European Review for Medical and Pharmacological Sciences 2016; 20: 180-187

The effects of N-acetylcysteine on pulmonary functions in patients undergoing on-pump coronary artery surgery: a double blind placebo controlled study

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Abstract. – OBJECTIVE: To investigate the effects of N-acetylcysteine (NAC) on pulmonary function tests and arterial blood gases in patients undergoing on-pump coronary artery surgery.

PATIENTS AND METHODS: The effect of NAC was assessed within the scope of a prospective, single center, double-blind, placebo-controlled, parallel group study. Eighty-two patients undergoing coronary artery bypass grafting were randomized into two groups to receive either placebo (group 1, n = 40) or NAC (group 2, n=42). Both the NAC group and the placebo-receiving control group also included a COPD subgroup consisting of patients with an FEV_1/FVC ratio of < 0.7 and an FEV_1 value of 50-80%. Pulmonary function tests were performed preoperatively and on postoperative day 60.

RESULTS: Both groups were similar with respect to age, gender, preoperative risk factors, ejection fraction (EF), mean cross-clamp time, ventilation time, intensive care unit (ICU) stay, atrial fibrillation (AF) and hospital stay ($p > 0.05$). Postoperative FVC and FEV_1 values in group 1 and the postoperative FEV_1, FEV_1/FVC and FEF 25-75 values in group 2 were lower in comparison to their preoperative values. However, in both group 1 and 2, the decreases observed in these parameters were not statistically significant ($p > 0.05$). In the COPD subgroup of group 1, a postoperative decrease was observed in the FEV_1 and FEF25-75 values, with the FEV_1 decreasing by 4.55%, and the FEF25-75 decreasing by 4.2% ($p < 0.05$). In the COPD subgroup of group 2, no significant decrease was observed in the pulmonary function test values ($p > 0.05$).

CONCLUSIONS: This study demonstrated that NAC administration in COPD patients undergoing on-pump coronary artery surgery resulted in the preservation of pulmonary functions.

Key Words:
N-Acetylcysteine, Pulmonary function tests, Bypass surgery, Coronary artery.

Introduction

Pulmonary dysfunction is one of the most common and serious complications of cardiac surgeries performed with cardiopulmonary bypass (CPB)[1,2]. The etiology of pulmonary dysfunction is multifactorial: the condition can result from a combination of the effects of general anesthesia, surgical injury, median sternotomy and CPB. CPB is often associated with systemic inflammation, which generally develops as a result of a CPB-induced postpump syndrome or systemic inflammatory response. Systemic inflammatory response syndrome (SIRS) during cardiac surgery can result in four types of injury: contact of the blood components with the artificial surface of the bypass circuit, ischemia-reperfusion injury, endotoxemia and operative trauma[3].

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SIRS can lead to post-cardiac surgery complications such as myocardial injury, renal dysfunction, atrial fibrillation (AF) and pulmonary injury[4-8]. Pulmonary injury observed during cardiac surgery is characterized by increased pulmonary vascular resistance (PVR), impaired gas exchange, and decreased pulmonary mechanics[9,10]. It is believed that the administration of antioxidant and anti-inflammatory agents might potentially alleviate SIRS in patients undergoing on-pump coronary artery surgery.

NAC is a free radical scavenger that exhibits beneficial antiinflammatory and antioxidant effects. NAC inhibits inducible nitric oxide synthase, suppresses cytokine expression/release, and inhibits the expression of adhesion molecules and of nuclear factor kappa B[5,11-13].

The main purpose of our study was to investigate the effect of NAC administration on the postoperative pulmonary function tests and arterial blood gases of patients undergoing on-pump coronary artery surgery.

Patients and Methods

The study protocol was approved by the Ethics Committee of Inonu University Medical Faculty (number 2007/160). Written informed consent was obtained from all patients prior to the surgery. The effect of NAC was assessed within the scope of a prospective, single center, double-blind, placebo-controlled, parallel group study. The study was conducted prospectively with 82 patients who underwent coronary bypass surgery at our clinic between November 2007 and December 2008. The exclusion criteria of the study were emergency operations, significantly impaired ventricular function (ejection fraction < 40%), severely restricted or obstructed pulmonary functions and hemodynamic instability following revascularization. The patients were divided into two groups, which were the placebo-receiving control group (group 1, n=40) and the NAC group (group 2, n=42). In group 2, NAC was administered preoperatively for 3 days at dose of 600 mg/day P.O., and 300 mg of NAC was added in the prime solution. Both the NAC group and the placebo-receiving control group also included a COPD subgroup consisting of COPD patients. Patients were considered as having COPD in case their FEV_1/FVC ratio was < 0.7, and their FEV_1 value was between 50-80%.

Operative Procedure

Anesthesia

All patients were monitorized following their transfer to the operation room. A pulse oximetry probe was attached to each patient in order to monitor peripheral arterial oxygen saturation. A 20 G branule was placed on the right radial artery to monitor systemic arterial pressure and arterial blood gas. Anesthesia was induced with a mixture consisting of 2% lidocaine (1 mg/kg), midazolam (0.2-0.3 mg/kg), fentanyl (5 μg/kg) and vecuronium (0.1 mg/kg). All patients were manually respirated, intubated after complete muscle relaxation, and connected to a mechanical ventilator. Anesthesia was maintained through the administration of a fentanyl (10-30 μg/kg) and midazolam (0.1-0.3 mg/kg/hour) mixture. For antibiotic prophylaxis, 1 g of cefazolin sodium was administered intravenously prior to the surgical procedures.

Surgical Technique

For both groups, coronary bypass grafting was performed with median sternotomy by using standard CPB procedure with single venous two-step right atrial and ascending aortic cannulation. Mild systemic hypothermia (32°C) was induced and CPB was carried out using a disposable membrane oxygenator (Dideco Sorin Group, Mirandola, Italy) and a roller pump (Cobe Cardiovascular Inc., Avrada, CO, USA). Myocardial preservation was achieved with antegrade and retrograde infusion of cold blood cardioplegia, which was repeated every 20 minutes. Throughout the CPB procedure, the hematocrit level was maintained between 22-25%, and the mean arterial pressure was maintained between 50-70 mmHg. Heparin was provided for anticoagulation in order to ensure an active coagulation time > 480s immediately before the CPB procedure. Warm blood cardioplegia was given before removing the aortic cross-clamp. Internal mammary artery (IMA) was preferred for Left Anterior Descending (LAD) artery anastomosis in all patients. However, saphenous venous grafts were used in cases where IMA grafts were not suitable. In suitable cases with multiple coronary artery disease, radial artery and/or saphenous venous grafts were attached in addition to the IMA graft. Distal anastomoses were performed under cross-clamp with 7-8/0 prolene sutures, while proximal anastomoses were performed under

cross-clamp with 6/0 prolene sutures. Epicardial temporary pacing wires were routinely inserted. The left pleura were opened routinely, and one of the drains was inserted in the left thorax while the other was inserted in the subxiphoid region. At the end of the CPB procedure, protamine was administered to reverse the anticoagulative effect of heparin.

Pulmonary Function Tests and Blood Gas Analysis

Pulmonary function tests, which included assessments of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and forced midexpiratory volume (FEF25-75), were performed preoperatively and at postoperative day 60 by using a spirometer (Vmax 22 Sensor Medics, Yorba Linda, CA, USA).

Arterial blood gases were analyzed (Rapidlab Bayer Health Care, Germany) preoperatively and at postoperative days 2, 7 and 60 by radial puncture. Blood gas analysis included the assessment of partial arterial oxygen pressure (PaO_2), partial arterial carbon dioxide pressure ($PaCO_2$) and arterial pH levels.

Statistical Analysis

Statistical analyses were performed using the SPSS 16.0 package program (SPSS Inc. Chicago, IL, USA). Measurable data were provided as mean ± standard deviation (SD), while qualitative data were provided as percentages. The Pearson chi-square and Fisher's exact chi-square tests were used for comparing qualitative data. Measurable data were tested with the Shapiro-Wilk normality test, which indicated that the countable data displayed normal distribution ($p > 0.05$). For this reason; two group mean comparisons were performed using the unpaired *t* test, while changes between the preoperative and postoperative period in the parameters used for evaluating pulmonary functions were evaluated using the paired *t* test. In both groups, the changes in blood gas levels were

Table I. Demographic and clinical characteristics of patients.

	Group 1 (control) (n = 40)	Group 2 (NAC) (n = 42)	*p* value
Age (years)	58.8 ± 9.9	58.6 ± 10.1	0.927
Sex (female %)	6 (15%)	7 (16.7%)	0.836
Preoperative myocardial infarction	29 (74.4%)	30 (71.4%)	0.767
Vessel disease count			
One vessel disease	2 (5%)	–	0.235
Two vessel disease	25 (62.5%)	15 (35.7%)	0.015
Triple vessel disease	13 (32.5%)	27 (64.3%)	0.004
Left main disease	–	–	–
Diabetes mellitus	8 (20,5%)	9 (22%)	0.875
Hypertension	15 (38.5%)	11 (26.8%)	0.267
Preoperative cerebrovascular disease	1 (2.5%)	2 (4.8%)	1.000
Current smoker	25 (64.1%)	26 (63.4%)	0.949
Family history	15 (38.5%)	13 (31.7%)	0.527
COPD (FEV_1/FVC < 0.7)	3 (7.7%)	4 (9.8%)	0.744
Hypercholesterolemia	11 (27.5%)	15 (35.7%)	0.424
Peripheral vascular disease	–	–	–
Carotid artery disease ≥ 20%	3 (7.5%)	3 (7.1%)	0.951
Preoperative PCI	4 (10%)	3 (7.1%)	0.643
Low left ventricular ejection fraction	4 (10%)	7 (16.7%)	0.376
EDP	9.4 ± 2.6	8.9 ± 3.1	0.476
Unstable angina	2 (5%)	3 (7.1%)	0.685
Obesity	5 (12.5%)	9 (21.4%)	0.283
Metabolic syndrome	14 (35%)	16 (38.1%)	0.771
Euroscore	3.4 ± 2.1	3.1 ± 2.2	0.585
BSA	1.8 ± 0.15	1.8 ± 0.16	0.954
BMI	26.3 ± 3,7	26.4 ± 3.9	0.831
Preoperative ejection fraction	48.5 ± 8.2	49.5 ± 7.9	0.609

COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; EDP: end diastolic pressure; BSA: body surface area; BMI: body mass index.

tested using the repeated measures one-way analysis of variance. A p value < 0.05 was considered as being statistically significant.

Results

Eighty two patients were randomized to two groups. The demographic and clinical characteristics of the patients are shown in Table I. There were no significant differences between the two groups with respect to age, gender, preoperative risk factors and ejection fraction (EF).

The preoperative and postoperative variables are shown in Table II. There were no significant differences between the two groups with respect to mean cross-clamp time, ventilation time, ICU stay, AF and hospital stay ($p > 0.05$).

The preoperative pulmonary function test and blood gas analysis variables did not differ significantly between the two groups ($p > 0.05$). The pulmonary function test results are shown in Table III. The pulmonary function test results for the COPD subgroups are shown in Table IV, while the blood gas analysis results are shown in Table V.

Postoperative FVC and FEV_1 values in group 1 and the postoperative FEV_1, FEV_1/FVC and FEF 25-75 values in group 2 were lower in comparison to their preoperative values. However, in both group 1 and 2, the decreases observed in these parameters were not statistically significant ($p > 0.05$).

In the COPD subgroup of group 1, a postoperative decrease was observed in the FEV_1 and FEF25-75 values, with the FEV_1 decreasing by 4.55%, and the FEF25-75 decreasing by 4.2% ($p < 0.05$). In the COPD subgroup of group 2, no significant decrease was observed in the pulmonary function test values ($p > 0.05$).

During blood gas analysis, it was determined that the pO_2 values on postoperative day 2 were lower than the values observed preoperatively and on postoperative day 7 and 60 in both groups. The difference between these values was statically significant ($p < 0.05$).

Discussion

Cardiopulmonary bypass (CPB) is often associated with systemic inflammation, which generally develops as a result of a CPB-induced post-pump syndrome or systemic inflammatory response. SIRS can lead to the development of

Table II. Preoperative and postoperative data.

	Group 1 (control) (n = 40)	Group 2 (NAC) (n = 42)	p value
LIMA used for CABG	39 (97.5%)	41 (97.6%)	0.972
Radial artery used for CABG	5 (12.5%)	6 (14.3%)	0.813
Number of grafts	2.62 ± 0.59	2.86 ± 0.78	0.134
Aortic cross-clamp time (min)	65.9 ± 15.7	74.5 ± 18.5	0.031
Perfusion time (min)	76.6 ± 16.9	84.4 ± 20.3	0,070
Inotropic support	2 (5%)	1 (2.4%)	0.611
IABP	–	–	–
Ventilation time (h)	6.4 ± 2.3	6.5 ± 2.7	0.870
ICU stay (day)	2.5 ± 0.9	2.5 ± 0.6	0.952
Re-exploration for bleeding	–	–	–
Atrial fibrillation	2 (5%)	7 (16.7%)	0.091
Hospital stay (day)	6.8 ± 1.3	6.5 ± 0.8	0.254
Postoperative cerebrovascular disease	1 (2.5%)	–	0.488
Renal dysfunction	–	–	–
GIS complications	–	–	–
Total arterial revascularization	3 (7.5%)	4 (9.5%)	0.743
Defibrillation after cross-clamp	6 (15%)	8 (19%)	0.663
Superficial wound infection	–	2 (4.8%)	0.494
Deep wound infection	–	–	–
Pleural effusion	3 (7.5%)	2 (4.8%)	0.604
Persistent air leak	–	1 (2.4%)	1.000
Subcutaneous emphysema	–	–	–
Pneumonia	–	–	–
Re-hospitalization	4 (10%)	2 (4.8%)	0.363

LIMA: Left Internal Mammary Artery; ICU: Intensive Care Unit; GIS: Gastrointestinal System.

Table III. Data on preoperative and postoperative pulmonary functions.

	Group 1 (control, n = 40)			Group 2 (NAC, n = 42)		
	Preoperative	Postoperative	*p* value	Preoperative	Postoperative	*p* value
FVC (liters)	3.58 ± 0.85 (100.04 ± 19.13%)	3.34 ± 0.83 (93.7 ± 20.25%)	0.010*	3.74 ± 1.06 (100.05 ± 20.40%)	3.61 ± 0.97 (100.01 ± 19.91%)	0.090
FEV_1 (liters)	2.64 ± 0.65 (94.75 ± 20.22%)	2.43 ± 0.61 (85.3 ± 20.64%)	0.004*	2.86 ± 0.77 (100 ± 18.47%)	2.68 ± 0.71 (94.96 ± 18.21%)	0.001*
FEV_1/FVC (%)	74.52 ± 11.04	73.5 ± 11.32	0.220	77.24 ± 7.69	74.88 ± 7.23	0.021*
FEF25-75 (liters/sec)	2.17 ± 1.13 (68.7 ± 36.5%)	1.99 ± 1.17 (59.9 ± 33.4%)	0.157	2.59 ± 1.09 (77.3 ± 29.9%)	2.24 ± 1 (66.9 ± 27.1%)	0.002*

FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 Second; FEF25-75: Forced Mid Expiratory Flow; *$p < 0.05$ compared with control group.

Table IV. Data on pulmonary functions in the COPD subgroup

	Group 1 (control, n = 20)			Group 2 (NAC, n = 10)		
	Preoperative	Postoperative	*p* value	Preoperative	Postoperative	*p* value
FVC (liters)	3.68 ± 0.61 (102.2 ± 47.2%)	3.56 ± 0.72 (97.65 ± 16.8%5)	0.149	4.03 ± 0.96 (112.22 ± 22.92%)	3.95 ± 0.83 (111.67 ± 26.42%)	0.503
FEV^1 (liters)	2.46 ± 0.48 (72.5 ± 7.72%)	2.34 ± 0.58 (67.95 ± 8.22%)	0.019*	2.76 ± 0.63 (74.22 ± 10.83%)	2.76 ± 0.52 (75.67 ± 14.9%)	0.325
FEV^1/FVC (%)	65.1 ± 6.92	64.25 ± 7.38	0.378	66 ± 1.76	67.30 ± 5.66	0.517
FEF25-75 (liters/sec)	1.51 ± 0.53 (44.6 ± 13.06%)	1.36 ± 0.54 (40.4 ± 13.71%)	0.036*	1.73 ± 0.35 (53.44 ± 12.82%)	1.69 ± 0.29 (52.67 ± 10.64%)	0.450

FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 Second; FEF25-75: Forced Mid Expiratory Flow; *$p < 0.05$ compared with control group.

Table V. Arterial Blood gas analysis results.

	Group 1 (control, n = 40)				Group 2 (acetylcysteine, n = 42)			
	Preop.	Postop. Day 2	Postop Day 7	Postop. Day 60	Preop.	Postop. Day 2	Postop. Day 7	Postop. Day 60
pH	7.44 ± 0.34	7.46 ± 0.05	7.47 ± 0.05*	7.43 ± 0.04£	7.44 ± 0.05	7.46 ± 0.03*	7.48 ± 0.05*	7.44 ± 0.03¥
pCO_2 (mmHg)	35.15 ± 5.12	35.15 ± 5.12	33.85 ± 4.67£	34.58 ± 3.97	35.74 ± 4.09	36.62 ± 4.29	33.52 ± 4.66£	34.14 ± 3.17£
pO^2 (mmHg)	77.46 ± 14.56	57.24 ± 8.54*	70.36 ± 12.24£	71.13 ± 12.73£	77.75 ± 9.58	58.62 ± 8.46*	69.25 ± 7.67*,£	72.86 ± 7.17*,£,¥

*Compared with Preoperative values $p < 0.05$. £Compared with Postoperative Day 2 values $p < 0.05$. ¥Compared with Postoperative Day 7 values $p < 0.05$.

post-cardiac surgery complications such as myocardial injury, renal dysfunction, AF and lung injury[4-8]. Experimental and clinical studies[14-17] that attempt to reduce the appearance of SIRS focus on blocking the activation of white blood cells, since many inflammatory mediators are believed to exert their damaging effects through these cells[3,14]. Methods and approaches used in these studies to reduce SIRS occurrence include off-pump coronary surgery, changes in perfusion temperature, use of heparin bound surfaces, ultrafiltration, leukocyte depletion, and the administration of complement inhibitors, glucocorticoids, aprotinin or NAC.

NAC is an effective antioxidant. NAC is a glutathione precursor that increases the levels of intracellular sulfhydryl[18]. Glutathione plays a central role in cellular defense against specific reactive oxygen species (ROS), and also acts at an extracellular level – either directly or via the glutathione peroxidase catalysis – to scavenge the generated ROS. NAC administration has the effect of increasing glutathione levels and reducing oxidoinflammatory damage. These characteristics make NAC a potentially useful therapeutic option for preventing commonly encountered complications related to oxidoinflammatory damage.

Pulmonary injury associated with CPB is generally characterized by increased PVR, impaired gas exchange and decreased pulmonary mechanics[9,10]. These effects are also observed during ischemia-reperfusion injury. Angdin et al[19] demonstrated that, following the occurrence of CPB, patients treated with antioxidant agents such as vitamins C and E, allopurinol and NAC had better preservation of endothelial function than patients treated with placebo. In addition, Karabay et al[20] reported that NAC contributed to the preservation of pulmonary functions, and also allowed reduced pulmonary functions to recover more rapidly.

Eren et al[21] previously evaluated the effects of NAC on the pulmonary functions of patients undergoing coronary artery bypass surgery with cardiopulmonary bypass. They reported in their study a significantly lower increase in postoperative A-a oxygen gradient and lower malondialdehyde increase in NAC-administered group. In our study, we compared the pulmonary functions of patients in the NAC and control groups. The pulmonary functions of the patients were evaluated using pulmonary function tests and arterial blood gas analysis. No significant dif-

ferences were observed between the NAC and control groups with respect to their pulmonary function tests and arterial blood gas analysis results. However, we observed the preservation of pulmonary functions in the COPD subgroup of the NAC-administrated group (a 4.55% decrease in FEV_1, and a 4.2% decrease in FEF 25-75 in the control group).

The milder side effects of NAC include clammy skin, fever, increased lung mucous, and irritation/soreness in the mouth, throat, or lungs. Uncommon side effects of NAC, which may require immediate medical attention, include wheezing, tightness in the chest, difficulty breathing (especially among asthmatics), and skin rash or irritation. These rare side effects were not observed in any of our patients during the study.

The number of the patients in the COPD subgroup was relatively small in this study; therefore, to be able to validate the beneficial effects of NAC administration in the COPD subgroup, it is necessary to conduct studies with larger populations.

Conclusions

This prospective, single center, double-blind, placebo-controlled, parallel group study demonstrated that the administration of NAC to COPD patients undergoing on-pump coronary artery surgery resulted in the preservation of pulmonary functions. However, it was also observed that NAC administration had no effect on other pulmonary parameters, on the duration of ventilatory support, and on the length of stay in the ICU.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Canet J, Gallart L, Gomar C, Paluzie G, Valles J, Castillo J, Sabate S, Mazo V, Briones Z, Sanchis J: Ariscat Group. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology 2010; 113: 1338-1350.
2) Apostolakis EE, Koletsis EN, Baikoussis NG, Siminelakis SN, Papadopoulos GS. Strategies to prevent intraoperative lung injury during cardiopulmonary bypass. J Cardiothorac Surg 2010; 5: 1.
3) Asimakopoulos G, Smith PLC, Ratnatunga CP, Taylor KM. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. Ann Thorac Surg 1999; 68: 107-115.
4) Groeneveld AB, Jansen EK, Verheij J. Mechanisms of pulmonary dysfunction after on-pump and off-pumpcardiac surgery: a prospective cohort study. J Cardiothorac Surg 2007; 2: 11.
5) Kurian GA, Padikkala J. N-acetylcysteine and magnesium improve biochemical abnormalities associated with myocardial ischaemic reperfusion in South Indian patients undergoing coronary artery bypass grafting: a comparative analysis. Singapore Med J 2010; 51: 381-388.
6) Baliga R, Ueda N, Walker PD, Shah SV. Oxidant mechanisms in toxic acute renal failure. Am J Kidney Dis 1997; 29: 465-477.
7) Neuman RB, Bloom HL, Shukrullah I, Darrow La, Kleinbaum D, Jones DP, Dudley SC. Oxidative stress markers are associated with persistent atrial fibrillation. Clin Chem 2007; 53: 1652-1657.
8) Ramlawi B, Otu H, Mieno S, Boodhwani M, Sodha NR, Clements RT, Bianchi C, Sellke FW. Oxidative stress and atrial fibrillation after cardiac surgery: a case-control study. Ann Thorac Surg 2007; 84: 1166-1173.
9) Snapper JR, Lu W, Lefferts PL, Thabes JS. Cylooxygenase products contribute to endothelin-induced pulmonary hypertension and altered lung mechanics in sheep. Pulm Pharmacol Ther 1997; 10: 111-118.
10) Pearl JM, Nelson DP, Wellmann SA, Raake JL, Wagner CJ, McNamara JL, Duffy JY. Acute hypoxia and reoxygenation impairs exhaled nitric oxide release and pulmonary mechanics. J Thorac Cardiovasc Surg 2000; 119: 931-938.
11) Arfsten D, Johnson E, Thitoff A, Jung A, Wilfong E, Lohrke S, Bausman T, Eggers J, Bobb A. Impact of 30-day oral dosing with N-acetyl-L-cysteine on Sprague-Dawley rat physiology. Int J Toxicol 2004; 23: 239-247.
12) Caglikulekci M, Dirlik M, Pata C, Plasse M, Tamer L, Ogetman Z, Ercan B. Effect of N-acetylcysteine on blood and tissue lipid peroxidation in lipopolysaccharide-induced obstructive jaundice. J Invest Surg 2006; 19: 175-184.
13) Dinicola S, De Grazia S, Carlomagno G, Pintucci P. N-acetylcysteine as powerful molecule to destroy bacterial biofilms. A systematic review. Eur Rev Med Pharmacol Sci 2014; 18: 2942-2948.
14) Johnson D, Thomson D, Hurst T, Prasad K, Wilson T, Murphy F, Saxena A, Mayers I. Neutrophil mediated acute lung injury after extracorporeal perfusion. J Thorac Cardiovasc Surg 1994; 107: 1193-1202.
15) Bando K, Pillar R, Cameron DE, Brawn JD, Winkelstein JA, Hutchins GM, Reits BA, Baumgartner WA. Leukocyte depletion ameliorates free radical-mediated lung injury after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1990; 99: 873-877.

16) Mihaljevic T, Tonz M, Von Segesser Lk, Pasic M, Grob P, Fehr J. The influence of leukocyte filtration during cardiopulmonary bypass on postoperative lung function. J Thorac Cardiovasc Surg 1995; 109: 1138-1145.

17) Morioka K, Muraoka R, Chiba Y, Ihaya A, Kimura T, Noguti H, Uesaka T. Leukocyte and platelet depletion with a blood cell seperator: eefects on lung injury after cardiac surgery with cardiopulmonary bypass. J Thorac Cardiovasc Surg 1996; 111: 45-54.

18) Weinbroum AA, Kluger Y, Ben Abraham R, Shapira I, Karchevski E, Rudick V. Lung preconditioning with n-acetyl-L-cysteine prevents reperfusion injury after liver no-flow-reflow: a dose-response study. Transplantation 2001; 71: 300-306.

19) Angdin M, Settergren G, Starkopf J, Zilmer M, Zilmer K, Vaage J. Protective effect of antioxidants on pulmonary endothelial function after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2003; 17: 314-320.

20) Karabay BC, Ucar Hi, Oc M, Tok M, Oc B, Farsak B, Yilmaz M, Guvener M, Yorgancioglu C, Dogan R, Demircin M, Pasaoglu I, Ersoy U. Koroner arter bypass cerrahisinde N-asetilsisteinin solunum fonksiyonları üzerine etkisi. Turk J Inv Car 2007; 11: 12-16.

21) Eren N, Cakir O, Oruc A, Kaya Z, Erdinc L. Effects of N-acetylcysteine on pulmonary function in patients undergoing coronary artery bypass surgery with cardiopulmonary bypass. Perfusion 2003; 18: 345-350.