Preoperative and Operative Risk Factors Being Effective in Development of Stroke in the Patients who Underwent On-Pump CABG Surgery and Mid-Term Follow-Up

On-Pump Koroner Baypas Cerrahisi Yapılan Hastalarda İnme Gelişmesinde Etkili Olan Preoperatif ve Operatif Risk Faktörleri ve Orta Dönem Takip

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ABSTRACT Objective: Stroke is one of the most devastating complications observed following on-pump coronay artery bypass graft (CABG) surgery. In this study, we evaluated the incidence of pre- and peri-operative risk factors being effective in the development of stroke in the patients who underwent on-pump CABG surgery and factors affecting mortality, survival among patients with postoperative stroke. **Material and Methods**: 1657 patients underwent isolated on-pump CABG surgery in our clinic between January 2002 and December 2009. Mean patient age was 58.90 ± 10.72 years (range, 24 to 85 years). 21.8% of patients were female and 78.2% were male. Predictors of stroke were determined by t-test in noncategorical data and by Chi-Square and Fisher's Exact test analysis in categorical data. Periods of intensive care stay and hospitalization were analysed by Mann-Whitney test. Log-Rank test was used in analysis of risk factors affecting survival. **Results:** Average stroke incidence was 0.9% (16 patients). Stroke predictors were hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, prior stroke or transient ischemic attack, low left ventricular ejection fraction, calcified ascending aorta, preoperative atrial fibrillation, postoperative prolonged intropic support, prolonged ventilator support, cross-clamp period and duration of operation ($p< 0.05$). Durations of stay in intensive care unit and hospital stay were remarkably longer and statistically significant in patients with stroke when compared to that of patients without stroke ($p= 0.000$). **Conclusions:** Stroke is a devastating complication of on-pump CABG. Preoperative risk factors and surgical procedures have important role in development of stroke, mortality and survival. Stroke increases hospitalization period remarkably.

Key Words: Coronary artery bypass; stroke; survival; risk factors

ÖZET Amaç: İnme, on-pump koroner arter baypas greft (KABG) ameliyatından sonra görülen en önemli komplikasyonlardan biridir. Biz bu çalışmada on-pump KABG ameliyatı yapılan hastalarda inme görülmesine etkili olan ameliyat öncesi, ameliyat sırasında ve ameliyat sonrası risk faktörlerinin görülme sıklığını ve postoperatif inme gelişen hastalarda mortalite ve sağ kalımı etkileyen faktörleri ortaya koyduk. **Gereç ve Yöntemler:** Ocak 2002 ve Aralık 2009 tarihleri arasında kliniğimizde 1657 hastada izole on-pump KABG ameliyatı yapıldı. Hastaların ortalama yaşı 58.90±10.72 yıl (24 ile 85 yaş arası) idi. Hastaların %78.2'i erkek, %21.8'i kadın idi. İnme belirleyicileri kategorikal verilerde Ki-kare ve Fisher Exact testi ile saptandı. Yoğun bakım, hastanede yatış ve takip süreleri Mann-Whitney testi ile analiz edildi. Log-Rank testi sağ kalımı etkileyen faktörlerin analizinde kullanıldı. **Bulgular:** Ortalama inme görülme sıklığı %0.9 (16 hasta) idi. İnme belirleyicileri hipertansiyon, hiperlipidemi, diyabet, kronik obstrüktif akciger hastalığı, önceki inme veya geçici iskemik atak, düşük sol ventriküler ejeksiyon fraksiyonu, kalsifiye assendan aort, ameliyat öncesi atrial fibrilasyon, ameliyat sonrası uzamış inotrop desteği, uzamış ventilatör desteği, kros-klemp süresi, ameliyat süresi idi ($p< 0.05$). Yoğun bakım ve hastanede yatış süreleri inme görülen hastalarda inme görülmeyen hastalara göre daha uzun idi ve istatistiksel olarak anlamlıydı ($p= 0.000$). **Sonuç:** İnme on-pump KABG ameliyatının önemli bir komplikasyonudur. Ameliyat öncesi risk faktörleri ve cerrahi prosedürler strok gelişmesi, mortalite ve sürvide önemli bir etkiye sahiptir. İnme, hastanede yatış süresini uzatır.

Anahtar Kelimeler: Koroner arter baypas; inme, felç; hayatta kalma; risk faktörleri

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Despite continuing improvements in surgical techniques, cardiopulmonary bypass and anesthetic methods stroke still has a devastating effect on patients and their families, while also increasing complications, hospitalization period and mortality in patients. Stroke incidence following coronary artery bypass grafting varies from 1 to 4%.[1,2] Risk factors and diseases accompanying coronary artery disease as well as intra-and postoperative factors play an important role in stroke development.[3]

Purpose of this study is to demonstrate preoperative, operative and postoperative factors affecting stroke incidence in patients who underwent on-pump coronary artery bypass graft (CABG) while also to evaluate the effect of stroke on perioperative mortality, morbidity and hospitalization period and factors affecting mortality, survival among patients with stroke.

MATERIAL AND METHODS

Between January 2002 and December 2009, 1657 patients underwent isolated on-pump CABG surgery in our clinic. Mean age was 58.90 ± 10.71 years (range, 24 to 85 years). 21.8% of patients were female and 78.2% were male. All patients were assessed based on patient history, physical examination, electrocardiography, biochemical analysis and transthoracic ecocardiography. Patients suspected of carotid artery disease and peripheral artery disease underwent Doppler ultrasound examination or digital subtraction angiography. Those who had symptomatically or asymtopmatically significant carotid artery disease were excluded from the study. Patients in whom brain damage developed after resuscitation or cardiac arrest were not included in the study. Cases of redo-CABG surgery, off-pump CABG surgery, simultaneous cardiac valve surgery, simultaneous carotid endarterectomy, simultaneous ventricular aneurysm surgery and simultaneous peripheral vascular surgery were not included in the study. Stroke was defined based on definiton by Society of Thoracic Surgeons as a focal neurologic deficit persisting for more than 72 hours.[4] Postoperative neurological events were assessed on the basis of clinical findings during daily patient care. Computerized tomography (CT) was performed on patients with stroke. Diagnosis was made in cooperation with neurologists and radiologists. In patients with a previous history of stroke, a new cerebrovascular event was diagnosed if new neurologic findings or prolonged worsening of their preexisting neurologic deficit were observed. Preoperative demographic data were as follows: smoking (n:955, 57.6%), diabetes mellitus (n:591, 35.6%), hypertension (n:764, 46.1%), peripheral vascular disease (n:76, 4.6%), chronic obstructive pulmonary disease (COPD) (n:74, 4.4%), prior stroke (n:13, 0.8%), renal failure or creatinine ≥2mg/dl (n:21, 1.2%), previous percutaneous transluminal coronary angioplasty (PTCA) (n:89, 5.3%), left ventricular ejection fraction (LVEF) >50% (n:854, 51.5%), 30-50% (n:689, 41.6%), <30% (n:103, 6.2%), hyperlipidemia (n:747, 45.1%), emergent and urgent operations (n:15, 0.9%), atrial fibrillation (AF) (n:23, 1.4), left main coronary artery disease (LMCAD) (n:96, 5.7%).

PERIOPERATIVE MANAGEMENT

The method of anesthesia was equally applied to all cases. Induction of anesthesia was provided through titration of 2 mg of midazolam I.V, 2-5 μg/kg of fentanyl I.V and 2-5 mg/kg of thipental sodium I.V. Muscle relaxation was achieved by 0.1 mg/kg pancuronium bromide and anesthesia was maintained by high dose fentanyl.

Cardiopulmonary bypass was undertaken using a standardized extracorporeal circulation polyvinyl chloride circuit (Cobe Cardiovascular Arvada,Co., Italy) utilizing non-pulsatile flow, arterial line filtration (40 μm; Medtronic, Anahaim, CA) and an alpha-stat management protocol. Bypass was established by proximal aortic cannulation and single dual cannulation of the right atrium, with a membrane oxygenator (Dideco-Sorin Group, Italy). All patients received a standard heparinization protocol of 300 IU/kg heparin bolus prior to cannulation, with an additional 10.000 I.U in the pump prime. Target activated clotting time greater than 400 was maintaned throughout bypass. The systemic perfusion was performed using hypothermic bypass strategy of systemic cooling between 28^0C and 32^0C. The systemic perfusion

pressure was electively maintained at 55-65 mmHg. Cardiopulmonary bypass flow rates were maintained between 2.0 and 2.4 $L.min^{-1}$ m^{-2}. Isothermic blood cardioplegia was initially administered antegradely and retrogradely, and thereafter continuously retrogradely. Initial cardioplegia utilized high potassium solution (30 mmol/L of KCl) to achieve asystole with further boluses of a low potassium solution (15 mmol/L of KCl) to maintain asystole.[5] Ascending aorta arteriosclerosis or atherosclerotic plaques were diagnosed preoperatively with teleradiography and transthoracic echocadiography. Intraoperatively ascending aorta was gently palpated and areas of thickening and calcification were identified and recorded. Distal anastomoses were constructed first; the cross-clamp was then removed and replaced with a partial occluding clamp in the mid-portion of the ascending aorta for attachment of the proximal coronary bypass grafts. Proximal anastomoses were performed with a partial occluding clamp in patients who hadn't ascending aortic atherosclerotic plaques. Proximal anastomoses were performed during a single aortic cross clamp in patients who had ascending aortic atherosclerotic plaques. Rewarming for all cases was performed with the temperature gradient between blood and heat exchanger not exceeding 10^0C, a maximum heat exchanger temperature of 41^0C to avoid damage to the blood elements, and the rate at which the patient was rewarmed not exceeding 0.5^0C per minute. Patients were separated from cardiopulmonary bypass with nasopharyngeal temperature in excess of 36^0C. All patients were treated with a second-generation cephalosporin before, during, and after surgery. In patients with ascending and proximal aortic arch atherosclerosis, arterial cannulation was achieved through the femoral artery, non-calcified areas of the ascending aorta, aortic arch, axillary artery or through the brachiocephalic trunk. If multiple areas of severe atherosclerosis or circumferential disease were present or there was extensive involvement of the midportion of the ascending aorta, this area was partially or totally replaced with a tubular Dacron graft during a period of hypothermic circulatory arrest. When coronary artery bypass grafting with saphenous veins was performed in these patients, the grafts were anastomosed to the Dacron graft. Emergency procedures were defined as those in patients who were taken directly from the cardiac catheterization laboratory to the operating room. Urgent operations were those performed within 24 hours of cardiac catheterization because of persisting symptoms in patients who required intravenous nitroglycerin for control of angina. Low cardiac output syndrome was defined as the use of postoperative inotropic support for >24 hours. Postoperatively, low cardiac output syndrome was treated with dopamine after preload, afterload, and heart rate had been optimized. Patients who did not respond to dopamine (10 μg/kg per min) received an intra-aortic balloon pump and additional inotropes as necessary to keep the cardiac index>2.0L/min per m^2 and systolic blood pressure>90 mm Hg. Prolonged ventilatory support was defined as pulmonary insufficiency requiring ventilatory support>24 hours postoperatively.

All the patients gave detailed informed about the operation together with informed consept forms.

STATISTICAL ANALYSIS

Following data accumulation, statistical models were formed and analysed using SPSS statistical software (version 15.0;SPSS Inc, Chicago, IL). Non-categorical data were analysed with t-test and categorical data with Chi-Square or Fisher's Exact test where appropriate. Mann-Whitney was used in analysing duration of intensive care unit stay and hospitalization periods. Log-Rank test was used in analysis of risk factors affecting survival. $p< 0.05$ was considered significant. Results were expressed as the mean ±SD unless otherwise indicated.

RESULTS

Patients with stroke had a mean age of 62.31 ± 8.18 and patients without stroke had a mean age of 58.87 ± 10.74 years. Table 1 reveals associations between stroke and preoperative, intraoperative and postoperative variables. The incidence of stroke was 0.96% (n= 16). All patients underwent an average of 2.66 ± 0.80 distal anastomoses.

TABLE 1: Preoperative, intraoperative, and postoperative data for postoperative stroke patients and non- stroke patients.

	Patients with Stroke (n= 16)	Patients without Stroke (n= 1641)	p Value
	Prevalence % (n)		
Age (yrs)	62.31 ± 8.18	58.87 ± 10.74	n/s
Sex (male)	87.5% (14)	78.1% (1282)	n/s
Smoking	75% (12)	57.46% (943)	n/s
Diabetes	75% (12)	35.2% (579)	0.001
Hyperlipidemia	87.5% (14)	47.1% (773)	0.001
Hypertension	81.2% (13)	45.7% (751)	0.005
COPD	18.7% (3)	4.3% (71)	0.031
LMCAD	6.2% (1)	5.7% (95)	n/s
Renal failure or creatinine ≥2mg/dl	–	1.2% (21)	n/s
Peripheral vasculardisease	–	4.6% (76)	n/s
Preoperative AF	18.7% (3)	1.2% (20)	0.001
Previous stroke or TİA	18.7% (3)	0.6% (10)	0.000
Aort calcification	68.7% (11)	2.6% (43)	0.000
Ejection fraction(%)			0.000
<30	31.2% (5)	5.9% (98)	
≥ 30-50	68.7% (11)	41.3% (678)	
>50	–	52% (854)	
Urgent and emergent operations	–	0.9% (15)	n/s
Previous PTCA	–	5.4% (89)	n/s
CPB time			n/s
< 3 hour	87.5% (14)	95.7% (1572)	
>3 hour	12.5% (2)	4.2% (69)	
Cross-clamp time			0.001
< 1 hour	62.5% (10)	93.1% (1528)	
> 1 hour	37.5% (6)	6.8% (113)	
Duration of surgery			0.000
<3 hour	12.5% (2)	41.1% (675)	
≥ 3-4 hour	50% (8)	50.2% (824)	
>4 hour	37.5% (6)	8.6% (142)	
Prolonged intrope use	56.2% (9)	15.1% (248	0.000
İntraaortic balloon support	12.5% (2)	8.0% (132)	n/s
Prolonged ventilatory support	18.7% (3)	3.3% (55)	0.016
Postoperative renal disease	12.5% (2)	3.3% (55)	n/s
Postoperative dialysis	6.2% (1)	1.4% (23)	n/s
Postoperative atrial fibrillation	31.2% (5)	16.2% (267)	n/s
Hemorrage-related reexploration	12.5% (2)	2.4% (40)	0.034
High blood transfusion requirement			
≥3 unite	12.5% (2)	5.2% (86)	n/s
ICU lenght of stay (days)	13.19 ± 24.51	2.57 ± 1.93	0.000
Mean hospital length of stay (days)	14.29 ± 6.74	6.31 ± 1.79	0.000

AF: Atrial fibrillation, CPB: Cardiopulmonary bypass, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, LMCAD: Left main coronary artery disease, TIA: Transient ischemic attack. PTCA: percutaneous transluminal coronary angioplasty.

There were (1.1%) (n= 19) postoperative myocardial infarctions. The lower was the ejection fraction, the higher was the rate of stroke development, being statistically significant (p= 0.000). Stroke predictors were hypertension (p= 0.005), hyperlipidemia (p= 0.001), diabetes (p= 0.001) ,

chronic obstructive pulmonary disease (p= 0.031), previous stroke or transient ischemic attack (TIA) (p= 0.000), low left ventricular ejection fraction (p= 0.000), calcification of ascending aorta (p= 0.000), preoperative atrial fibrillation (p= 0.001), postoperative prolonged inotropic support (p= 0.000), postoperative prolonged ventilatory support (p= 0.016), cross-clamp time (p= 0.001), operational period (p= 0.000) (Table 1). In 5 patients with moderate (n= 1) or severe (n= 4) atherosclerotic disease (9.8% of the total), a part or the entire ascending aorta was replaced with a Dacron tube graft using short time hypothermic circulatory arrest due to performing with open technique of distal anastomosis. Stroke rate was zero in these 5 patients. Computerized brain tomography was performed in all patients who had both previous history of stroke or TIA and postoperative stroke or TIA (n= 29). Incidence of stroke was higher, yet statistically insignificant in patients with cardiopulmonary bypass (CPB) time of more than 3 hours, intraaortic balloon support, hemorrhage- related reexploration, postoperative serum creatinin levels ≥2 mg/dl, those requiring postoperative dialysis, and those with postoperative AF and high blood transfusion requirement (≥3 unite). Reexploration for bleeding was required in 2.5% (n= 42) of patients. Patients with stroke stayed longer in the intensive care unit (median 13.19 ± 24.51 versus 2.57 ± 1.93 days), and had longer postoperative hospital stays (median 14.29 ± 6.24 versus 6.31 ± 1.79 days(p= 0.000). Four years survival rate was 96% (n= 1591). Mean follow-up was 40.27 ± 21.24 month among patients with stroke. In follow-up, mortality rate was 12.5% (n= 2). Cardiopulmonary bypass time (≥3 hours) was effecting mortality among patients with stroke in follow-up (p< 0.05). Survival was shorter among patients with stroke having cardiopulmonary bypass time (≥3 hours), low ejection fraction and postoperative renal insufficiency (p< 0.05).

DISCUSSION

Despite recent improvements in myocardial preservation as well as anesthetic and cardiopulmonary bypass techniques and postoperative care, stroke observed after CABG performed through cardiopulmonary bypass is a disabling neurological complication.[6] Identification of risk factors allows preoperative risk stratification and may facilitate improved patient selection. Additionally, this information may contribute to reduce the risk of stroke by providing an opportunity for adequate medical and surgical intervention. Causes of stroke seen after cardiac surgery have been reported to be multifactorial while advanced age has also been reported to be an important predictor of stroke.[4,6] The effect of stroke on age is possibly related to risk factors such as systemic atherosclerosis, cerebrovascular diseases and cognitive decline that increase during the advanced age.[2,3] A reduced LVEF may lead to perioperative haemodynamic instability and low-output state directly affecting physiological brain perfusion and contributing to neurological events.[3]

Possible sources of cerebral macroemboli during coronary bypass may be the ascending aorta, carotid arteries, intracerebral arteries, or intracardiac cavities. However, embolization of atherosclerotic debris may also occur when the aorta is not being surgically manipulated due to the sandblast effect of CPB. Aortic atherosclerosis is increasingly recognized as a major risk factor for stroke. Paleness of the ascending aorta or thickening of the adventitial tissue can be an indicator of troublesome atherosclerosis. Surgical palpation when positive has a high degree of specificity as reported by Volman et al.[7] in a study involving 24 institutions. Barasch and colleagues[8] have shown that discrete echogenic masses in the aortic root could be identified with transthoracic echocardiography. Embolization of atherosclerotic debris is most likely to occur during aortic cannulation/decannulation, cross-clamp application/removal and construction of proximal anastomosis. John and colleagues[9] have reported calcified ascending aorta to be effective on stroke incidence. Borger and colleagues[10] have stated that cerebral embolization could be reduced by 50% in CABG surgery via distal aortic arch cannulation and with a single cross-clamp technique. Bucerius and colleagues have demonstrated a 16.8% incidence of postoperative stroke for patients with a history of previous neu-

rologic events in patients 16 184 underwent cardiac surgery.[11] Large emboli that escape from or through the arterial pump line filter-consisting of air or platelet/thrombin aggregates or fat embolism- have also been implicated as a potential source of embolic stroke.[12,13] The association between prolonged CPB and cross clamp time and perioperative stroke has been demonstrated by other investigators.[6,14] Increased transfusion may reflect profuse bleeding, hypotension and consequent cerebral hypoperfusion.[11,15] Atrial fibrillation has consistently been found to increase stroke rate in various clinical settings.[9,16] We found that patients with hypertension were at increased risk for stroke (p= 0.004) similar to other studies.[6,11] Diabetes was a predictor of stroke in our analysis, and had also been identified as a risk factor by other investigators.[6,11,16] In our analysis, the average age of patients with stroke was higher than that of the patients without stroke, yet it was statistically insignificant. History of previous cerebrovascular disease was one of the most important predictors of stroke. Palpable atherosclerotic plaque lesions in the ascending aorta were noted in a large proportion of stroke patients. The stroke rate for the 5 our patients with severe or moderate aortic atherosclerosis who were treated by replacement of the ascending aorta using hypothermic circulatory arrest due to performing with open technique of distal anastomosis was zero. Our analysis revealed that cross clamp time longer than one hour was a predictor of stroke.

Although seen at higher rates in patients with postoperative stroke, CBP time which lasted 3 hours or more was not statistically significant predictor for stroke. History of preoperative atrial fibrillation was associated with high risk of postoperative stroke. Patients with low ejection fraction had higher rates of stroke incidence and it was statistically significant. In our study being differently from other studies, high transfusion requirement wasn't a risk factor for stroke in our analysis. Patients with stroke had a prolonged intensive care unit and hospital stay when compared with patients without stroke, probably related to delayed mobilization (p= 0.000). This finding has been previously reported by several other investigators.[3,6] In our study being unlike from other studies, we investigated factors affecting mortality in follow-up and survival in our patients. Cardiopulmonary bypass time (≥3 hours) was affecting mortality among patients with stroke in follow-up. Prolonged cardiopulmonary bypass time (≥3 hours), low ejection fraction and postoperative renal insufficiency were risk factors shortening survival of patients with stroke. Our limitation was that we detected aortic atherosclerosis by teleradiography, surgical palpation and transthoracic echocardiography, not by ultrasonography, transesophageal or epiaortic echocardiography.

In conclusion, Stroke is a devastating complication of coronary bypass surgery. The etiology of postoperative stroke is multifactorial, and any factor or a combination of factors may play a role in stroke development in patient. Our analysis, chart reviews and CT findings strongly suggest that macroemboli are the principal cause of stroke during on-pump CABG. The most likely source of these macroemboli is the ascending aortic atherosclerosis. Identification of risk factors for stroke, mortality and survival may contribute to risk reduction by providing an opportunity for adequate medical and surgical intervention.

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