), before removal of aortic cross clamp (T_2), and 30 minutes following cross clamp removal (T_3) for neutrophil count, MDA and GSH-Px levels and NO measurement.

Neutrophil percentages: Neutrophil percentages were determined by measuring complete blood counts (Beckman Coulter Gen-S, USA) of the blood samples obtained from coronary sinus.

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Serum MDA measurement: MDA level was measured spectrophotometrically at 532 nm wave length by assessing the pink colored complex formed on the incubation of thiobarbituric acid (TBA) with plasma in boiling water bath by using a modified Yagi method (10). The MDA level was expressed as nmol/ml.

Erythrocyte GSH-Px enzyme activity measurement: Based on the method developed by Paglia and Valentine (11), the absorbance difference, formed on oxidization of NADPH to $NADP^+$ in a GSH-Px-catalyzed reaction which reduced glutathione (GSH) was converted to oxidized glutathione (GSSG) was measured spectrophotometrically at 340 nm. The erythrocyte GSH-Px value was expressed as U/grHb.

NO measurement: Total nitrite (nitrate+nitrite) concentration was assessed by "modified cadmium reaction" method. Nitrite amount was measured in a spectrophotometer (Schimadzu UV-1201) at 545 nm wave length by reading the color formed on sulfanilamide and sulfanilamide-dependent N-naphtylethilendi-amine (NNDA) diazotization reaction (12). Nitrite levels were calculated as µmol/ml.

Statistical analysis

Data are expressed as mean±SD. Statistical analyses were performed using SPSS for Windows, version 10.0 software (Chicago, IL, USA). Normality of data distribution was tested by Shapiro-Wilk method. For comparison of demographical and operative parameters unpaired t test, Chi-square and Fischer's exact tests were used. For comparison of changes in hemodynamic and biochemical parameters between groups two-way ANOVA, post-hoc Dunnett, and Newman-Keuls tests were utilized. A $p<0.05$ was considered as statistically significant.

Results

The patient's demographic and clinical variables are summarized in Table 1. The mean age of the patients was 62.9±4.9 years in the control group and 63.4±5.9 years in the NAC group. Both groups did not differ significantly by demographic and clinical variables.

Hemodynamic data

Hemodynamic variables are summarized in Table 2. There were no significant differences between two groups in hemodynamic variables. When measurements at T_1 were considered as basal, there were significant changes in only SVR and PVR values at the postoperative 24th (T_5) and 48th (T_6) hours ($p<0.05$ and $p<0.01$, respectively). Preoperative CK-MB levels were within the normal range in both groups (Fig. 1). Creatine kinase-MB levels were significantly higher at 1th, 12th and 24th hours postoperatively compared to their preoperative values (T_1). Both groups', CK-MB mass were elevated at the postoperative 1st hour (24.18±3.76 U/L vs. 26.14±2.96 U/L, p=0.75), and reached a peak at the postoperative 12th hour (28.43±4.02 U/ml vs. 31.04±3.79 U/ml, p=0.30). However, we could not detect significant differences in CK-MB levels between the two groups at any time.

Neutrophil count increased in both groups compared to the beginning levels in coronary sinus blood samples of the ischemia

period. This increase was statistically significant in the control group ($p<0.05$) (Fig. 2). At post reperfusion period, statistically significant increases were observed in both groups ($p<0.05$). However the increase in control group was statistically significant when compared to the increase in NAC group ($p<0.05$).

In both groups, higher MDA levels were detected at ischemia and reperfusion periods as compared with pre-ischemic period. Increase in T_3 period in control group was significant ($p<0.05$), but not in the NAC group (Fig. 3). There was no obvious difference between the groups in terms of T_1 and T_2 periods. However, the difference between two groups was found to be significant at the reperfusion period (T_3) ($p<0.05$).

There were no significant differences between the groups at any period with respect to the GSH-Px activity (Fig. 4). The GSH-Px activity at the T_2 period was slightly increased in both groups, but these increases were not significant. At the T_3 period there was an insignificant decrease in the GSH-Px activity in both groups.

The NO levels were insignificantly increased during reperfusion period (T_3) compared to the T_1 period. The NO levels did not significantly differ between the groups in any period (Fig. 5).
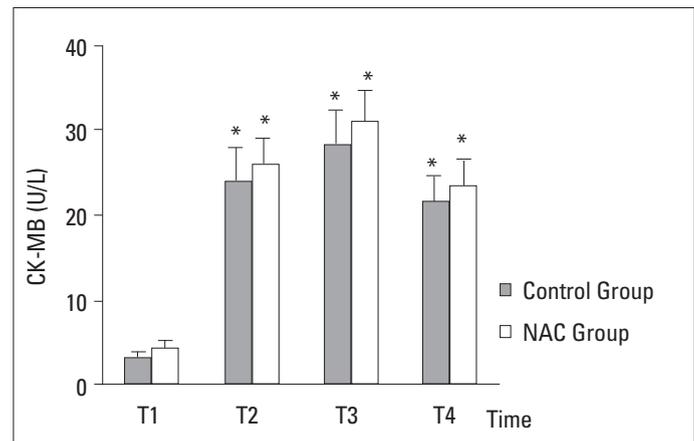
Figure 1. Comparison of pre- and postoperative CK-MB levels in patients groups

CK-MB-creatine kinase MB isoenzyme, NAC-N-acetylcysteine, T_1-before anesthetic induction, T_2-1 hour postoperatively, T_3-12 hour postoperatively, and T_4-24 hour postoperatively.
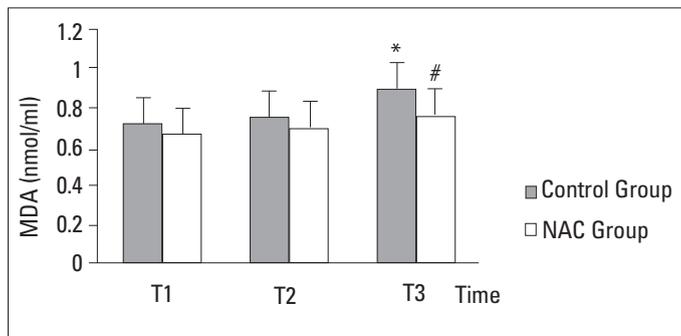• $p< 0.05$ T_1 vs T_2, T_3, and T_4 in both groups
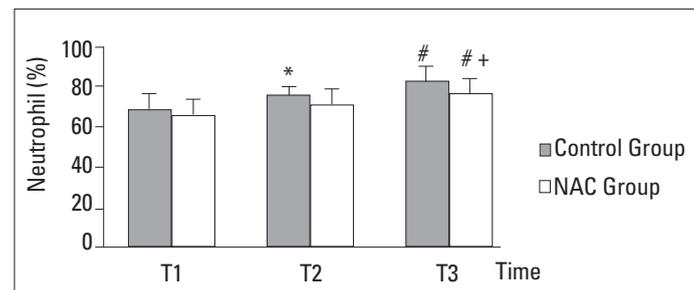
Figure 2. Comparison of pre- and postoperative neutrophil counts in coronary sinus blood samples in patients groups

NAC- N-acetylcysteine, T_1-before cardiopulmonary bypass, T_2-before removal of aortic cross clamp, and T_3- 30 minutes following cross clamp removal
* $p<0.05$ T_2 vs T_1 in control group;
# $p<0.05$ T_3 vs T_1 and T_2 in both groups;
+ $p<0.05$ control group vs NAC group in T_3

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Table 1. Demographic, clinical and operative data of the patients

Parameters	Control group (n=15)	NAC group (n=15)	p
Age, years[1]	62.9±4.9 60.3 (58 - 67)	63.4±5.9 60.3 (56-69)	0.90
Sex, female/male ratio[2]	2/15	4/15	0.38
Body surface area, m2[1]	1.86 ± 0.1 1.84 (1.82-1.88)	1.84 ± 0.1 1.82 (1.80-1.86)	0.53
Previous MI, n(%)[3]	9 (60)	11 (73.3)	0.45
Unstable angina pectoris, n(%)[2]	6 (40)	4 (26.6)	0.45
Ejection fraction, %[1]	49.6 ± 5.3 47.5 (45-55)	48.6 ± 4.8 46.6 (42-52)	0.74
Number of anastomoses[1]	3.2 ± 0.4 3.0 (3-4)	3.3 ± 0.4 3.1 (3-5)	0.72
IMA number, n(%)[3]	14 (93.3)	15(100)	0.81
Cardiopulmonary bypass, min[1]	91.2 ± 9.7 89.8(81-101)	96.5 ± 9.5 91.2 (86-106)	0.76
Cross-clamp time, min[1]	56.7 ± 8.7 60.5(44- 65)	57.5 ± 8.8 64 (48-68)	0.78
Inotropic support, n(%)[2]	4 (26.6)	3 (20.0)	0.64
Perioperative MI, n(%)[2]	1 (6.6)	0 (0.0)	0.79

Data are represented as mean±SD (Median, min-max) values and proportion/percentage. Student t[1] and Fischer exact test[2], Chi-square test.[3]
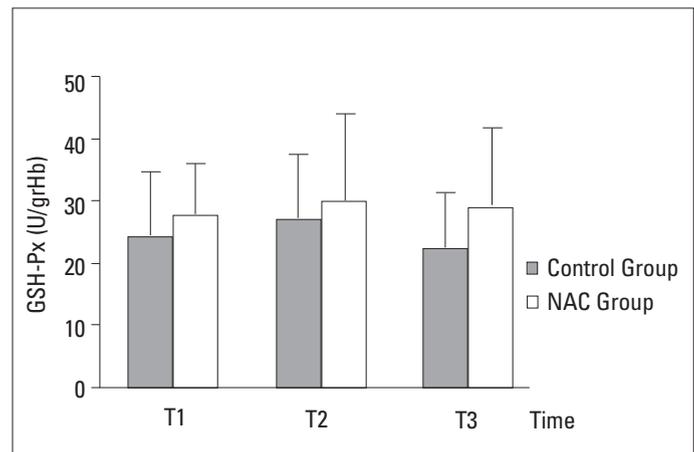IMA - internal mammarian artery, MI - myocardial infarction, NAC - N-acetylcysteine

Figure 3. Comparison of pre- and postoperative MDA levels in coronary sinus blood samples in patients groups

MDA- malondialdehyde, NAC- N-acetylcysteine, T_1- before cardiopulmonary bypass, T_2- before removal of aortic cross clamp, and T_3- 30 minutes following cross clamp removal
* $p<0.05$ T_1 vs T_3 in control group;
# $p<0.05$ control vs NAC group in T_3

Figure 4. Comparison of pre- and postoperative GSH-Px in coronary sinus blood samples of patients groups

GSH-Px- glutathione peroxidase activities, NAC- N-acetylcysteine,
T_1- before cardiopulmonary bypass, T_2- before removal of aortic cross-clamp, T_3- 30 minutes following cross clamp removal

Discussion

Our study describes the effects of the low dose NAC as an adjunct to cardioplegia in coronary artery bypass surgery with CPB on ischemia-reperfusion markers. We found the plasma MDA levels and coronary sinus neutrophil percentage to be significantly lower in patients received NAC as adjunct to crystalloid/blood cardioplegia compared with control subjects. In spite of these changes, the positive effect on myocardial oxidative stress markers did not reflect on hemodynamic parameters and we were not able to observe any clinical improvement.

The basic mechanism in reperfusion dependent oxidative stress is the peroxidation of unsaturated fatty acids with the effect of FOR on cell membrane and lysosomes (13). The changes in the mechanisms that arrange the intracellular calcium concentration formed on exposure to FOR are probably the true causes of reperfusion abnormalities. The effects of free radicals on contractile proteins, membrane ion transport and calcium

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Table 2. Hemodynamic parameters before and after operation

| Variables	T_1	T_2	T_3	T_4	T_5	T_6
MAP, mmHg						
Control group	85.2±10.4	80.3±6.8	80.8±5.2	85.0±5.4	84.4±6.4	88.4±6.7
NAC group	90.4±11.6	83.2±8.4	85.4±7.6	87.8±7.5	86.9±7.1	90.3±7.3
HR, beats/min						
Control group	80.2±12.7	90.1±9.2	88.9±8.3	87.1±8.6	80.9±7.6	7.8±6.6
NAC group	83.8±14.8	91.0±12.0	90.1±10.9	84.2±8.1	82.9±7.8	81.8±9.3
CVP, mmHg						
Control group	5.5±2.9	6.3±2.9	7.2±4.1	7.8±2.7	8.4±3.2*	8.0±2.8
NAC group	6.3±3.2	5.0±3.7	6.1±4.2	7.0±2.9	7.8±3.5	7.5±3.3
MPAP, mmHg						
Control group	20.4±4.7	21.0±4.3	20.3±3.2	20.1±3.3	19.6±3.1	19.8±2.6
NAC group	21.1±5.1	19.4±4.1	19.6±3.6	19.0±4.1	19.1±3.8	19.3±3.5
PCWP, mmHg						
Control group	9.8±4.1	9.6±4.4	9.5±3.8	9.6±3.7	9.7±4.2	0.0±3.5
NAC group	10.4±4.6	8.9±4.6	9.1±4.1	9.2±4.0	9.4±4.5	9.9±3.7
CI, l/min/m²						
Control group	2.4±0.6	2.2±0.6	2.3±0.6	2.5±0.5	2.6±0.4	2.8±0.3
NAC group	2.5±0.7	2.3±0.5	2.4±0.6	2.6±0.4	2.9±0.5	3.0±0.2
SV, ml						
Control group	58.6±15.6	47.7±12.3	49.4±13.2	55.3±9.8	62.2 ±10.5	70.2±7.8
NAC group	56.4±14.8	8.8±11.6	51.3±12.8	59.0±7.7	64.8±11.6	74.8±9.5
SVR, dyn/s/cm⁵						
Control group	1405±232	1403±255	1340±198	1314±225	1253±188[a]	1232±205[b]
NAC group	1475±271	1481±298	1415±310	1344±268	1186±246[a]	1162±183[b]
PVR, dyn/s/cm⁵						
Control group	199.1±52	219.9±92	196.0±49	178.6±54	156.5±61$	138.2±37#
NAC group	194.1±66	195.6±85	181.4±58	157.7±46	150.3±54$	129.8±49#

Data are represented as mean±SD. Two-way ANOVA analysis, post-hoc Dunnet and Newman-Keuls tests - * p< 0.05 T_1 vs T_5 in control group for CVP, [a] p<0.05 T_1 vs T_5 in both groups for SVR, [b] p< 0.01 T_1 vs T_6 in both groups for SVR, $ p<0.05 T_1 vs T_5 in both groups for PVR, # p< 0.01 T_1 vs T_6 in both groups for PVR
CO- cardiac output, HR- heart rate, MAP- mean arterial pressure, NAC: N-acetylcysteine, PVR- pulmonary vascular resistance, SV- systolic volume, SVR- systemic vascular resistance,
T_1- before anesthesia induction, T_2- postoperative 1st, T_3- postoperative 6th, T_4- postoperative 12th, T_5- postoperative 24th, T_6- postoperative 48th hour.

hemostasis mechanisms were described. Free oxygen radicals also inhibit some critical enzymes in anaerobic and aerobic metabolic pathways. Thus metabolic reserve of the reperfused myocardium is restricted and the intracellular calcium overload increases (3).

The myocardial protective potential of sulphydryl (-SH) group containing thiol compounds against reperfusion damage was firstly discussed in 1989 (14). Thiol compounds can easily bind the free-SH groups of structural and membrane proteins. This property gives a protective role against peroxides and other radicals. It was reported that NAC, a glutathione precursor, increased cytoplasmic SOD activity, scavenged the free hydroxyl radicals, decreased lipid peroxidation and neutrophil mediated FOR formation (8). Dhalla et al. (4) detected lower MDA levels in NAC treated group in a myocardium reperfusion model in rats. In experimental CBP studies on dogs, Fischer et al. (15) reported that

NAC decreased oxidative stress, protected myocardial functions, accelerated myocardial edema resolution. Koramaz et al. (7) searched the effect of NAC on oxidative stress. They added 50 mg/kg NAC to the cardioplegic solutions of CABG applied patients and observed that postoperative MDA levels were significantly lower than in the NAC-free group. In our study, MDA levels were significantly lower in the NAC group than that in the control group.

Vento et al. (8) added a dose of 0.04 mol/l NAC to the cardioplegia solution in CABG patients and found a high difference of total radical antioxidant potential (TRAP) between aorta and coronary sinus. They also showed that myocardial glutathione levels were protected and post reperfusion leucocyte sequestration was minimal in coronary sinus blood samples. We could not find any difference between groups in terms of GSH-Px levels. This might be due to using of 10-fold less NAC than their study. In addition, NAC is a direct glutathione precursor and we

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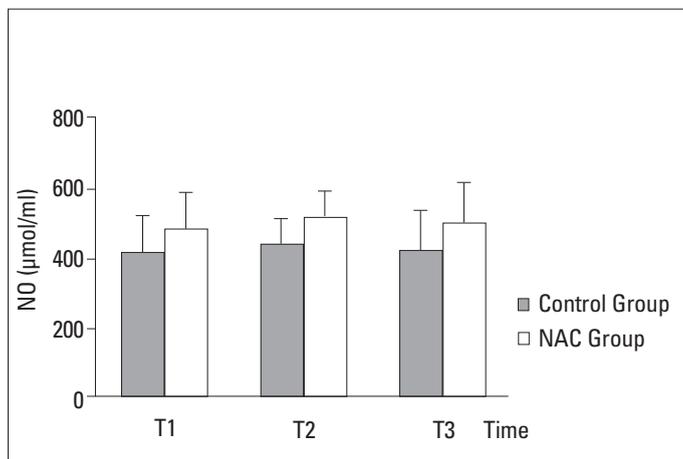
Figure 5. Comparison of pre- and postoperative NO levels in coronary sinus blood samples of patients groups

NAC- N-acetylcysteine, NO- nitric oxide, T_1- before cardiopulmonary bypass, T_2- before removal of aortic cross clamp, and T_3- 30 minutes following cross clamp removal

did not study this parameter. However, we found both MDA levels and neutrophil count significantly lower in coronary sinus blood samples of NAC group when compared to those of control and this finding supports the literature data.

Nitric oxide prevents thrombocyte aggregation and adhesion, suppresses the superoxide anions (17). At ischemia phase, NO synthase release is induced and formation of peroxinitrite (ONOO-) increases (18). At the early phase of reperfusion, first NO synthase enzyme is activated, but then NO release from the endothelium decreases (19). This results in leucocyte adhesion and aggregation. This event occurs at maximum at the 20th. minute of reperfusion. This interaction occludes capillaries, causes edema formation and is known as no-reflow phenomenon (20). Prevention of endogenous NO loss by giving exogenous NO donors or precursors may prevent those events (21). N-acetylcysteine may help scavenge FOR from endothelial and plasma cells by increasing the decreased bioavailability of NO induced by FOR (22). It increases NO bioavailability by converting to S-nitroso-N-acetylcysteine and S-nitrosocysteine structure (23). Half-life of NO is 0.1-1 seconds. When it encounters sulphydryl containing NAC, it is found primarily in S-nitrosoalbumin form in plasma; and in nitrosyl-hemoglobin and S-nitrosohemoglobin form in red blood cells (24). In our study, insignificantly high levels of NO were detected in the study group in the reperfusion period. We looked directly for NO, not its derivatives. This could explain our finding.

There is no a complete consensus in studies searching the effects of free radical scavengers on myocardial infarction area. It has been shown that NAC given in reperfusion period could not limit the infarction area (25). Additional studies also showed that although NAC was effective against FOR and prevented severe apoptosis, this positive effect did not reflect on hemodynamic parameters (2, 8, 15). They explained it as their patients had good preoperative ventricles and concluded that they would had better results in bad ventricles. We performed similar study with NAC but we used clinically relevant doses of NAC, which are much lower doses than those used in the above-mentioned studies. It is thought that the short-term efficacy of NAC may be explained by

its long half-life and it could be used only intraoperatively. For that reason, El Hamamsy et al. (9) used it by oral route beginning from 24 hours preoperatively and continued intra- and postoperatively by intravenous route. In spite of this, they were not able to observe any clinical improvement. They have also studied the blood interleukin-6 levels, yet it has been stated as unchanged.

Study limitations

The major limitation of the study is the low number of patients. Low dose of NAC and its use only as adjunct to cardioplegia are the other limitations of the study.

Conclusion

Myocardial injury associated with CPB cannot be explained only by one reason. Besides oxidative stress, existing inflammatory response syndrome may also cause clinical deterioration and this may be aggravated by surgical stress, ischemia-reperfusion injury and contact between blood and foreign bodies. Therefore, it may not be possible to obtain clinical improvement by decreasing only one risk factor. Although NAC is a good antioxidant, its antiinflammatory effects have not yet been well documented. We can conclude that some clinical improvements can be expected by using a powerful antioxidant - NAC together with some antiinflammatory drugs or some modifications in CPB systems.

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