

Effect of Different Anesthetic Techniques on Mental Outcome in Elderly Patients Undergoing Off-Pump Coronary Artery Bypass Graft Surgery

Atan Kalpte Koroner Arter Baypas Greft Cerrahisi Yapılan Yaşlılarda Farklı Anestezi Tekniklerinin Zihin Üzerindeki Sonuçları

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ABSTRACT Objective: In this article, we aimed to test the hypothesis that maintenance of hemodynamic stability with anesthesia and no-touch aortic technique in off-pump coronary artery bypass graft surgery (CABG) may diminish postoperative mental complications in elderly patients. **Material and Methods:** Between June 2009 and December 2009, 88 elderly patients (53 males, 35 females; mean age 71±7 years; range 64 to 78 years) with a physical status of ASA II-III who underwent elective off-pump CABG surgery in our hospital's operating rooms and cardiovascular and thoracic intensive care units were included in this prospective randomized study with signed informed consents. Patients undergoing off-pump CABG surgery performed by a surgeon were randomly assigned into two groups, including total intravenous anesthesia (group TIVA, n=40; mean age 66±4) or inhalational anesthesia (group IA, n=40; mean age 69±3). The effect of off-pump CABG surgery on mental outcome was assessed with S100 protein, a neurochemical marker of brain injury under ischemic conditions. Comparison of mental function before and after off-pump CABG surgery, hemodynamic stability and time to discharge were the main outcomes of the study. **Results:** Hemodynamic values were stable in both groups. None of the patients showed marked increase in serum concentrations of S100 postoperatively (p<0.001). The mean total off-pump CABG time was 48±15 minutes in both groups. There was no difference between the groups in terms of time to discharge. **Conclusion:** We believe that well-performed hemodynamic stability with either intravenous or general anesthesia may offer a well-controlled mental function in elderly patients undergoing off-pump CABG surgery.

Keywords: Coronary artery bypass, off-pump; coronary artery bypass; anesthetics, inhalation; anesthetics, intravenous

ÖZET Amaç: Bu çalışmada, atan kalpteki koroner arter baypas greft (KABG) cerrahisinde hemodinamik stabilitenin anestezi, iyi premedikasyon ve dokunmasız aort tekniğiyle sağlanmasının yaşlılarda ameliyat sonrası zihinsel komplikasyonları azaltabileceği hipotezi test edildi. **Gereç ve Yöntemler:** Haziran-Aralık 2009 tarihleri arasında, hastanemizin ameliyathaneleri ve kardiyovasküler ve torasik yoğun bakım ünitelerinde elektif olarak atan kalpte KABG cerrahisi geçiren ve fiziksel durumu ASA II-III olan 88 yaşlı hasta (53 erkek, 35 kadın; ortalama yaş 71±7 yıl; dağılım aralığı 64 ile 78 yıl) bilgilendirilmiş onam alınarak bu prospektif ve randomize çalışmaya dahil edildi. Tek cerrah tarafından yürütülen atan kalpte KABG cerrahisi geçiren hastalar total intravenöz anestezi (grup TIVA, n=40; ortalama yaş 66±4) veya inhalasyon anestezi (grup IA, n=40; ortalama yaş 69±3) olmak üzere iki gruba ayrıldı. Atan kalpte KABG cerrahisinin beyindeki sonuçları iskemik durumlarda nörokimyasal belirteç olan S100 proteini ile değerlendirildi. Çalışmanın temel sonuçları, atan kalpte KABG cerrahisi öncesi ve sonrasında zihinsel fonksiyonların kıyaslanması, hemodinamik stabilite ve taburculuk süresi ile değerlendirildi. **Bulgular:** Her iki grupta da hemodinamik değerler stabildi. Hastaların hiçbirinde ameliyat sonrası S100 proteininde belirgin artış gözlenmedi (p<0.001). Toplam atan kalpte KABG cerrahisi zamanı her iki grupta da ortalama 48±15 dakika idi. Taburculuk süresinde her iki grup arasında farklılık saptanmadı. **Sonuç:** Atan kalpte koroner arter cerrahisi geçiren yaşlı hastalarda intravenöz veya genel anestezide stabil hemodinami sağlanmasının zihinsel fonksiyonları olumlu etkilediği kanaatindeyiz.

Anahtar Kelimeler: Koroner arter baypas, pompasız; koroner arter baypas; anesteziikleri, inhalasyon; anesteziıklar, intravenöz

Cardiopulmonary bypass (CPB) has several associated deleterious effects that include a systemic inflammatory response, coagulopathy, central nervous system complications, and a variable degree of end-organ damage. The recent upsurge in interest in off-pump coronary artery bypass (OPCAB) surgery attempts to avoid these destructive effects. With rapid improvement in surgical techniques, the use of an intracoronary shunt that maintains coronary perfusion while avoiding aortic cross-clamping appears to produce good results in elderly patients with multivessel disease and a variety of comorbid conditions.

During OPCAB surgery, anesthetists face two problems: maintaining hemodynamic stability during heart enucleation, which is necessary for accessing each coronary artery and managing intraoperative myocardial and mental ischemia when coronary and mental flow is interrupted.

Coronary artery bypass graft surgery is becoming more common in the elderly.^{1,2} However, they can develop delirium, confusion, and agitation in the postoperative period. This is possibly caused by reduced blood distribution during the ischemic period of OPCAB surgery and impaired drug distribution. A poor mental outcome after surgery reduces the ability of patients to communicate their needs, cooperate with medical staff, and may also interfere with recovery.

The aim of our study was to test the hypothesis that maintaining hemodynamic stability with anesthesia, good premedication, and the no-touch aortic technique in OPCAB surgery may diminish postoperative mental complications in elderly patients.

MATERIAL AND METHODS

PATIENTS AND STUDY GROUPS

After institutional ethics committee approval, 88 elderly patients (53 males, 35 females; mean age 71 ± 7 years; range 64 to 78 years) who had undergone elective OPCAB surgery gave their signed consent for participation in the study. Data analysis was conducted between June 2009 and Decem-

ber 2009 in our hospital. Exclusion criteria included the following: more than 50% carotid artery stenosis, severe chronic obstructive pulmonary disease (COPD) requiring daily therapy with steroids or bronchodilators, renal insufficiency (creatinine concentration >150 mmol liter⁻¹), severe liver disease (alanine aminotransferase or aspartate aminotransferase >75 IU liter⁻¹), a history of allergy to propofol or its constituents, and a history of seizure or stroke. The Mini-Mental State Examination Test (MMSE) was used to screen the patients for dementia. Patients who obtained a preoperative score of 23 (highest score=30) points were included in the study.

The patients were randomized before surgery into either the total intravenous (i.v.) anesthesia (TIVA; propofol-remifentanyl infusion) group and the inhalational anesthesia (IA; isoflurane 0.5-2% concentration) group using a computer-generated randomization code. The medical and physical details were recorded.

ANESTHESIA

Intravenous access and direct blood pressure monitoring by catheterization of the radial artery was established, regardless of the anesthetic technique used, either upon arrival or in the operating room.

Monitoring also included arterial and central venous blood pressure measurements, electrocardiography (ECG) (leads II, aVF, and V5), pulse oxymetry, and end-tidal carbon dioxide (CO₂). Pace paddles were prophylactically placed on the patient's body to overcome cardiac rhythm disturbances, and a urinary catheter was also inserted to monitor urine output.

TOTAL INTRAVENOUS ANESTHESIA GROUP

Preoperative sedation consisted of midazolam 0.03 mg kg⁻¹ i.v. five minutes before surgery. Anesthesia was induced with 15-25 µg kg⁻¹ fentanyl with etomidate 0.3 mg kg⁻¹ i.v. Tracheal intubation was facilitated by vecuronium bromide 0.1 mg kg⁻¹, and anesthesia was maintained with continuous propofol infusion at 2-6 mg kg⁻¹min⁻¹ and remifentanyl infusion 0.1-0.3 µg kg⁻¹ min⁻¹. Positive pressure ventilation with 50% oxygen in the

air was used. The tidal volume (8-10 mL.kg⁻¹) and respiratory rate (10-12 min⁻¹) were adjusted according to the end-tidal pressure of CO₂ to achieve normal ventilation (end-tidal pressure of CO₂ 35-40 mmHg). The propofol infusion rate was adjusted according to hemodynamic changes.

INHALATIONAL ANESTHESIA GROUP

Preoperative sedation consisted of midazolam 0.03 mg kg⁻¹ i.v. five minutes before surgery, and anesthesia was induced with 10-15 µg kg⁻¹ fentanyl with i.v. etomidate 0.3 mg kg⁻¹. Tracheal intubation was facilitated by vecuronium bromide 0.1 mg kg⁻¹, and anesthesia was maintained before and during OPCAB with 0.5-2% isoflurane and oxygen.

Persistent hypertension (systolic blood pressure >130 mmHg) in both anesthesia groups was treated with nitroglycerine, either with or without nitroprusside infusion, to achieve a systolic arterial blood pressure of 90-120 mmHg (targeted mean arterial blood pressure 60-70 mmHg during OPCAB). Metoprolol 2-5 mg i.v. was used to achieve a heart rate of 50-60 min⁻¹ during OPCAB. Hypotension was treated with 500 mL of a colloid solution, either with or without dopamine infusion, at the end of OPCAB. Body temperature was maintained in all patients with a warming blanket and continuously monitored with a nasopharyngeal temperature probe.

After induction of anesthesia in both groups, a central venous line was inserted. Additional monitoring consisted of a transoesophageal echocardiography (TEE) probe which was inserted to aid in the early detection of aortic atherosclerosis, myocardial wall motion abnormalities, or myocardial ischemia.

SURGICAL TECHNIQUE

The chest was opened by a complete median sternotomy for double or triple CABG surgery. The left or right internal mammary arteries and peripheral vessels were harvested. Intravenous heparin was administered in a dose of 150 U/kg after thoracic artery dissection. An activated clotting time around 250 seconds during the operation was attained. After creating a pericardial cradle, the surgeon ex-

posed the target vessels and used multiple or single traction sutures to restrict the local motion of the heart. Proximal anastomoses was achieved by branching bypass grafts on peripheral arteries emerging from the aortic arch, so manipulation of the ascending aorta was avoided. A 75% reversal of heparin was performed with i.v. protamine at thorax closure. The activated coagulation time was measured to ensure the appropriate heparin effect and reversal.

S100 PROTEIN ANALYSIS

Serum venous blood samples were collected preoperatively (T0), in the intensive care unit (ICU) (T1), and 24 hours (T24) after extubation. The blood was allowed to clot, and after centrifugation (10000 rpm, 10 minutes), the serum was stored at -20 °C for later analysis. Serum S100 protein levels were analyzed with the use of electrochemiluminescence immunoassay (ECLIA) using the Cobas e411 hormone analyzer (Roche Diagnostics Co., Mannheim, Germany), and a sample for quality control was included in each assay. The inter-assay and intra-assay coefficients of variations were 2.1% (0.08 µg/L) and 1.0% (0.09 µg/L) for the lowest mean value and 2.0% (2.13 µg/L) and 0.7% (2.25 µg/L) for the highest mean value. The median expected value was 0.046 µg/L in apparently healthy adults (206 samples). The negative and positive predictive values of the test were 99.7% and 11%, respectively. The sensitivity was reported to be 98.8%, and the reference range of serum concentrations of healthy subjects was <0.005 µg/L.

FOLSTEIN MINI-MENTAL SCALE EXAMINATION

This tests orientation, attention, calculation, instantaneous recall, short-term memory, language, and visuomotor ability, and it screens for cognitive impairment with an emphasis on orientation. The highest possible score is 30. This test was chosen considering the time available and the physical limitations of the elderly patients after cardiac surgery.

STATICAL ANALYSIS

The results were expressed as mean (SD) or median (range) as appropriate. Between-group analysis was

done with an unpaired t-test. Serial comparisons were calculated using either one-way analysis of variance (ANOVA) or a two-way, between-group ANOVA with repeated measurements over time. Non-parametric data was analyzed with the Mann-Whitney U-test. Differences were considered significant if $p < 0.05$. Statistical analysis was performed with the Statistical Package for the Social Sciences for Windows (SPSS, Inc., Chicago, Illinois, USA) version 10.0 software program.

RESULTS

There were no significant differences in preoperative clinical characteristics with regard to gender, left ventricular ejection fraction, or cardiovascular risk factors between the two groups (Table 1). Eighty (n=40 for each group) of 88 patients who enrolled in the study completed it. Six patients were excluded because their bypass time was greater than 80 minutes, and two patients were converted to CPB because of sustained atrial fibrillation.

The hemodynamic values were stable throughout the study and were similar in the two groups. We observed no significant bradycardia, hypotension, or atrial fibrillation in either group. There was no significant difference between the groups in the intraoperative use of nitroglycerine (TIVA group, n=22; IA group, n=20) or subsequent use of beta (β) blockers (TIVA group, n=18; IA group, n=19). The serum S100 protein levels were within normal

TABLE 1: Preoperative clinical data.

	Group TIVA (n=40)	Group IA (n=40)
Age (year)	66±4*	69±3*
Gender		
Male	23	22
Female	17	18
Weight (kg)	78.3 (9)	77.6 (8)
Left ventricular ejection fraction		
Good (>50%)	8	10
Fair (30-50%)	23	17
Poor (<30)	9	13
Three vessel disease	40	40

*SD; Standard deviation (mean± SD); Values are expressed as the number of patients.

TABLE 2: Serum levels ($\mu\text{g/L}$) of S100 protein before surgery (T0), in the ICU (T1), and 24 hours (T24) after extubation in both groups.

	T0	T1	T24
Group TIVA (n=40)			
S100	0.047±0.013	0.046±0.012	0.043±0.010
Group IA (n=40)			
S100	0.056± 0.015	0.061±0.019	0.054±0.013

SD; Standard deviation (mean± SD); $p > 0.05$.

TABLE 3: Mental function test results.

	Group TIVA (n=40)		Group IA (n=40)	
	Baseline	24h after extubation	Baseline	24h after extubation
MMST	28.8±1.3	27.6±2.1	28.7±1.3	26.8±2.8

SD; Standard deviation (mean± SD); $p > 0.05$.

MMST: Mini-mental state examination test

ranges (mean: 0.046 $\mu\text{g/L}$, range 0.03-2.25) at T₀ but were statistically slightly higher in the IA group (0.056±0.015 to 0.061±0.019 $\mu\text{g/L}$) than the TIVA group (0.047±0.013 to 0.046±0.012 $\mu\text{g/L}$; $p < 0.01$) at T₁. However, the S100 levels were within normal ranges at T₂₄ (Table 2). There was no case of myocardial infarction in either group. A significant proportion of the patients had triple vessel (62.9%) CABG surgery, with only 37.1% undergoing double vessel CABG surgery. The actual length of hospital stay did not differ between the groups [TIVA group, 5.0 (range, 4-12); IA group, 5.0 (range, 4-15); values are expressed using the median (range)].

There were no differences in the baseline state-trait anxiety (MMSE) scores between the groups (Table 3). These scores were similar in both groups at T₂₄, and none of the patients suffered a cerebrovascular accident after surgery.

DISCUSSION

The trend towards less invasive approaches and decreased healthcare costs make OPCAB surgery an attractive alternative to conventional cardiopulmonary bypass. The course of patients in the early postoperative period is usually improved with

OPCAB surgery, and the durations of ventilatory support, length of ICU stay, and length of hospital stay are significantly diminished.³

The results are not clear-cut concerning the neurological outcome. In contrast to CABG surgery with extracorporeal cardiopulmonary circulation, cross-clamping and cannulation of the ascending aorta as well as the flow jet from the arterial cannula of CPB are eliminated in OPCAB surgery. This should reduce the incidence of embolic events from the atheromatous aorta.⁴⁻⁶

The glial protein S100 has recently been shown to be an early marker of brain injury after cardiac surgery, and the majority of S100 studies have been related to cardiac surgery and CPB.⁷ The authors were also able to demonstrate that elevated S100 levels were of short duration, even in patients with a poor neurological outcome on the third and sixth day after surgery. The protein S100 has also been known to return to normal levels within 18 hours after surgery.⁷ This finding is in accordance with our study in which the statistically slight increase in S100 (0.056 ± 0.015 to 0.061 ± 0.019 µg/L) at T₁ in group IA disappeared at T₂₄.

In one pilot study, the level of S100 at the end of surgery was much higher in the group following conventional CABG than in the off-pump group.⁷ However, in another study, after OPCAB surgery with lower amounts of mental emboli, the increase of S100 was reduced compared with conventional CPB.^{8,9} In the present trial, OPCAB surgery was done with the no-touch aortic technique to prevent embolic events and stroke in elderly patients.

The OPCAB techniques have benefits related to anesthesia, as well. Pharmacological management is far more predictable with OPCAB surgery because there is no pump-related effect on plasma drug concentrations.⁸ There are also fewer serum electrolyte disturbances, especially in the glucose, potassium, and calcium levels. Postoperative fluid management is also simplified because of reduced third space sequestration.⁹

Beating heart surgery requires the anesthetist to pro-actively maintain stable hemodynamics and

rhythm in an environment that changes rapidly because of regional ischemia and cardiac manipulation. Adequate premedication is required, and tachycardia should be avoided to prevent an imbalance between oxygen demand and supply. Monitoring should include ECG, pulse oxymetry, invasive blood pressure, capnography, TEE, temperature measurement, and central venous catheterization, as was done in our study.

Anesthesia and surgery might affect the mental outcome in the elderly, and the risk increases with age. Age-associated vascular changes may also be linked to the rising prevalence of cerebrovascular disease in patients presenting for cardiac surgery. The presence of cerebrovascular disease may predispose affected patients to cerebral O₂ imbalance during surgery.¹⁰ Although there is no approved drug or surgical technique for the prevention of neurological injury, there are some simple techniques that may reduce the potential for mental injuries. There is increasing experimental evidence that some anesthetic agents may be more suitable than others, although the anesthetic technique has not been shown to influence postoperative morbidity in OPCAB surgery patients. Volatile anesthetics, such as isoflurane and sevoflurane, have been shown to induce pharmacological improvement of tolerance to ischemia by brief ischemic bouts followed by reperfusion (known as ischemic preconditioning). This provides protection against ischemia.^{11,12} Although i.v. anesthesia maintains hemodynamic stability in OPCAB surgery, propofol usually requires the readjustment of infusion doses because of its venodilating properties.^{13,14} Nevertheless, as of yet, there are no randomized studies which have been able to accurately define the most appropriate anesthetic protocol for OPCAB surgery. Since hemodynamic stability can be achieved with many different agents, those which mediate pharmacological preconditioning may be favored.^{11,12}

Elderly patients with previous cerebrovascular disease or stroke in their history were excluded from our study. Increases in the S100 levels were not detected at T₂₄. However, the S100 levels slightly increased in almost all patients at T₁, which

could be related to advanced age. The hemodynamic disturbances during heart manipulation and the ischemic events caused by coronary occlusion were mediated by both anesthetic techniques. For this reason, no patient suffered a cerebrovascular accident after OPCAB surgery.

In our study, positive mental outcome could be related to hemodynamic stability with i.v. anesthetics. Furthermore, we believe that it is possible for hemodynamically well-controlled elderly CABG patients having OPCAB surgery to have less or no mental dysfunction immediately after surgery, which would lead to them being discharged early from the hospital. Moreover, well-designed retrospective multicenter studies should be carried out to elucidate definitively whether the anesthetic agents and hemodynamic stability really do affect the mental outcome in high-risk elderly patients who undergo OPCAB surgery.

LIMITATIONS OF STUDY

One limitation of our study was that there was only a single surgeon operating in a single hospital with standard anesthetic and surgical techniques. This could have allowed for the reproducibility of findings. We also did not consider patients who had undergone cardiac surgery with extracorporeal car-

diopulmonary circulation. Postoperative cognitive dysfunction or outcome was not supported with detailed neuropsychometric tests because our institution does not permit such psychological examinations. The analysis of S100 release was also not used to evaluate longer term (e.g., one or two years later) outcomes to allow insight into the underlying pathophysiology of brain dysfunction. Overall, future prospective studies with longer follow-up periods to confirm this hypothesis may contribute to favorable cognitive outcomes after OPCAB surgery in high-risk elderly patients.

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Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Idea/Concept: Esra Özer; **Design:** Esra Özer; **Control/Supervision:** Onur Özlü; **Data Collection and/or Processing:** Rengin Yılmaz; **Analysis and/or Interpretation:** Esra Özer; **Literature Review:** Esra Özer; **Writing the Article:** Esra Özer; **Critical Review:** Esra Özer; **References and Fundings:** Esra Özer; **Materials:** Rengin Yılmaz.

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