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Original Article

Does Warfarin Help Prevent Ischemic Stroke in Patients Presenting with Post Coronary Bypass Paroxysmal Atrial Fibrillation?

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Purpose: This study examines the efficacy of warfarin in preventing ischemic stroke due to paroxysmal atrial fibrillation (PAF) after coronary artery bypass grafting (CABG).
Methods: Postoperative PAF occurred in 151(33.5%) of 447 patients undergoing conventional CABG. The patients were divided into two groups: group I consisting of 93 patients administered two types of antiplatelet agents and group II consisting of 58 patients treated with a single antiplatelet agent and warfarin. We compared the two groups in terms of CHADS2 score, incidence of ischemic stroke, and independent risk for stroke associated with post-CABG PAF.
Results: The group I CHADS2 score (2.24 ±1.67) was significantly lower than the group II score (2.64 ± 1.22), p = 0.0452. However, 12 patients in group I (12.9%) suffered postoperative ischemic stroke, a rate significantly higher than that of group II (1 patient, 1.7%; p = 0.0173). Any recurrence of PAF or atrial fibrillation with bradycardia was assessed at the time of stroke onset. Logistic regression analysis showed that the absence of warfarin therapy constituted a risk factor for post-CABG stroke associated with PAF (Odds 13.04, p = 0.027).
Conclusion: Warfarin therapy administered concomitantly with an antiplatelet agent dramatically reduced the incidence of ischemic stroke associated with postoperative PAF.

Keywords: persistent atrial fibrillation, coronary bypass surgery, warfarin, stroke

Introduction

Paroxysmal atrial fibrillation (PAF) is the most common complication following coronary artery bypass grafts (CABG). The reported incidence of PAF after CABG varies widely, with reported incidence ranging from 5% to 40%.[1)] PAF was recognized as a major cause of morbidity soon after the introduction of CABG, associated especially closely with ischemic stroke.[2)] Recent major advances in CABG, in general, and in post-CABG trials have shown that antiplatelet therapy and lipid lowering therapy can reduce graft complications, while warfarin had no effects.[3)] Thus, many cardiologists and cardiac surgeons have recently chosen to recommend the use of two types of antiplatelet agents in place of warfarin following coronary intervention or CABG.[4)] It is well known that warfarin therapy is dramatically effective in preventing stroke among patients presenting with atrial fibrillation, compared, in particular, to antiplatelet therapy.[5)] Nevertheless, whether warfarin actually prevents stroke among patients with PAF in the early stage after CABG remains unclear. This study sought to examine the efficacy of anticoagulant therapy in preventing ischemic

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stroke due to PAF after CABG, comparing it to antiplatelet therapy.

Patients and Methods

From January 2008 to June 2011, we administered isolated conventional CABG to 447 patients at our hospital. Post-operative PAF requiring defibrillation therapy emerged in 151patients (33.5%). Of these patients, 118 (78.1%) were male. The average of patient age was 70.1 ± 7.7 years, ranging from 45 to 87. The patients were divided into two groups: group I consisting of 93 patients administered two types of antiplatelet agents (aspirin 100 mg and ticlopidine 200 mg, daily) and group II consisting of 58 patients treated with 100 mg aspirin and warfarin. In group II, the international normalized ratio (INR) was maintained between 1.6 and 3.0. Individual consent for study participation was obtained from all patients, and institutional review board approval was provided before publication of this manuscript and reporting of information.

The surgical procedure: Cardiopulmonary bypass was implemented through the right atrium to the ascending aorta. The ascending aorta was clamped, and cold crystalloid cardioplegic solution administered to achieve cardiac arrest. We generally used the left internal thoracic artery, one radial artery, and the saphenous vein grafts. Drug selection depended on the random decision by the main operator or in charge resident doctor in the ward. All medication was initiated on the morning on the first postoperative day. All patients were routinely monitored through telemetry with continuous display of the ECG on multiple oscilloscopes simultaneously in the intensive or continuous care unit. The monitoring continued until the day of discharge. Significant postoperative PAF was defined as arrhythmias requiring defibrillation, either by intravenous medication or electrical defibrillation. Furthermore, patients were medically treated with digoxin (0.125 mg, daily) and beta-blocker (atenolol 25 mg, daily) following defibrillation therapy. A clinically diagnosed cerebrovascular accident was always confirmed by a magnetic resonance imaging scan.

We compared the two groups in terms of preoperative patient's profiles, CHADS2 scores, incidence of ischemic stroke during three months following surgery, and independent predictors for stroke associated with post-CABG PAF using univariate Fisher's exact test or unpaired Student's t-test. Statistical significance was defined as p value of less than 0.05. All analyses were conducted with Stat View software (SAS Institute Inc., Cary, NC).

Table 1 Patient profile

	Group I	Group II	P value
Age	69.8 ± 7.3	70.6 ± 8.3	NS
Sex	M74, F19	M45, F13	NS
Diabetes Mellitus	61 (65.6%)	49 (84.5%)	0.0141
Hypertension	90 (96.8%)	51 (87.9%)	NS
Hyperlipidemia	90 (96.8%)	54 (93.1%)	NS
Smoking	39 (41.9%)	22 (37.9%)	NS
Old Cerebral Infarction	16 (17.2%)	15 (25.9%)	NS
Chronic Renal Failure	11 (11.8%)	17 (29.3%)	0.0097
Carotid Stenosis	15 (16.1%)	22 (37.9%)	0.0034
Low Ejection Fraction	9 (9.7%)	5 (8.6%)	NS
CHADS2 score	2.24 ± 1.17	2.64 ± 1.22	0.0452

M: male; F: female; CHADS C: congestive heart failure; H: hypertension; A: age>75 years; D: diabetes; S: stroke

Results

The average age and gender were similar for the groups (**Table 1**), as was the prevalence of hypertension, hyperlipidemia, smoking history, and previous incidents of cerebral infarction. However, the prevalence of diabetes, chronic renal failure, and carotid arterial stenosis of 30 to 50 % were significantly higher in group II than that in group I (**Table 1**). CHADS2 scores were significantly higher in group II (2.64 ± 1.22) than that in group I (2.24 ± 1.17), suggesting that the estimated risk of stroke for patients in group II was significantly higher. Perioperative patient medications such as β-blockers, calcium antagonists, angiotensin receptor blockers, and statins were similar for both groups (**Table 2**). We found no differences in emergency surgeries, average numbers of grafts, cardiopulmonary bypass duration, or need for perioperative mechanical support by intra-aortic balloon pumping between the groups (**Table 3**). Requirements for electrical defibrillation therapy for PAF were also similar (**Table 3**). In group I, 12 patients (12.9%) exhibited a postoperative course complicated by stroke; in comparison, just one patient (1.7%) in group II suffered a stroke. The incidence of stroke was significantly higher in group I than in group II (P = 0.0452; **Table 3**). Eight patients suffered a stroke during postoperative days 7 through 9. Five patients suffered a stroke within 2 months following their discharge from

Table 2 Preoperative Medications

	Group I	Group II	P value
β-blocker	71(76.3%)	50(86.2%)	NS
Ca. Antagonist	83(89.2%)	48(82.8%)	NS
ARB	64(68.8%)	37(63.8%)	NS
Statin	93(100%)	56(96.6%)	NS

Ca: calcium; ARB: angiotensin receptor blocker

Table 3 Results

	Group I	Group II	P value
Emergency	38 (40.9%)	17 (29.3%)	NS
Graft Number	3.66 ± 0.80	3.41 ± 0.70	NS
CPBT(min)	90.4 ± 17.8	86.4 ± 15.5	NS
IABP	23 (24.7%)	8 (13.8%)	NS
PAF on set(day)	2.71 ± 1.36	2.47 ± 0.89	NS
Elect.DC	23 (24.7%)	13 (22.4%)	NS
Stroke	12 (12.9%)	1 (1.7%)	0.0452
Hospital death	1 (1.1%)	0	NS

CPBT: cardiopulmonary bypass time; IABP: intra-aortic baloon pumping; PAF: paroxysmal atrial fibrillation; Elec. DC: electrical difibrillation

the hospital. The conditions of 10 patients who suffered a stroke were complicated by recurrent PAF at the time at which the stroke occurred. We observed severe bradycardia with atrial fibrillation in 3 patients at the time of their stroke. Hospital mortality was one patient due to in group I (**Table 3**). Multivariate logistic regression analysis showed that therapy that excluded warfarin therapy was associated with the incidence of postoperative stroke only for patients with PAF after CABG (odds ratio: 13.037; 95% confidence interval: 1.340–126.874; P = 0.027; **Table 4**).

Discussion

In this study, the incidence of post-CABG PAF was roughly 33%, close to results reported in previous studies.[1,6–8] The condition increases both the risk for and severity of strokes and is associated with significant morbidity, mortality, decreased quality of life, and related health care costs. In a study by Almassi et al, postoperative PAF doubled the stroke rate.[9] Recently, many cardiac surgeons have begun recommending the use of two types of antiplatelet agents after CABG in place of warfarin.[4] This is despite warfarin's record as the therapy of choice for reducing the risk of stroke in PAF patients.[10] Although a number of randomized clinical studies have established the value of warfarin in reducing the risk of stroke in patients with atrial fibrillation,[11] no studies to date have demonstrated that warfarin therapy reduces early-stage post CABG stroke risks associated with PAF.

The American College of Cardiology/American Heart Association/ European Society of Cardiology and the American College of Chest Physicians guidelines recommend warfarin therapy for moderate-to-high stroke-risk patients in the absence of any compelling contraindications.[11–13] Several stroke risk stratification schemes have been established. Of these, the CHADS2 score, a user-friendly, reasonably accurate method for estimating annual stroke risks, is widely used.[14] The CHADS2 scheme is easily applied to assess a patient's baseline stroke risk and forms the basis for therapeutic recommendations. In the present study, CHADS2 scores for both groups tended to be above 2. Warfarin therapy is strongly recommended for patients with a CHADS2 score of 2 or higher.[12] However, for post-CABG patient management, two types of antiplatelet therapy are preferred over warfarin therapy, particularly for graft management. If defibrillation therapy results in resolution of post-CABG PAF, clinicians generally tend to hesitate to add warfarin therapy, due to the risk of bleeding complications in the early stages following CABG. Patients in the present study generally had CHADS2 score of 2 to 3, corresponding to an annual stroke risk of roughly 5 %.[15] In the absence of other complications, warfarin therapy is clearly indicated for all these patients. The results suggest warfarin therapy helped prevent strokes in these patients, even though the CHADS2 score for the warfarin group was higher than for antiplatelet therapy group. Connolly et al. have reported that warfarin therapy is superior to concomitant aspirin and clopidogrel therapy in preventing strokes among patients with atrial fibrillation.[16]

Drug selection in this study was determined by the main operator. Despite the similar average patient age, group II included more patients with latent atherosclerosis, such as diabetes, carotid stenosis, and chronic renal failure. Thus, the surgeons may have been more likely to select warfarin therapy for group II patients, a fortunate course of event with respect to stroke prevention. However, the CHADS2 sores of group I patients also tended to be above 2. Warfarin therapy is strongly recommended for such patients, as mentioned above. Post-CABG PAFs tend to cluster within the first 4 postoperative days.[8] In this study, post-operative PAFs also occurred at approximately 2 to 3 days after surgery. If defibrillation therapy successfully halted PAF, the patients were deemed to

Table 4 Risk Analysis using Fisher's exact test

n=151

	Yes (Y) / No (N)	Case / Subject	(%)	P value
Low Output	Y	0 / 14	(0.0)	p = 0.611
Syndrom	N	13 / 137	(9.5)	
Hemodyalisis	Y	0 / 28	(0.0)	p = 0.128
	N	13 / 123	(10.6)	
IABP	Y	2 / 31	(6.5)	p = 1.000
	N	11 / 120	(9.2)	
Carotid	Y	5 / 37	(13.5)	p = 0.308
Stenosis	N	8 / 114	(7.0)	
Warfarin	Y	1 / 58	(1.7)	p = 0.017*
therapy	N	12 / 93	(12.9)	
Body Surface	～<1.55	3 / 37	(8.1)	p = 0.196
Area	1.55～<1.65	3 / 32	(9.4)	
	1.65～<1.75	1 / 42	(2.4)	
	1.75～	6 / 38	(15.8)	
Emergency	Y	3 / 55	(5.5)	p = 0.376
	N	10 / 96	(10.4)	
Hypertension	Y	13 / 141	(9.2)	p = 0.602
	N	0 / 10	(0.0)	
Diabetes Mellitus	Y	9 / 110	(8.2)	p = 0.750
	N	4 / 41	(9.8)	
Hyper Lipiedmia	Y	13 / 144	(9.0)	p = 1.000
	N	0 / 7	(0.0)	
Smoking	Y	7 / 61	(11.5)	p = 0.379
	N	6 / 90	(6.7)	
Sex	M	12 / 119	(10.1)	p = 0.302
	F	1 / 32	(3.1)	
PAF when post	0, 1	0 / 18	(0.0)	p = 0.576
operative day	2	5 / 56	(8.9)	
	3	5 / 53	(9.4)	
	4～	3 / 24	(12.5)	
>75 years old	Y	3 / 48	(6.3)	p = 0.756
	N	10 / 103	(9.7)	
History of stroke	Y	3 / 31	(9.7)	p = 0.731
	N	10 / 120	(8.3)	
CHADS2	0～2	9 / 96	(9.4)	p = 0.770
	3～	4 / 55	(7.3)	

*：$p < 0.05$

present a lesser risk of stroke. However, 10 of the patients (more than 70%) whose condition was complicated by stroke suffered from recurrent PAF at the time of stroke onset. In three patients exhibiting severe bradycardia and atrial fibrillation at the time of stroke onset, the symptoms may be attributable to the side effects of antiarrhythmic therapy. A CARAF study has shown that 50% of patients with new onset atrial fibrillation presented with recurrent PAF within one year after defibrillation therapy.[17] The study also showed a 6% to 7% incidence of stroke in the follow-up period.[17] If a post-CABG patient presents with several risk factors for stroke, such as a CHADS2 score above 2, warfarin therapy should be recommended and continued until the absence of recurring PAF has been confirmed by repeated 24 hour ECG monitoring.

Conclusion

PAF may recur during the early post-CABG stages. Concomitant warfarin therapy and antiplatelet agent therapy is key to preventing ischemic strokes associated with postoperative PAF.

Disclosure Statement

Mitsumasa Hata and coauthors have no conflicts of interest.

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