Original Article

Prevalence of Thromboembolism and Predictors for Bleeding Complications in Patients who Underwent Valvular Heart Surgery with Warfarin Interruption: An Analysis in High-Risk Group

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Objective: Warfarin therapy is crucial to prevent thromboembolism in patients with valvular heart disease and prosthesis. For valvular heart surgery, it is still controversial to either bridging with heparin or no bridging of warfarin prior to the procedure. In clinical practice at the Queen Sirikit Heart Center, Khon Kaen University, no bridging therapy is the main treatment. The present study aimed to evaluate the prevalence of thromboembolism and predictors for bleeding complications in the high risk patients who underwent valvular heart surgery with warfarin interruption.

Materials and Methods: The present study was a retrospective cohort study and conducted at The Queen Sirikit Heart Center, Thailand. The present study period was between January 1st, 2015 and December 31st, 2015. The inclusion criteria were adults with high risk for thromboembolism who underwent valvular heart surgery and stop taking warfarin before surgery for three to five days. The main outcome was evidence of any thromboembolism or bleeding events at 90 days after surgery. Prevalence of thromboembolism and predictors for post-operative bleeding were analyzed.

Results: During the study period, there were 416 patients met the study criteria. Of those, 24 patients (5.76%) were in high-risk group. There were two patients (8.33%) had thromboembolism events: ischemic stroke. Among 24 patients who had warfarin interruption, 11 patients (45.83%) had bleeding events. Baseline characters and laboratory results of those with and without bleeding were comparable. There was no one significant factor between both groups: Bleed MAP score. The bleeding group had significantly higher score of 1 and 2 than the non-bleeding group (63.64% vs. 0% for score of 1 and 27.27% vs. 0% for score of 2; p<0.001).

Conclusion: Thromboembolism and bleeding in high risk patients who underwent valvular heart surgery with the non-bridging regimen were 8.33% and 45.83%. Bleed MAP score is suggestive for postoperative bleeding in this setting.

Keywords: Prevalence; Predictors; Valvular heart disease; Warfarin; Thromboembolism; Bleeding

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Warfarin is an oral anticoagulant for several medical conditions such as atrial fibrillation, embolic stroke, deep vein thrombosis, pulmonary embolism, or valvular heart disease or prosthesis. The challenge in warfarin treatment is its interruption during operative procedures. Approximately 10% to 20% of patients taking warfarin and underwent surgery may increase risk for thromboembolism, hemorrhage and death[1,2]. Warfarin interruption is typically stopped 5 days before an elective surgery. For patients with atrial fibrillation, valvular heart disease/prosthesis or thromboembolism, bridging anticoagulant prior to an elective surgery is challenging. Risk evaluation between thromboembolism or bleeding complications should be performed.

A database showed that the periprocedural thromboembolism with anticoagulant interruption in non bridging group was about 0.53% and increased to 0.92% with bridging anticoagulant[1]. Data on prevalence of thromboembolism or bleeding between bridging or non-bridging anticoagulant are varied[3,4]. Risk factors for postoperative bleeding included bridging therapy, renal failure, low body mass index, or aspirin use with an international normalized ratio (INR) >3.0[2,5]. Currently, it is still controversial to either bridging with heparin or not bridging in high risk patients who underwent major cardiac surgery such as valvular heart surgery. In clinical practice at the Queen Sirikit Heart Center, Khon Kaen University, no bridging therapy is the main treatment. This study aimed to evaluate the prevalence of thromboembolism and predictors for bleeding complications in the high risk patients

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who underwent valvular heart surgery with warfarin interruption.

Materials and Methods

The present study was a retrospective cohort study and conducted at the Queen Sirikit Heart Center, Khon Kaen University, Thailand. The study period was between January 1st, 2015 and December 31st, 2015. The inclusion criteria were: 1) adult patients with high risk for thromboembolism, 2) underwent valvular heart surgery, and 3) stop taking warfarin prior to the surgery for three to five days.

The high risk patients were defined as 1) prosthetic mitral/cage-ball or tilting disc aortic valve or previous TIA/ stroke within 6 months, 2) atrial fibrillation with CHADS2 score of 5 to 6 (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and stroke) or previous TIA/ stroke within 3 months or rheumatic valvular heart disease, 3) previous history of thromboembolism within 3 months, or severe thrombophilia.

Baseline characters, physical signs, and laboratory results of all eligible patients were recorded. Risk factors such as comorbidity, types of valvular heart disease, medication use especially warfarin and antiplatelet were recorded. The Bleed MAP score[1] was used to estimate perioperative bleeding risk in all patients. The Bleed MAP score is a summation of these following risks; prior bleeding (Bleed), mechanical mitral heart valve (M), active cancer (A), and low platelets (P). The score ranges from 0 to 4. There were two primary outcomes in the study; thromboembolism and bleeding within 90 days of operative procedures. The thromboembolism was defined as TIA/ stroke, deep vein thrombosis, pulmonary embolism and prosthetic valve dysfunction, while bleeding events were any bleeding.

Statistical analysis. Rates of thromboembolism and bleeding were calculated. Baseline and clinical characteristics of high risk patients with and without bleeding were compared using descriptive statistics. Data were presented as mean (SD) or median (range) for numerical variables with and without normal distribution. Categorical data were presented as number (percentage). Differences between the two groups for numerical variables were executed by independent t-test or Wilcoxon rank sum test where appropriate, while differences between two groups for categorical variables were computed by Chi-square test or Fisher exact test where appropriate. All data analysis was performed using STATA software (StataCorp LP, College Station, TX, USA).

Results

During the study period, there were 416 patients met the study criteria. Of those, 24 patients (5.76%) were in high-risk group. There were two patients (8.33%) had thromboembolism events: ischemic stroke. Both patients had the INR level when restarted warfarin of 1.43 and 1.44, respectively.

Among 24 patients who had warfarin interruption, 11 patients (45.83%) had bleeding events. Baseline characters and laboratory results of those with and without bleeding were shown in Table 1 and 2. There was no one significant factor between both groups: Bleed MAP score (Table 2). The bleeding group had significantly higher score of 1 and 2 than the non-bleeding group (63.64% vs. 0% for score of 1 and 27.27% vs. 0% for score of 2; $p<0.001$).

Discussion

The prevalence of thromboembolism was low at 8.33% but higher than the previous study (0.53%)[3]. Note that the sample size in this study was quite small (24 patients) compared with 22,334 patients in the review of 39 studies. While, bleeding events was higher than the previous study (45.83% vs. 2.80%). The higher rates of both thromboembolism and bleeding may be explained by study population. In the present study, only high risk patients were studied. Additionally, bridging therapy of warfarin was performed in the previous study.

Even though those with and without bleeding had comparable characteristics (Table 1 and 2) including INR level, those with higher Bleed MAP score had higher risk for bleeding (Table 2). As previously reported, this score is effective and should be used for bleeding monitoring in this setting[1].

There are some limitations in this study. First, sample size was smaller than calculated. Second, some data were missing particularly NSAIDs use due to retrospective study design. Third, the study protocol collected the INR levels at specific time such as two weeks, or three months after surgery. But, the INR levels were not scheduled in real practice as stated in the protocol. Finally, some clinical related factors were not studied[7-10]. Further prospective studies for patients with high-risk who underwent valvular heart surgery with warfarin interruption should be performed.

Conclusion

Thromboembolism and bleeding in high risk patients who underwent valvular heart surgery with the non-bridging regimen were 8.33% and 45.83%. Bleed MAP score is suggestive for postoperative bleeding in this setting.

What is already known on this topic?

Bridging therapy for warfarin is recommended in the high risk patients who underwent valvular heart surgery.

What this study adds?

The present study showed low rate of thromboembolism but quite high bleeding rate of high risk patients who underwent valvular heart surgery with non-bridging warfarin.

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Table 1. Baseline characters of high risk patients categorized by presence of post operative bleeding

Factors	No bleeding (n=13)	Bleeding (n=11)	p-value
Gender			0.408
Female	4 (30.8)	6 (54.5)	
Male	9 (69.2)	5 (45.5)	
Age, year*	52 (20 to 75)	49 (12 to 85)	0.505
Mean (SD) of BMI (kg/m^2)	21.3 (3.0)	20.2 (1.8)	0.346
Mean (SD) of Hb (mg/dL)	11.8 (1.6)	10.2 (2.9)	0.115
Mean (SD) of platelet ($/mm^3$)	251,307 (69,540)	283,000 (103,844)	0.383
Serum creatinine (mg/dL)*	0.9 (0.8 to 1.1)	1.1 (0.7 to 1.4)	0.907
Underlying condition			
Hypertension	1 (7.7)	2 (18.2)	0.576
Diabetes mellitus	2 (15.4)	1 (9.1)	0.999
Heart failure	5 (38.5)	6 (54.5)	0.431
Atrial fibrillation	3 (23.1)	5 (45.5)	0.390
Myocardial infarction	0 (0)	2 (18.2)	0.199
RWMA	2 (15.4)	4 (36.4)	0.357
Ejection fraction (%)	59.9 (11.3)	53.3 (20.4)	0.329
Valvular disease			
Mitral stenosis	1 (7.7)	1 (9.1)	0.999
Mitral regurgitation	4 (30.8)	1 (9.1)	0.327
Aortic stenosis	1 (7.7)	1 (9.1)	0.999
Aortic regurgitation	2 (15.4)	0 (0)	0.482
Etiology of valvular disease			
Rheumatic	3 (23.1)	2 (18.2)	0.999
Degenerative	0 (0)	1 (9.1)	0.458
Infective endocarditis	4 (30.8)	0 (0)	0.098
Prosthetic valve dysfunction	2 (15.4)	6 (54.5)	0.082
Prolapse valve	1 (7.7)	0 (0)	0.999
Procedure			
Mitral valve			0.096
Tissue	4 (50)	0 (0)	
Metallic	3 (37.5)	1 (16.7)	
Repair	1 (12.5)	5 (83.3)	
Aortic valve			0.999
Tissue	3 (60)	2 (50)	
Metallic	2 (40)	2 (50)	
Previous TIA	1 (7.7)	0 (0)	1.000
Previous Stroke	7 (53.8)	2 (18.2)	0.105
Previous smoking	2 (33.3)	1 (12.5)	0.538
Medications			
Aspirin	5 (38.5)	4 (36.4)	0.999
Clopidogrel	0 (0)	1 (9.1)	0.458

Data presented as number (percentage) unless indicated otherwise.
* Indicated median (range)
BMI = body mass index; Hb = hemoglobin; RWMA = regional wall motion abnormality; TIA = transient ischemic attack.

Table 2. INR level, time to stop/restart, dose of warfarin and Bleed MAP score of high risk patients categorized by presence of post operative bleeding

Factors	No bleeding (n=13)	Bleeding (n=11)	p-value
INR			
When stop warfarin	1.32 (0.95 to 3.96)	2.25 (0.97 to 6.79)	0.171
Before restart warfarin	1.36 (1.15 to 2.05)	1.65 (1.26 to 3.25)	0.692
At 2 weeks	2.42 (1.73 to 3.34)	2.74 (1.78 to 3.96)	0.999
At 3 months	2.50 (1.42 to 3.61)	2.27 (1.35 to 3.21)	0.999
Time to restart warfarin (day)	1 (1 to 2)	1 (0 to 3)	0.439
Dose			
When stop warfarin	0 (0 to 35)	17.5 (0 to 31)	0.999
Before restart warfarin	21 (10.5 to 35)	19.25 (0 to 31.5)	0.999
At 2 weeks	21 (5.25 to 35)	21 (0 to 52.5)	0.999
At 3 months	17.5 (10.5 to 35)	21 (0 to 35)	0.999
Bleed MAP score, n (%)			<0.001
0	13 (100)	1 (9.09)	
1	0 (0)	7 (63.64)	
2	0 (0)	3 (27.27)	

Data presented as median (range) unless indicated otherwise.
INR = International normalized ratio

Potential conflicts of interest

The authors declare no conflict of interest.

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