Early Results of Combined and Staged Coronary Bypass and Carotid Endarterectomy in Advanced Age Patients in Single Centre

Hikmet Iyem[1,*] and Suat Buket[2]

[1]*Dicle University, Department of Cardiovascular Surgery, Diyarbakir, Turkey*

[2]*Kent Hospital, Department of Cardiovascular Surgery, Izmir, Turkey*

Absract: *Aim:* In present study, we aimed to compare the staged and combined surgery in patients with severe carotid stenosis and coronary atherosclerosis and detect the factors affecting mortality and morbidity.

Material and method: Between 2004 and 2008, 120 patients with predominant ischemic heart disease were enrolled to study. Patients were divided into three groups on basis surgery procedure. Group 1 (n=40) includeed patients had coronary artery disease without carotid disease underwent coronary artery by-pass graft (CABG) operation. Group 2 (n=40): included patients underwent combined surgery procedure including CABG and carotid endarterectomy (CEA). Patients underwent staged CABG and CEA were enrolled to Group 3 (n=40). All patients were in advanced aged and were had the same risk factors atributable atherosclerosis

Results: Mean age of the patients in all groups were 68±6, 69±3, 71±2 respectively, and 83% were male. Eight patients died in all groups at follow-up(seven in group 2 and 3, and one in group 1) and the difference between both groups was statistically significant (p<0.001). The follow-up period in the intensive care unit, and hospitalization period were not statistically different between CABG group and combined CEA plus CABG group.

Conclusion: We think that the results of staged or combined CABG plus CEA surgery are satisfactory in patients with severe carotid disease and advanced coronary artery disease. However, the mortality and morbidity in both procedures are higher than those of alone.

INTRODUCTION

Cardiovascular diseases are the most cause of death in the developed countries. Modeling studies in many developed countries, particularly the United States, Netherlands, New Zealand, and United Kingdom, suggest that 55% to 65% of recent, substantial CHD mortality declines can be attributed to declines in major risk factors, the remainder being attributable to medical and surgical treatments [1]. In the USA 39.4% of all of deaths is due to cardiovascular diseases and coronary heart diseases account for the the biggest part (54%) of cardiovascular disease leading death of cardiovascular diseases. In addition, 18% of cardiovascular caused deaths is due to stroke [2]. Postoperatif neurological problem is one of the serious complication of cardiac surgery. Frequency of serious perioperative neurological complication among patients undergoing coronary artery bypass surgery has been determined in range of 0.5% - 7% [2-4]. The possible mechanisms of neurological complication seen after elective CABG surgery are decrease in the brain blood flow due to hypotension or hypoperfusion, macro or micro embolisation and intracranial or extracranial vascular disease cause cerebrovascular event [5]. Although carotid arterial stenosis is seen in 2.4%- 14% of patients with coronary artery disease undergoing CABG; coronary artery disease is seen

in 40%-50% of patients undergoing carotid endarterektomy (CEA) [6-9]. Berens *et al.* l reported that stroke was seen by rate of 10.9% in >65 years old patients with >80% carotid arterial stenosis [10]. The frequency of perioperative myocardial enfarction in patients underwent isolated CEA has been determined in range of 1.5% to 5% [11]. CEA is recommended in patients with symptomatic carotid disease undergoing CABG due to coronary artery disease, but it is not well determined which procedure including staged or combined CEA plus CABG should be performed in current literature. The mechanism for stroke in patients with asymptomatic serious carotid stenosis undergoing CABG is still controversial [12]. In present study, we aimed to compare the staged and combined surgery in patients with severe carotid stenosis and coronary atherosclerosis and detect the factors affecting mortality and morbidity.

MATERIALS AND METHOD

Between May 2004 and February 2008, 120 patients with predominant ischemic heart disease were enrolled to study. Group 1 (n=40) includeed patients had coronary artery disease without carotid disease underwent coronary artery bypass graft (CABG) operation. Group 2 (n=40): included patients underwent combined surgery procedure including CABG and carotid endarterectomy (CEA). Patients underwent staged CABG and CEA were enrolled to Group 3 (n=40). The approval of the ethical commitee of our hospital and informed consent from all patients were taken. All patients were in advanced aged and were had the same risk

*Address correspondence to this author at the Dicle Universitesi, Tip Fakultesi Kalp Damar Cerrahisi AD, Diyarbakir, Turkey; Tel: +90 412 248 80 01; Fax: +90 412 248 80 12; E-mail: hikmetiyem@gmail.com

factors atributable atherosclerosis. All groups were compared in terms of preoperative risk factors, operative technique, preoperative and postoperative morbidity, mortality, and the factors affecting this parameters.

Preoperative Evaluation

58.9% of patients has been expiriencing chronical angina pectoris which is in the class II-III accarding to Canadian classification. Eighteen patients in the group 2, and 16 patients in group 3 were neurologically asymptomatic. Firstly, coloured dupplex ultrasonografy, and then carotid digital substraction anjiografy were performed to all patients undergoing CEA. In 5 patients Type A ulcerated lesion was found by Dupplex ultrasonografy, and in remain >70% carotid stenosis was found (Table **1**).

Table 1.   Distribution of Carotid Lesions

	Number of Patients
Bilateral %50-70	1*
Unilateral %50-70	4*
Bilateral right or left side >%70	3
Unilateral or bilateral <%50	-
Unilateral>%70	71
Bilateral >%70	1

*Patient with ulcerated plaque.

Anesthesia and Surgical Technique

Coronary revascularization and CEA procedures were performed in all patients in simultaneous fashion under general anesthesia. The same surgeons and operative team performed all procedures. Routine CABG and CEA protocol of our cardiovascular surgery clinic was applied to all patients. Anesthesia was induced with 20 mcg/kg fentanyl citrate, 0.12 mg/kg pancuronium, 2 mg/kg propofol. After tracheal intubation, mechanical ventilation was instiued with 6-8 ml/kg tidal volume and 10-12 /min respiratory rates. Anesthesia was maintained with 10 mcg/kg of fentanyl and 1 mg/kg propofol as infusion. 2 mg of pancuronium were given every 45 minutes throughout the operation. Five electroencephalographic (EEG) leads were placed and EEGS were monitored continuously with a Life Scan brain activity monitor (Diatek Patient Management System, Inc., SanDiego, CA). In all patients CEAs were performed prior to sternotomy. In case of bilateral internal carotid artery lesions, we performed CEA on the side with the higher degree lesion, the side related to neurological symptoms, or the dominant hemisphere. CEA was not performed in patients had totally occluded carotid vessels. Saphenous vein grafts were prepared during CEA. A standard oblique cervical incision was made. After isolation of the common, internal, and external carotid arteries, 2 ml of heparin was administered. Vessels were clamped and an arteriotomy was created in the common carotid artery and extended into the internal carotid artery. Changes in the electroencephalogram pattern after cross clamping not leading to an increase in the mean arterial pressure were considered indications for intraluminal shunting. Intraluminal carotid shunt was not needed in any patient. The

artery was opened beyond the distal extent of the plaque. The plaque was removed in the standard fashion. If the artery was thought to be small, the arteriotomy was closed with a saphenous vein patch. After completion of the CEA, the neck incision was left open until heparin reversal after CPB. After performing CEA, CPB was instituted with standard techniques. Aortic and two stage venous canulla were used to institute the CPB using a roller pump, membrane oxygenation and identical priming solution. Systemic blood flow was maintained at 2.2-2.4 L/m², mean arterial blood pressure at 60-70 mm Hg during CPB. Systemic hypothermia (28ºC) and hemodilution were applied. Distal anastomoses were done during the cross clamp (CC) period. Proximal anastomoses were done with partial occluding clamp in beating heart. The left anterior descending artery in all patients anatomosed with left internal mammarian artery flaps. The other vessels anastomosed with greater saphenous vein grafts. Postoperatively pharmacological support was instituted according to haemodynamic situation. The pericardial (No:28) and mediastinal (No:32) chest tubes were inserted to all patients.

In group 3 including patients undergoing staged surgery, CEA was performed firstly, and CABG was performed two days later. However, both surgery were performed at same time without delaying in unstable patients.

Statistical Analysis

Statistical analysis was performed with SPSS software version 10.0 (SPSS Inc, Chicago, III). Clinical data were expressed as mean values ± standard deviation, percents. Differences between the groups were investigated by Levine test, Bonferroni corrected t-test and Chi- Square test. Both groups and parameters inside each groups were compared using nonparametric Wilcoxon Signed Ranks test (two tailed). We investigated the effects of the variables by calculating odds ratios in univariate analyses for all patients. Differences were considered as significant if p value <0.05. Univariate analyses of demographics and variables to identify potential stroke risk factors was performed by the student's t test, Wilcoxon Signed Ranks test or the X^2 test. Multivariate determinants of the stroke were obtained by the stepwise multivariate logistic regresyon analysis. Candidate variables with a value of $p \leq 0.20$ were entered into a logistic model. Regression coefficiencies that are significantly different from 1.00 ($p \leq 0.05$) in the completed model are considered associated with stroke. Odds rations and 95% confidence limits as well as probability values, are reported.

RESULTS

Mean age of the patients in all groups were 68±6, 69±3, 71±2 respectively, and 83% were male. Demographical variables such as age, sex, and preoperative risk factors in groups were given on Table **2**. Among the preoperative risk factors, having diabetes mellitus, systemic hypertension, hyperlipidemia, unstable angina pectoris, left main coronary arterial disease, cerebrovascular event and chronic obstructive pulmonary disease were significantly higher in combined (group 2) or staged (group 3) CABG plus CEA groups compared only CABG group (group 1) (Table **2**).

In 5 patients unilateral CEA plus CABG and in 75 patients bilateral CEA plus CABG were performed. The mor-

Table 2.   Demographics and Preoperative Factors of the Patients

	Only CABG	Combined CEA+ CABG	Staged CEA+CABG	P Value
Number of patients	40	40	40	-
Age (mean ± SD)	68±6	69±3	71±2	a=ns, b=ns, c=ns
Male	31(%77.5)	32(%80.0)	34(%85.0)	a=ns, b=ns, c=ns
Female	9(%22.5)	8(%20.0)	6 (%15.0)	a=ns, b=ns, c=ns
Coronary Risk Factors				
Diabetes mellitus	25(%62.5)	34(%85.0)	36(%90.0)	a<0.05,b<0.05, c=ns
Hypertension	26(%65.0)	33(%82.5)	32(%80.0)	a<0.05,b<0.05, c=ns
Hyperlipidemia	25(%62.5)	34(%85.0)	31(%77.5)	a<0.05,b<0.05, c=ns
Smoking	32(%80)	37(%92.5)	38(%95.0)	a=ns, b=ns, c=ns
Comorbidity				
Cerebrovascular accident	1(%2.5)	6(%15.0)	7(%17.5)	a<0.05,b<0.05, c=ns
Peripheral vascular disease	1(%2.5)	2(%5.0)	1(%2.5)	a=ns, b=ns, c=ns
COPD	12(%30.0)	21(%52.5)	24(%60)	a<0.05,b<0.05, c=ns
Peptic/gastric ulcer	1(%2.5)	3(%7.5)	2(%5.0)	a=ns, b=ns, c=ns
Cancer	1(%2.5)	-	1(%2.5)	a=ns, b=ns, c=ns
Cardiac Profile				
Preoperative MI	5(%12.5)	7(%17.5)	6(%15.)	a=ns, b=ns, c=ns
Atrial fibrillation	2(%5.0)	1(%2.5)	3(%7.5)	a=ns, b=ns, c=ns
LVEF(%)	43.1±11.3	45.3±16.1	47.5±9.2	a=ns, b=ns, c=ns
LMC	3(%7.5)	9(%22.5)	8(%20.0)	a<0.05, b<0.05, c=ns
Unstabil anjina pectoris	3(%7.5)	7(%17.5)	9(%22.5)	a<0.05, b<0.05, c=ns
Laboratory Data				
Creatinine level (mg/dL)	1.1±0.5	1.3± 0.6	1.0± 0.9	a=ns, b=ns, c=ns
BUN level (mg/dL)	55.2±18.7	59.3±12.3	52± 11.4	a=ns, b=ns, c=ns

COPD: Chronic obstructive pulmonary disease, BUN: Blood urea nitrogen,
LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, ns: not significant,
a: p value for group Only CABG versus group Combined CEA+ CABG.
b: p value for group Only CABG versus group Staged CEA+ CABG.
c: p value for group Combined CEA+ CABG versus group Staged CEA+ CABG.

tality was recorded in one patient due to arrythmia in group 3 and in seven patients in group 2. In this study, patchplasty was done in 12 of 80 (10%) patients underwent CEA, in remain, the incision of carotid artery was closed primarily. The mean clamping time was 21.24±6.05 (ranged 15 to 36 minutes) (Table **3**).

The compared perioperative and potoperative variables in three groups were shown in Table **4**. The follow-up time in the intensive care unit, and duration of hospitalization were not statistically different between CABG group (group 1) and CEA plus CABG groups (group 2 and 3). No case of bleeding or hematoma was recorded at incision side.

In our study mortality was occured in 8 patients (seven in group 2 and 3, and one in group 1). This difference between CABG alone and CABG plus CEA groups in term of mortalitys was statistically significant(p<=.001).

Table 3.   Operative Variables of Carotid Endarterectomy

	Patient (n=)
Unilateral carotid stenosis	75(%93.75)
Right carotid endarterectomy	39(%48.75)
Left carotid endarterectomy	36(%45.0)
Bilateral carotid stenosis	5(%6.25)
EEG monitoring	80(%100)
Patchplasty	12(%15.0)
Primary closure	68(%85.0)
Carotid clamping time (min) mean±SD	21.24±6.05

On the univariate analysis, among the preoperative risk factors diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive lung disease, history of cerebrovascular disease, left main coronary artery disease, unstable angina pectoris, and among the postoperative risk factors, stroke, reexploration due to bleeding and arrythmia were found as factors affecting on mortality (Tables **2-5**). However, on multivariate analysis, among the perioperative risk factors history of serebrovascular disease, left main coronary artery disease and among the postoperative risk factors stroke were found to as factors affecting mortality with statistical significance(p=0.002, p=0.032, p=0.005, respectively) (Table **6**). No statistically significant difference was found when the staged and combined CEA plus CABG groups compared in terms of stroke and neurological deficit. Postoperative stroke was seen in two patients in combined CEA plus CABG group, and in three patients in staged CEA plus CABG group (Table **5**).

Table 4. Operative and Postoperative Variables

	Only CABG	Combined CEA+ CABG	Staged CEA+CABG	P value
Cross clamp time(min)	41.2±20.9	44.9±11.6	42.9±14.2	ns
CPB time (min)	61.7±24.7	62.2±32.7	59.9±21.8	ns
Graft number (n)	3.04±0.8	3.1±0.7	3.06±0.6	ns
Perioperative MI (n=)	1(%2.5)	2(%5.0)	1(%2.5)	ns
Ventilation time (hr)	14.4±10.2	13.8±11.4	13.8±11.4	ns
Mediastinal drainage (mL)	639.8±36.3	652±23.2	625.6±17.5	ns
IIABP (n=)	3(%7.5)	4(%10.0)	2(%%5.0)	ns
ICU stay (hour)	22.7±16.7	25.3±43.2	27.4±43.5	ns
Hospital stay (day)	7.1±2.6	7.3±8.8	7.5±5.6	ns
Early mortality (n=)	1(%2.5)	3(%7.5)[a]	4(%10.0)[b]	ns

Bonferroni corrected t-test: no significant differences between groups.
CPB: Cardiopulmonary bypass ICU: Intensive care unit, MI: Myocardial infarction,
IIABP: Intraoperative intraaortic bollon pump.
ns: not significant.
a: p value for group Combined CEA+ CABG versus group Only CABG.
b: p value for group Staged CEA+ CABG versus group Only CABG.

Table 5. Postoperative Complications and Factors Affecting Morbidity and Mortality

Complications	Only CABG N=	Combined CEA+ CABG N=	Staged CEA+CABG N=	P value
Acute renal failure	2(%5)	3(%7.5)	4(%10.0)	a=ns, b=ns, c=ns
Postoperative dialysis	1(%2.5)	3(%7.5)	3(%7.5)	a<0.05, b<0.05, c=ns
Multiple organ failure	-	-	1(%2.5)	a=ns, b=ns, c=ns
Pulmonary complications	-	4(%10.0)	6(%15)	a<0.05, b<0.05, c=ns
Arrhythmia	1(%2.5)	3(%7.5)	5(%12.5)	a<0.05, b<0.05, c=ns
Mediastinitis	-	-	1(%2.5)	a=ns, b=ns, c=ns
Transient ischemic episode	-	3(%7.5)	2(%5.0)	a<0.05, b<0.05, c=ns
Transient hemiparesia	-	2(%5.0)	3(%7.5)	a<0.05, b<0.05, c=ns
Permanent hemiplegia	-	2(%5.0)	2(%5.0)	a<0.05, b<0.05, c=ns
Stroke	-	2(%5.0)	3(%7.5)	a<0.05, b<0.05, c=ns
Low cardiac output	1(%2.5)	4(%10.0)	3(%7.5)	a<0.05, b<0.05, c=ns
Reexploration for bleeding	2(%5)	3(%7.5)	4(%10.0)	a<0.05, b<0.05, c=ns
Wound infection	1(%2.5)	1(%2.5)	1(%2.5)	a=ns, b=ns, c=ns

CEA: Carotid endarterektomy, CABG: Coronary arterial bypass greft
ns: not significant,
a: p value for group Only CABG versus group Combined CEA+ CABG.
b: p value for group Only CABG versus group Staged CEA+ CABG.
c: p value for group Combined CEA+ CABG versus group Staged CEA+ CABG.

DISCUSSION

The prevalence of significant carotid disease in the cardiac surgical population reflects the systemic nature of the atherosclerotic process. In an analysis of 1779 patients, 14.7% have 50% or greater stenosis and 6.3% have 75% or greater carotid artery stenosis. Carotid artery stenosis grater than 50%, redo surgery, peripheral vascular disease, longer pump time and hypercholesterolemia were found to be independently associated with an increased risk of the stroke and mortality [13]. D'agostino, *et al*. [14] assessed the incidence and risk factors of stroke in 1835 patients undergoing CABG and found that corotid stenosis>50% was a risk factor in this population. It was found that, mortality rate of combined CEA plus CABG was 2-12%, and stroke rate in this group of patients was 1-15% [15-18]. When staged and combined surgeries were compared different results were given according to clinics and years. Borger *et al*. [19] were studied 16 different studies which are made on 844 combined and 920 staged surgeries. They found stroke rate as 6% in combined surgery and 3.2% in staged surgery. They found death rate as 4.7% in combined surgery and as 2.9% in staged surgery; and no statistically significant difference was reported in terms of these variables between two groups. However, Hamulu *et al*. [20] found stroke rate as 2.3% in combined surgery and as 3.0% in staged surgery; and there were no statistically significant difference in stroke rate between two groups and in addition, the death rate was found higher in combined surgery group compared staged group (5.7% vs. 1.5%, p<0.05). In present study, we found the similar results. The stroke rate was similar in both groups of combined and staged surgery (5% vs %7.5 p>0.05). In addition, the mortality rate also was similar in both groups (7.5% in combined and 10% in staged group p>0.05). These results showed that the mortality increases independently from staged or combined surgery was performed in patients undergoing CABG plus CEA. The studies evaluated the efficacy and complications seen during perioperative and postoperative terms of combined CEA plus CABG were shown on Table **7** [21-34].

The advantages of combined surgery such as shorter hospitalization period [35], lower cost [25], acceptable early mortality and morbidity [36, 37], lower stroke risk on long term period [37, 38] were reported. However, there are several studies reported the disadvantages of combined surgery such as higher stroke and death rates compared to staged

Table 6. Factors Affecting Mortality on Multivariate Logistic Regression Analysis

	Variable Estimate	Standart Error	P Value	Odds Ratio	95% CI
Preoperative history of cerebrovascular disease	0.074	0.033	0.0002	1.05	1.021-1.125
Left main coronary arterial lesion	0.772	0.329	0.038	2.20	1.012-4.241
Postoperative stroke	0.819	0.519	0.035	2.23	1.075-5.556

Table 7. The Studies on Combined CEA+CABG and Complication Rates

Author	Year	Patients (n=)	Mean Age (y)	Death (%)	Stroke (%)
Pome [21]	1991	52	61	0	5.7
Rizzo [22]	1992	127	65	5.5	5.5
Vermeulen [23]	1992	230	63	3.5	3.0
Chang [24]	1994	189	66	2.0	1,0
Akins [25]	1995	200	67	2.5	3.0
Daily [26]	1996	100	68	4.0	0
Mackey [27]	1996	100	68	8.0	9.0
Trachiotis [28]	1997	88	68	3.4	3.4
Takach [29]	1997	255	65	3.9	3.9
Horst [30]	1999	63	64	7.9	0
Plestis [31]	1999	213	65	5.6	5.1
Gott [32]	1999	55	66	5.4	3.6
Hamulu [20]	2000	88	66	5.7	2.3
Dylewsky [33]	2001	33	68	6.1	0
Zacharias [34]	2002	189	69	2.6	2.6
Kolh [35]	2006	311	67	6	7
Our study	2007	40	69	7.5	5

surgery in current literature [39]. So, the management of concurrent carotid and coronary artery disease is controversial because of lack of prospective randomized trials evaluating the advantages or disadvantages of both surgeries. In our study there were no statistically significant difference between three groups in term of folow-up time in intensive care unit and hospitalisation periods. However, mortality and morbidity were significantly lower in isolated CABG group compared CEA plus CABG groups [40].

Borger *et al*. [19] concluded that trials must be conducted by 1500 patients if we accept expected stroke and death rate as %7.5 to get enough results by randomised trials. Recently advancing techniques such as carotid angioplasty and stenting, are also alternative techniques in risky patients undergoing cardiac surgery. Timaran *et al*. [41] evaluated outcomes of carotid artery stenting(CAS) before CABG versus combined CEA and CABG and assessed the risk for adverse events in 27,084 cases of concurrent carotid revascularizations and CABG and found that patients undergoing CAS-CABG had fewer major adverse events than those undergoing CEA-CABG. CAS-CABG patients had a lower incidence of postoperative stroke (2.4% vs 3.9%), and combined stroke and death (6.9% vs. 8.6%) than the combined CEA-CABG group (P < .001), although in-hospital death rates were similar (5.2% vs 5.4%) and finally they concluded that CAS might provide a safer carotid revascularization option for patients who require CABG.

In a study reported by Hertzer, *et al*. [42] 129 unstable coronary bypass patients with unilateral, asymptomatic carotid lesions were prospectively randomized to receive either combined operations or CABG alone followed by delayed endarterectomy. The risk of stroke was 2.8% for the combined operations, whereas that for patients in whom delayed CEA was performed within 2 weeks was 14.4% (6.9% at the time of coronary grafting and 7.5% at the time of delayed carotid operation). Brenner, *et al*. [43] examined the issue of combined and staged CABG / CEA. They demonstrated that staged procedures may result in a higher risk of myocardial infarction, particularly in the perioperative period of the carotid operation, with no difference in stroke rates. Indeed they found a very high incidence of stroke in patients undergoing such "reverse-staged" procedures.

If the combined procedure does indeed result in a higher risk of stroke or death, there are several possible reasons. One reason may be that the combined procedures are more technically difficult, from both a surgical and an anesthetical point of view, resulting in more perioperative complications. Another reason may be that combined operations result in excessive stress on the cardiovascular and cerebrovascular systems, resulting in large fluctuations in patient hemodynamics during relatively long operative procedures.

CONCLUSION

We think that the results of staged or combined CABG plus CEA surgery are satisfactory in patients with severe carotid disease and advanced coronary artery disease. However, the mortality and morbidity in both procedures are higher than those of alone.

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