Early results following synchronous coronary artery bypass grafting and carotid endarterectomy: a propensity score matched comparison with solely carotid endarterectomy

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Background: The optimal management for patients with concomitant severe coronary artery disease (CAD) and carotid artery stenosis (CAS) remains controversial.

Methods: One hundred and two solely carotid endarterectomy (CEA) patients were matched to 34 synchronous CEA and coronary artery bypass grafting (CABG) patients according to the propensity score during 7 years. We retrospectively analyzed the baseline characteristics and 30-day results of both groups.

Results: The two groups were similar with regard to age, sex, the degree of CAS, the incidence of hypertension, diabetes mellitus (DM), smoking, hyperlipidemia and symptomatic CAS. Higher incidence of contralateral >70% CAS occurred in synchronous CEA/CABG group (29.4% vs. 13.7%, P=0.038). More CAD was present in synchronous CEA/CABG group (12.7% vs. 100%, P<0.001). The left ventricular ejection fraction was higher in solely CEA group (0.73±0.26 vs. 0.55±0.09, P<0.001). The Charlson's Weighted Index of Comorbidities (WIC) was higher in synchronous CEA/CABG group (4.32±1.07 vs. 1.98±1.67, P<0.001). The operation time was 295±49 min for synchronous CEA/CABG and 143±39 min for solely CEA (P<0.001). The intraoperative blood loss was 771±334 mL for synchronous CEA/CABG and 70±54 mL for solely CEA (P<0.001). No death occurred in both groups within 30 days. The cumulative occurrence of primary endpoint [myocardial infarction (MI), stroke and death] was 1 (2.94%) in synchronous CEA/CABG group source of complications was 11 (32.4%) in synchronous CEA/CABG group compared with 23 (22.6%) in solely CEA group (P=0.169).

Conclusions: Our study suggested that the 30-day mortality and morbidity rate of synchronous CEA/ CABG was comparable to solely CEA. Our results add to the controversy of the outcomes of synchronous CEA/CABG procedure. Further prospective randomized controlled trial is needed to definitely evaluate the results of synchronous CEA/CABG.

Keywords: Carotid endarterectomy (CEA); coronary artery bypass grafting (CABG); synchronous

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Introduction

Carotid artery stenosis (CAS) accounts for 7% to 10% of strokes (1), which is a main cause of death, just behind coronary artery disease (CAD) and cancer (2). Atherosclerotic disease can affect both the carotid and coronary arteries (3). The prevalence of carotid artery atherosclerosis in patients with angina pectoris was reported to be 73% (4) and the severity of CAS was significantly correlated with the extent of CAD (5). Carotid endarterectomy (CEA) has been proven to be effective in treating patients with CAS and the most frequent cause of death in CEA follow-up is CAD (6).

It was reported that selective coronary revascularization before CEA could improve long-term freedom from myocardial infarction (MI) and late survival (7). But revascularize coronary artery in patients with CAS increases the risk of stroke. While revascularize carotid artery in patients with CAD increases the risk of MI (8). Until now, the optimal management for patients with concomitant severe CAS and CAD remains a controversy. This dilemma seems to be solved by synchronous carotid and coronary artery revascularization, which has been reported by several centers (8, 9).

However, the cohorts of synchronous carotid and coronary artery revascularization may have selection bias. In order to reduce the selection bias, we use a propensity score matched analysis to evaluate the early results following synchronous coronary artery bypass grafting (CABG) and CEA versus solely CEA.

Methods

Study population

The study population consisted of 257 consecutive patients with CAS who underwent CEA at the cardiovascular department of China-Japan Friendship Hospital between January 2009 and December 2015. Among the 257 patients, 34 underwent synchronous CABG and CEA because of concomitant CAD and CAS. Then we used 8 variables (age, sex, hypertension, diabetes mellitus (DM), smoke, hyperlipidemia, CAS degree and CAS symptom) in the logistic regression to calculate the propensity score. Each patient has a propensity score according to the baseline characteristics. Then solely CEA patients counterparts to synchronous CEA/CABG patients were selected by using greedy matching techniques with a 3:1 ratio. The study procedures were in accordance with institutional guidelines. All data were collected retrospectively. All the patients have signed the written informed consent.

Definitions

Selection criteria for CEA were: (I) patients with transient ischemia attacks (TIA) or stroke (within 6 months) referable to 50% to 99% CAS; (II) asymptomatic patients with >70% CAS; (III) asymptomatic patients with unilateral occlusion and contralateral >50% stenosis.

Patients with overt symptom of CAD (stable or unstable angina pectoris, previous MI) were selected for coronary angiography. CAD was defined as a lumen diameter stenosis of >50% in at least one major coronary artery. Selection criteria for CABG were: (I) 2-vessel or 3-vessel symptomatic CAD; (II) left main trunk symptomatic CAD; (III) the diameter of targeted coronary was >1.5 mm; (IV) left ventricular ejection fraction >40%.

Surgical management

Aspirin and statin were given for all the patients. For synchronous CEA/CABG patients, aspirin and clopidogrel were stopped 5 days prior to surgery and low molecular weight heparin was used instead. Then aspirin (100 mg/d) started 3 days after the surgery and lasts for life, clopidogrel (75 mg/d) started 3 days after the surgery and lasts for 3 months. Both CEA and CABG were carried out by the same surgical team under general anesthesia.

For the CEA procedure, the incision was made along the anterior border of sternocleidomastoid muscle. Then expose and isolate the common, internal and external carotid artery. A bolus heparin (1 mg/kg) was administered intravenously before clamping carotid artery. The arteriotomy was then made longitudinally and endarterectomy was carried out. The carotid shunt and polytetrafluoroethylene (PTFE) patch were used routinely in every CEA procedure.

For patients underwent synchronous CEA/CABG, the CABG procedure was started after CEA with a median sternotomy. The neck incision was left open until the heparin was reversed after CABG. CABG was carried out either with cardiopulmonary bypass (on-pump CABG) or without cardiopulmonary bypass (off-pump CABG). Cardiopulmonary bypass was established in a standardized manner with hypothermia and a roller pump. Ascending aortic cannulation and 2-stage vena cava cannulation were used to establish the CPB. Intermittent hyperkalemic cardioplegia was used for myocardial protection. Intraaortic balloon pump (IABP) was used for off-pump CABG procedures. A stabilizing retractor (Octopus, Medtronic) was used to immobilize the targeted vessel, an intraluminal shunt and CO_2 blower were used during anastomosis. The autologous saphenous vein was harvested during the CEA procedure by another surgeon. A 4.5-mm hole on the aorta was punched with a puncher. Distal anastomosis was routinely constructed after proximal anastomosis. During the procedure, the activated clotting time was maintained over 300 s for off-pump CABG and over 480 s for on-pump CABG by heparin administration. The effect of heparin was reversed with protamine sulphate at 1:1 ratio. Patients were transferred to intensive care unit (ICU) after the procedure.

Endpoint

The primary endpoint was the occurrence of MI, stroke or death within 30 days after the surgery. The secondary endpoint was surgery related complications, such as cranial nerve injury, hyper-perfusion syndrome, acute renal failure, pneumonia and wound infection. The intubation time, ICU time and hospital stay were also recorded.

Postoperative MI was defined by the occurrence of specific abnormalities on the ECG (new Q waves >0.04 ms or >25% reduction in R wave) that were consistent with myocardial ischemia associated with significant elevation of serum troponin level. Stroke was diagnosed if the modified Rankin score was higher than 3 at 30 days after the operation. Acute renal failure was defined as >50% elevation of creatinine or >50% decrease of glomerular filtration rate after surgery. Wound infection was defined as local inflammation with positive bacterial culture and delayed wound healing.

Statistical analysis

The nonparsimonious multiple logistic regression model was used for the calculation of each patient's propensity score. Then we match solely CEA patients with synchronous CEA/CABG patients (3:1 match) with R software version 3.2.3 (Package "MatchIt") according to the propensity score. Continuous variables are present as the mean \pm SD and discrete variables are present as percentages. A two-sided unpaired *t*-test was performed for continuous variables, and the chi-square test or Fisher's exact test was used to analyze discrete variables. Data analysis was performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). A P value of <0.05 was considered statistically significant.

Results

Demographics and clinical features

The final study population consisted of 136 patients (108 men; mean age 64.30 ± 8.61), of which 34 underwent synchronous CEA/CABG and 102 underwent solely CEA. The demographics and clinical features of the patient cohort are presented in *Table 1*.

Of the 34 synchronous CEA/CABG patients, 28 (82.4%) were men and 6 (17.6% were women. The mean age was 62.71 ± 6.14 years (range, 52-75 years). Hypertension was present in 29 (85.3%) patients and DM was present in 27 (79.4%). Eleven (32.4%) patients had hyperlipidemia and 18 (52.9%) were smokers. The mean degree of carotid stenosis ipsilateral to the CEA was 88.44% \pm 7.90% (range, 70–90%). 32 (94.1%) had symptomatic CAS, of which 17 (50%) had previous stroke and 15 (44.1%) had TIA. All patients in the group had symptomatic CAD, of which 8 (23.5%) had stable angina pectoris, 19 (55.9%) had unstable angina pectoris and 7 (20.6%) had MI. With regard to the number of coronary arteries involved, 6 (17.6%) had 1-vessel disease, 7 (20.6%) had 2-vessel disease and 21 (61.8%) had 3-vessel disease.

Of the 102 solely CEA patients, 80 (78.4%) were men and 22 (21.6%) were women. The mean age was $64.83 \pm$ 9.25 years (range, 42–85 years). Hypertension was present in 89 (87.3%) patients and DM was present in 79 (77.5%) patients. 33 (32.4%) patients had hyperlipidemia and 48 (47.1%) were smokers. The mean degree of CAS ipsilateral to the CEA was $86.98\% \pm 11.67\%$ (range, 50-90%). Eightysix (84.3%) had symptomatic CAS, of which 39 (38.2%) had previous stroke and 47 (46.1%) had TIA. Thirteen (12.7%) had symptomatic CAD with stable angina pectoris. With regard to the number of coronary arteries involved, 4 (3.9%) had 1-vessel disease, 6 (5.9%) had 2-vessel disease and 3 (2.9%) had 3-vessel disease.

The two groups were similar with regard to age, sex, the degree of CAS, the incidence of hypertension, DM, smoking, hyperlipidemia and symptomatic CAS. Higher incidence of contralateral >70% CAS occurred in synchronous CEA/CABG group (29.4% vs. 13.7%, P=0.038). More CAD was present in synchronous CEA/ CABG group (12.7% vs. 100%, P<0.001). The left ventricular ejection fraction was higher in solely CEA group

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Table1 Demographics and clinical features

Variables	CEA (%)	CEA/CABG (%)	Р
No. of patients	102	34	_
Age	64.83±9.25	62.71±6.14	0.213
Male	80 (78.4)	28 (82.4)	0.624
Hypertension	89 (87.3)	29 (85.3)	1.000
DM	79 (77.5)	27 (79.4)	0.811
Hyperlipidemia	33 (32.4)	11 (32.4)	1.000
Smoker	48 (47.1)	18 (52.9)	0.552
Carotid symptomatic			
Stroke	39 (38.2)	17 (50)	0.227
TIA	47 (46.1)	15 (44.1)	0.842
CAS degree	86.98±11.67	88.44±7.90	0.498
Contralateral lesion			
Occlusion	6 (5.9)	14 (41.2)	0.576
>70 stenosis	14 (13.7)	10 (29.4)	0.038
50–70% stenosis	26 (25.5)	6 (17.6)	0.350
<50% stenosis	48 (47.1)	12 (35.3)	0.232
Coronary symptomatic			
Stable angina	13 (12.7)	8 (23.5)	0.132
Unstable angina	0 (0)	19 (55.9)	<0.001
Myocardial infarction	0 (0)	7 (20.6)	<0.001
CAD			
1-vessel disease	4 (3.9)	6 (17.6)	0.023
2-vessel disease	6 (5.9)	7 (20.6)	0.029
3-vessel disease	3 (2.9)	21 (61.8)	<0.001
WIC	1.98±1.67	4.32±1.07	<0.001
Left ventricular ejection fraction	0.73±0.26	0.55±0.09	<0.001

CEA, carotid endarterectomy; CABG, coronary artery bypass grafting; TIA, transient ischemia attack; DM, diabetes mellitus; WIC, Charlson's Weighted Index of Comorbidities; CAD, coronary artery disease.

 $(0.73\pm0.26 vs. 0.55\pm0.09, P<0.001)$. The Charlson's Weighted Index of Comorbidities (WIC) was higher in synchronous CEA/CABG group (4.32±1.07 vs. 1.98±1.67, P<0.001).

Intraoperative variables

Table 2 shows the intraoperative variables. Carotid shunt and PTFE patch angioplasty were used in every CEA

procedure. In synchronous CEA/CABG group, 28 (82.35%) off-pump CABG procedures were carried out with IABP support. Six (17.65%) CABG procedures were carried out with CPB. The operation time was 295±49 min for synchronous CEA/CABG and 143±39 min for solely CEA (P<0.001). The intraoperative blood loss was 771±334 mL for synchronous CEA/CABG and 70±54 mL for solely CEA (P<0.001).

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Table 2 Intraoperative variables of the two groups

Variables	CEA/CABG [34]	CEA [102]	Р		
Carotid shunt (%)	34 (100.0)	102 (100.0)	1.000		
PTFE patch angioplasty (%)	34 (100.0)	102 (100.0)	1.000		
Off-pump CABG (%)	28 (82.4)	-	-		
IABP (%)	28 (82.4)	-	-		
Operation time (min)	295±49	143±39	<0.001		
Blood loss (mL)	771±334	70±54	<0.001		

PTFE, polytetrafluoroethylene; IABP, intra-aortic balloon pump.

30-day outcomes

Table 3 shows the 30-day outcomes for both groups. The intubation time was 34.02 ± 15.62 h for synchronous CEA/CABG and 2.54 ± 0.60 h for solely CEA (P<0.001). The ICU time was 60.87 ± 46.51 h for synchronous CEA/CABG. No ICU stay was need for solely CEA patients. The hospital stay was longer for synchronous CEA/CABG (19.41±3.22 vs. 8.82 ± 2.31 d, P<0.001). No death occurred in both groups within 30 days.

In synchronous CEA/CABG group, one patient experienced stroke contralateral to the CEA side. Two patients experienced TIA, of which one is ipsilateral and one contralateral to the CEA side. Six patients suffered from cranial nerve injury manifesting two deviations of tongue, three face numbness and one hoarseness. Two hyperperfusion syndrome, one wound infection, two pneumonias and 1 acute renal failure also occurred.

In solely CEA group, three MI occurred. Three patient experienced TIA, of which one is ipsilateral and two contralateral to the CEA side. Ten patients suffered from cranial nerve injury manifesting three deviations of tongue, three face numbness and four hoarseness. Eight hyperperfusion syndrome and two acute renal failures also occurred.

All the cranial nerve injury in both groups alleviated without special treatment. The cumulative occurrence of primary endpoint was 1 (2.94%) in synchronous CEA/CABG group and 3 (2.94%) in solely CEA group, no statistical difference was found between the two groups (P=1.000). The cumulative occurrence of complications was 11 (32.4%) in synchronous CEA/CABG group compared with 23 (22.6%) in solely CEA group (P=0.169).

Discussion

After several RCTs (10-12) have been published, the

strategy for managing symptomatic CAS is rather clear and the Asymptomatic Carotid Atherosclerosis Study (ACAS) has demonstrated that CEA is beneficial for >60% asymptomatic patients (13). MI most frequently causes perioperative and late death after CEA, especially in those patients with CAD (6). Among patients with >60% CAS, 3-15% patients had significant CAD need CABG (14). Although there is agreement that cardiac mortality represents a substantial problem in CEA patients, whether pre-CEA cardiac catheterization for every patient is proper remains controversial. Hertzer et al. (15) illustrated a 26% cardiac comorbidity in CEA patients by indiscriminate catheterization. However, Mackey et al. (6) suggested that cardiac catheterization for patients with overt CAD symptoms were more cost-effective. In our study, we carried out coronary angiography only for patients with overt CAD symptoms and 82.61% have severe CAD, which is higher than indiscriminate catheterization (15).

The management of concomitant CAS and CAD remains controversial. In a RCT carried out by Illuminati et al. (7), systematic coronary angiography prior to CEA followed by selective PCI or CABG significantly reduces the incidence of late MI and increases long-term survival. Hertzer et al. (15) also reported an improved longterm outcome of CABG before CEA. However, CABG before CEA will increase the risk of stroke in CABG procedure (8). Another alternative strategy is CEA followed by CABG, which can lead to a higher MI rate (16) and not applicable to patients whose cardiac status is unstable (17). So synchronous CEA/CABG seems to be a rational approach (18). In the current study, we carried out a propensity score matched comparison to evaluate the safety and feasibility of synchronous CEA/CABG. Synchronous CEA/CABG was indicated if the expected cardiac mortality exceeds the expected mortality of synchronous CEA/CABG.

Table 3 30-day outcomes of the two groups

Variables	CEA/CABG [34]	CEA [102]	Р
MI (%)	0 (0)	3 (2.9)	0.573
Stroke (%)	1 (1.0)	0 (0)	0.184
Death (%)	0 (0)	0 (0)	1.000
TIA (%)	2 (2.0)	3 (2.9)	0.599
Deviation of tongue (%)	2 (2.0)	3 (2.9)	0.599
Face numbness (%)	3 (2.9)	3 (2.9)	0.165
Hoarseness (%)	1 (1.0)	4 (3.9)	1.000
ICU stay (h)	60.87±46.51	-	-
Intubation time (h)	34.02±15.63	2.54±0.60	<0.001
Hospital stay (d)	19.41±3.22	8.82±2.31	<0.001
Hyper-perfusion syndrome (%)	2 (2.0)	8 (7.8)	1.000
Wound infection (%)	1 (1.0)	0 (0)	0.184
Pneumonia (%)	2 (2.0)	0 (0)	0.061
Acute renal failure (%)	1 (1.0)	2 (2.0)	1.000

MI, myocardial infarction; TIA, transient ischemia attack; ICU, intensive care unit.

In our series, we performed CEA followed by CABG routinely to avoid cerebral hemodynamic disturbances. CABG was performed prior to CEA in unstable CAD. Our results suggested that the rate of MI, stroke, and death within 30 days were similar in synchronous CEA/CABG and solely CEA group. The solely CEA group has higher MI rate but the difference was not statistically significant. Therefore, we believe that a synchronous approach can solve the CAS and CAD simultaneously without the increase of morbidity and mortality, but the long-term results need further investigation. Although equivalent or superior results were reported with staged CEA and CABG (19,20), the synchronous approach has shorter hospital stay, lower costs and decreased anesthetic exposure (21,22).

Morbidity and mortality rates for synchronous CEA/ CABG were variable according to the current data. Aydin *et al.* (23) reported that the mortality rate was 0.9% and the stroke rate was 3% in 110 synchronous CEA/CABG procedures. Gopalda *et al.* (24) analyzed 16,639 synchronous CEA/CABG patients, the mortality rate was 4.5% and neurologic complications were 4.9%. Shishehbor *et al.* (25) reported a 5% mortality and 7% stroke morbidity in 195 synchronous CEA and open heart surgeries. However, in Coyle's study (26), the mortality rate was 10.8% and the stroke rate was 15.4%. The morbidity and mortality rates of synchronous CEA/CABG appear highly dependent on patient selection criteria. We use the Charlson's WIC to evaluate the comorbidities of patients before surgery. In our experience, the mortality and morbidity rate was acceptable for proper patients.

Mishra *et al.* (27) retrospectively analyzed synchronous CEA and on-pump or off-pump CABG. The results showed that equally good results can be reproduced using CPB or off-pump techniques. However, the on-pump group takes more time. Meharwal *et al.* (28) achieved satisfactory results with synchronous CEA and off-pump CABG. In our study, 82.35% (28/34) CABG were off-pump with IABP implantation. Four patients with CPB suffered from psychological complication and recovered soon. No other significant difference was found between patients with on-pump or off-pump CABG.

In our CEA procedure, PTFE patch and carotid shunt were used in every patient. Carotid patch angioplasty has been proved effective in reducing the risk of perioperative arterial occlusion and restenosis (29,30). However, the use of carotid shunt was controversial nowadays. It was acceptable that carotid shunt can improve intraoperative cerebral perfusion (31) and reduce cerebral ischemia time (32). The complications of carotid shunt, such as intima damage and cerebral embolization causation were also noticed by investigators (33). For the consideration of shortening cerebral ischemia time and easiness of the CEA procedure, we prefer to use the carotid shunt.

There may be limitations to our study. First, this is a retrospective study, and all limitations inherent in any retrospective study may also exist here. Second, although we have used propensity score matched analysis to reduce bias, some variables such as cardiac symptom were not matched between the two groups. Third, we only observed 30-day outcome without tracing long-term results.

In conclusion, our study suggested that the 30-day mortality and morbidity rate of synchronous CEA/CABG was comparable to solely CEA. Our results add to the controversy of the outcomes of synchronous CEA/CABG procedure. Further prospective randomized controlled trial is needed to definitely evaluate the results of synchronous CEA/CABG.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/jxym.2017.03.11). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of our hospital (No. 2013-KY-85) and written informed consent was obtained from all patients.

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