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Comparison of Fibrinolytic versus Surgical Therapy in the Treatment of Obstructive Prosthetic Valve Thrombosis: A Single-Center Experience

Dr. Ermis

Necip Ermis, MD,[1] Hakan Atalay, MD,[2] Hakan Altay, MD,[3] Muhammet Bilgi, MD,[3] Suleyman Binici, MD,[3] Alpay T. Sezgin, MD[3]

[1]Cardiology Department, nonu University, Turgut Özal Medical Center, Malatya; Departments of [2]Cardiovascular Surgery and [3]Cardiology, Baskent University, Medical School, Adana, Turkey

ABSTRACT

Objective: Prosthetic heart valve thrombosis (PVT) is a rare but severe cardiac condition. There are only a few data regarding comparison of the fibrinolytic and surgical approaches for the treatment of PVT. In this study, we compared the results of fibrinolytic therapy versus surgery in patients who presented to our institution with a diagnosis of obstructive-type PVT.

Methods: From January 2001 to August 2008 in our institution, 33 patients who met clinical and echocardiographic criteria for obstructive-type PVT were included in the study. Fifteen of these patients underwent fibrinolytic treatment with streptokinase, which consisted of an initial bolus of 250,000 U followed by 100,000 U/h. Eighteen patients were treated with surgery.

Results: The 2 groups had similar baseline characteristics, including New York Heart Association functional status, types and positions of prosthetic valves, international normalized ratio values, and presentation symptoms. Full hemodynamic success was achieved in 12 patients who underwent fibrinolytic therapy and in 15 patients in the surgery group. The mean (±SD) streptokinase infusion time was 17.8 ± 11.1 hours. Two major hemorrhages and 2 cases of systemic embolism were observed in the fibrinolytic group. The 2 groups did not differ with respect to mortality rate (P = .79). The duration of hospitalization was longer in the fibrinolytic group than in the surgery group (10.7 ± 6.6 days versus 6.9 ± 6.7 days, P = .045).

Conclusions: Although fibrinolytic therapy is generally recommended for the treatment of PVT for specific patient groups, our results suggest that it may be as efficacious and safe as surgery, depending on patient selection.

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Correspondence: Necip Ermis, MD, İnönü University, Turgut Özal Medical Center, Cardiology Department, Elazıg yolu 15.km, 44100, Malatya, Turkey; 90-422-3410660 ext 4508; fax: 90-422-341-07-28 (e-mail: necipermis@yahoo.com).

INTRODUCTION

Prosthetic heart valve thrombosis (PVT) is a complication attributable to any type of thrombus attached to a mechanical prosthetic valve that causes dysfunctional hemodynamics or systemic embolization [Edmunds 1996]. Recent-onset dyspnea, fatigue, or other signs of systemic embolization are clinical findings of PVT. It is a rare but life-threatening condition, depending on its generation and biocompatabilities, the location of the prosthesis valve, and the adequacy of anticoagulation therapy [Edmunds 1982; Thorburn 1983; Kontos 1989]. Although surgery is the traditional treatment option, surgical mortality rates range from 4.7% in low-risk groups to 37% to 54% in high-risk groups [Husebye 1983; Deville 1987; Montero 1989; Deviri 1991; Martinell 1991; Roudaut 2003b; Durrleman 2004].

Beginning with the first report in 1971 regarding the application of fibrinolytic therapy for a thrombus stuck on a tricuspid valve [Luluaga 1971], more than 500 left-side prosthetic valve thrombi have been successfully treated with fibrinolytic therapy as an alternative to surgery [Reddy 1994; Agrawal 1997; Gupta 2000; Ozkan 2000; Kumar 2001; Lengyel 2001; López 2002; Roudaut 2003a; Tong 2004; Lengyel 2005; Cáceres-Lóriga 2006a]. Although the success rate of fibrinolytic therapy for treating PVT is 77% to 90%, it is also associated with mortality, embolism, and bleeding risk (2.5%-11.8%, 4%-15%, and 2.9%-8.3%, respectively).

Currently, there are only a few data regarding comparison of the fibrinolytic and surgical approaches for the treatment of PVT [Lengyel 2001; Azpitarte 2001]. Therefore, our aim was to compare the results of fibrinolytic therapy versus surgery in patients who presented to our institution with a diagnosis of obstructive-type PVT.

METHODS

Patients

From January 2001 to August 2008 in our institution, 33 patients who met the clinical and echocardiographic criteria for obstructive-type PVT were included in the study. The patients' symptoms, times of symptom onset, New York Heart Association (NYHA) functional capacities, and findings of systemic embolization were recorded. In addition, we also recorded the types of anticoagulants and antiplatelet

agents used, international normalized ratio (INR) values, and heart rhythm data at admission. Data regarding implantation, type, size, and position of the prosthetic heart valves were also obtained from the hospital registries. Over the last 7 years in our institution, 18 patients with PVT were treated with surgery, and 15 patients underwent fibrinolytic therapy. The treatment strategy was based on the presence of comorbid conditions, the physician's preferences, and the availability of cardiac surgery at the time.

Diagnosis

Depending on the clinical suspicion, PVT was confirmed with transthoracic echocardiography and fluoroscopic examinations. All patients later underwent transesophageal echocardiographic (TEE) examination by an experienced echocardiographer for a detailed investigation and to plan the treatment strategy. The efficacy of fibrinolytic treatment was evaluated by a TEE evaluation repeated 24 hours after the completion of fibrinolytic therapy. The criteria for successful thrombolysis were TEE-documented disappearance of thrombus, normalization of leaflet mobility, and normalization of the transvalvular gradient and prosthetic valve area.

Fibrinolytic Therapy

Only streptokinase therapy with a 30-minute loading dose of 250,000 U followed by 100,000 U/h was used as fibrinolytic therapy. Streptokinase infusion was continued until a completely successful response was obtained; otherwise, streptokinase infusion was lengthened up to 48 hours. Patients with a bleeding tendency, hemorrhagic cerebral infarcts, large thrombus burdens at the prosthetic valve, or thrombosis in the left atrium did not undergo fibrinolytic therapy. Intravenous heparin infusion was discontinued during fibrinolytic therapy. Following successful fibrinolytic therapy, heparin and warfarin therapies were restarted; heparin infusion was continued until an INR value >2.5 was achieved.

Surgery

Surgery was performed as the first-line therapy in 18 patients. The operative procedure was either valve re-replacement with a mechanical valve in 15 patients and declotting/pannus excision in 3 patients.

Complications

Major bleeding was defined as necessitating blood transfusion or a decrease in the blood hemoglobin concentration of >2 mg/dL. Detailed neurologic and cerebral computed tomographic examinations were performed if neurologic symptoms occurred during or after fibrinolytic therapy.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows (version 11.0; SPSS, Chicago, IL, USA). Continuous variables were expressed as the mean ± SD. Differences between groups for continuous variables were tested with the Student *t* test for unpaired data after normality was demonstrated. Otherwise, a nonparametric test (Mann-Whitney *U* test) was used. Between-group differences in categorical factors were compared with the chi-square test or the Fisher exact test, when appropriate. Logistic regression models were used to construct a multivariate model for predicting mortality. A stepwise selection technique was used to identify factors for the final multivariate model. A *P* value <.05 were considered statistically significant.

Table 1. Baseline Characteristics of the Patients*

Variable	Thrombolytic Treatment (n = 15)	Surgery (n = 18)	*P*
Age, years	51.3 ± 16.3	53 ± 13.6	.66
Male sex, n	7 (46.7%)	6 (33.3%)	.53
Prosthetic heart valve position, n			
Mitral	11 (73.4%)	13 (72.2%)	.94
Aortic	2 (13.3%)	3 (16.7%)	.87
Tricuspid	2 (13.3%)	2 (11.1%)	.93
Type of prosthetic valve, n			
Bileaflet	10 (66.7%)	10 (55.6%)	.79
Monoleaflet	5 (33.3%)	8 (44.4%)	
Time since valve replacement, mo	66 ± 40.8	74.4 ± 50.3	.15
Time between symptom onset and diagnosis, d	9.9 ± 17	28.8 ± 35.9	.005
Inadequate anticoagulation, n			
INR <2.5	11 (73.3%)	12 (66.7%)	.94
INR ≥2.5	4 (26.7%)	6 (33.3%)	
Aspirin use, n	10 (66.7%)	7 (38.9)	.11
Atrial fibrillation, n	7 (46.7%)	12 (66.7%)	.34
NYHA functional class ≥III, n	13 (86.7%)	13 (72.2%)	.32
Presenting symptoms, n			
Dyspnea	13 (86.7%)	14 (77.8%)	.68
Angina	2 (13.3%)	1 (5.6%)	.71
Cerebrovascular accident	1 (6.7%)	1 (5.6)	.96
Shock	3 (20%)	2 (11.1%)	.87
Heart rate on presentation, beats/min	96.1 ± 23.6	93.2 ± 19.5	.94
Systolic blood pressure, mm Hg	107.3 ± 15.8	111 ± 16.1	.91

*Data are expressed as the mean ± SD or number (percent). INR indicates international normalized ratio; NYHA, New York Heart Association.

RESULTS

The baseline characteristics of the patients are summarized in Table 1. In both groups, the main clinical signs at the time of presentation were dyspnea, angina, cerebrovascular accident, and shock. There were no significant differences between the fibrinolytic therapy and surgery groups with respect to baseline characteristics, except for the time between symptom onset and diagnosis, which was significantly longer in the surgery group (Table 1).

Table 2. Prosthetic Heart Valve Type and Position with Hemodynamic Measurements at Baseline and after Thrombolytic Treatment in the Thrombolytic Group*

Case No.	Valve Type and Position	Mean Gradient at Baseline, mm Hg	Mean Gradient after Thrombolytic Treatment, mm Hg	Total Thrombolytic Time, h
1	Mitral, SJ, BL	24	7.4	20
2	Mitral, SJ, BL	22	4.2	15
3	Mitral, MT, MO	6	5.4	14
4†	Aortic, MT, MO	86	—	2
5	Mitral, ATS, BL	11	5	24
6	Mitral, CM, BL	26	6.8	14
7	Tricuspid, MT, MO	24	24	48
8	Mitral, ATS, BL	25	6.2	14
9	Mitral, ATS, BL	16	5.3	14
10	Mitral, SJ, BL	20	4	14
11	Tricuspid, MT, MO	13.7	5.3	36
12	Mitral, SO, BL	13	5	14
13	Mitral, CM, BL	8	6	14
14	Aortic, MT, MO	54	18	14
15†	Mitral, SO, BL	14	—	10

*SJ indicates St. Jude Medical; BL, bileaflet; MT, Medtronic Hall; MO, monoleaflet; ATS, Medtronic ATS Medical; CM, CarboMedics; SO, Sorin.
†Patient died.

Efficacy of Fibrinolytic Therapy

Values for baseline and posttreatment hemodynamic parameters for the patients in the fibrinolytic therapy group are presented in Table 2. The mean (±SD) streptokinase infusion time was 17.8 ± 11.1 hours. Two major hemorrhages and 2 cases of systemic embolism were observed in the fibrinolytic therapy group. There was no difference between the 2 groups with respect to the mortality rate (P = .79). The duration of hospitalization was longer in the fibrinolytic therapy group than in the surgery group (10.7 ± 6.6 days versus 6.9 ± 6.7 days, P = .045). Full fibrinolytic success was achieved in 12 cases (80%). One patient with tricuspid valve thrombus did not respond to fibrinolytic therapy and was successfully treated with surgery. Failure of fibrinolytic treatment was observed in 2 patients with a monoleaflet prosthetic valve and in 1 patient with a bileaflet prosthetic valve.

Safety of Fibrinolytic Treatment

Overall, hemorrhagic complications were observed in 4 patients. Two of these cases involved major bleeding: one patient with a subdural hemorrhage who was successfully treated with surgery and the other with a gastrointestinal hemorrhage successfully treated medically. Systemic embolism was observed in 2 patients (stroke and coronary emboli). These patients were in NYHA classes III and IV at baseline; they did not respond to fibrinolytic therapy and died. Logistic regression analysis revealed no independent association between complications and such variables as age, sex, systolic blood pressure, heart rate, baseline INR value, NYHA functional class, history of stroke, and thrombotic valve type. During 3.7 ± 2.1 years of follow-up, rethrombosis was observed in 1 patient who was treated successfully with streptokinase.

Efficacy and Safety of Surgery

An uneventful hospital course was achieved in 14 patients (Table 3). A cerebral embolus observed in 1 patient led to partial disability. Three patients in NYHA functional class IV died from low cardiac output syndrome. Two of these patients had bileaflet prostheses, and the third had a monoleaflet prosthesis, all in the mitral position. Logistic regression analysis revealed that only NYHA functional class was associated with mortality (P = .04; odds ratio, 2.2). There was no association between death and such variables as age, sex, systolic blood pressure, heart rate, baseline INR value, and thrombotic valve type.

The mean duration of hospitalization in the surgery group was 6.9 ± 6.7 days. During 3.5 ± 1.7 years of follow-up, rethrombosis of the prosthetic heart valve was observed in 1 patient; this patient died before other therapy could be applied.

Comparison of the Efficacies for the 2 Treatment Strategies

There were no significant differences between the 2 treatment strategies regarding the incidence of death and stroke (Table 4). The rethrombosis rates for prosthetic heart valves also were not different. The duration of hospitalization was longer in the fibrinolytic therapy group than in the surgery group (10.7 ± 6.6 days versus 6.9 ± 6.7 days; P = .045). A longer duration of hospitalization in the fibrinolytic therapy

Table 3. Comparison of Success Rates for Thrombolytic Therapy and Surgery

Prosthetic Heart Valve	Thrombolytic Group, n	Surgery Group, n	*P*
Mitral	10/11 (91%)	10/13 (76.9%)	.15
Aortic	1/2 (50%)	3/3 (100%)	.4
Tricuspid	1/2 (50%)	2/2 (100%)	.5
Total	12/15 (80%)	15/18 (83.3%)	.49

group was related to the time needed for optimizing INR values and the presence of comorbidities.

DISCUSSION

PVT is a severe cardiac disorder with a high risk for mortality. The principal causes of this undesirable condition are generally inefficient anticoagulation therapy, endocardial fibrosis related to the operation technique, and a reaction against the prosthetic heart valve or suture material [Ozkan 2000; Roudaut 2003a, 2003b; Tong 2004; Cáceres-Lóriga 2006a, 2006b]. Additionally, left atrial dilatation, atrial fibrillation, left ventricular systolic dysfunction, replacement of >1 prosthetic valve, pregnancy, and traumatic replacement of a prosthetic valve may be other risk factors for PVT [Husebye 1983; Cáceres-Lóriga 2006b]. The position of the prosthetic valve also affects thrombogenicity because prostheses in the tricuspid position carry a 20-fold greater risk for thromboembolism than prostheses in the mitral or aortic position [Edmunds 1982; Thorburn 1983; Kontos 1989].

The treatment modalities for PVT are surgery, fibrinolysis, and effective anticoagulation treatment. Although surgery is usually the favored therapeutic approach, it is associated with high mortality rates for obstructive left-side PVT, depending on the clinical status [Husebye 1983; Deville 1987; Montero 1989; Deviri 1991; Martinell 1991; Roudaut 2003b; Durrleman 2004]. The mortality rate for surgery was 16% in our study, and all of the deaths were for patients in NYHA functional class IV. The lowest perioperative mortality rate was reported by Deviri et al [1991]. In that study, the early-mortality rate for 100 patients who underwent surgical treatment for obstruction of various types of mechanical valves was 12.3%. The perioperative mortality rate was 17.5% for patients in NYHA functional class IV and 4.7% for patients with symptoms of NYHA functional classes I to III [Deviri 1991].

Recently, fibrinolytic treatment has evolved as an alternative therapy for PVT, especially for patients at high risk for surgical mortality, and several fibrinolytic protocols have been used over the past 3 decades. There is no universally accepted consensus, however, regarding the optimal fibrinolytic agent and treatment protocol for PVT, although streptokinase is a widely used agent (61%) [Reyes-Cerezo 2008].

The success rates of fibrinolytic therapy have ranged from 67% to 90% for left-side PVT [Reddy 1994; Agrawal 1997; Gupta 2000; Ozkan 2000; Kumar 2001; Lengyel 2001; López 2002; Roudaut 2003a; Tong 2004; Lengyel 2005; Cáceres-Lóriga 2006a]. In accordance with these previous reports, we observed an 80% success rate in our study. Gupta et al [2000] reported a complete hemodynamic response rate of 81.8% for 110 consecutive patients, with a 19% systemic embolism rate. Roudaut et al [2003a] reported similar success and mortality rates for 110 consecutive patients with PVT treated with streptokinase, urokinase, and recombinant tissue-type plasminogen activator infusion. Complications were observed in 25.2% of the patients: 15% of the patients experienced systemic embolism, 11.8% of the patients died, and 4.7% of the patients had major bleeding. A meta-analysis of 515 patients found that a successful hemodynamic response was achieved in 84% of patients, with rates of mortality, systemic embolism, and major hemorrhage of 5%, 9%, and 3%, respectively [Lengyel 2005]. Therefore, systemic embolism and intracranial hemorrhage are the main complications that limit the use of fibrinolysis for the treatment of PVT.

Table 4. Comparison of Complication Rates for Thrombolytic Therapy and Surgery in Patients with Prosthetic Valve Thrombosis

Types of Complications	Thrombolytic Treatment (n = 15)	Surgery (n = 18)	*P*
Cerebral embolism, n	1 (6.7%)	1 (5.6%)	.71
All embolic complications, n	2 (13.3%)	1 (5.6%)	.43
Central nervous system bleeding, n	1 (6.7%)	0 (0%)	.46
Death, n	2 (13.3%)	3 (16.6%)	.79
Total hospitalization time, d	10.7 ± 6.6	6.9 ± 7.7	.045
Rethrombosis, n	1 (6.7%)	1 (5.6%)	.71

Although we have used the traditional regimen of a slow streptokinase infusion for our cases (a 30-minute loading dose of 250,000 U followed by 100,000 U/h), a few reports have described the use of thrombolytic medications other than streptokinase and different dosing regimens. Biteker et al reported an overall success rate of 84% and a 3% mortality rate in the TROIA Trial [Biteker 2008]. That study compared different thrombolytic medications (including tissue plasminogen activator [tPA], streptokinase, and tPA plus streptokinase) and different dosing regimens. Although mortality and success rates were similar for the groups, a lower tPA dose (25 mg) and slower infusion rates (6 hours) were found to be superior to the traditional thrombolytic protocols, with no mortality and fewer embolic and hemorrhagic complications. Actually, we have used thrombolytic medications other than streptokinase in a few cases at our clinic; however, we excluded these cases to obtain a homogeneous group for this study.

The presence of atrial fibrillation, a history of ischemic stroke, and a large mobile thrombus visible with TEE are predictors of complications during fibrinolysis treatment [Gupta 2000; Tong 2004]. In our study, thrombolytic therapy was preferred if the patient had comorbidities (an advanced age or additional disorders that make surgery very high risk, such as chronic obstructive lung disease, decompensated

heart failure, systemic and other disorders, and so forth). It was also used in patients for whom surgery was otherwise the first choice but who had to undergo fibrinolytic therapy because they were critically ill and a surgical team was unavailable at the time. Additionally, if the echocardiographic appearance of the thrombus (TEE evidence of a small soft mass without accompanying left atrial thrombus) convinced the physician that the patient might benefit from thrombolytic therapy, thrombolytic therapy was preferred to surgery. In the multicenter PRO-TEE study, a thrombus size of ≥0.8 cm^2 according to TEE imaging was found to be a significant predictive factor for systemic embolism, irrespective of NYHA functional class [Tong 2004]. Therefore, measurement of thrombus size by TEE is recommended for risk stratification in the management of PVT. In our cases, although we did not measure the thrombus burden in every patient, the presence of a large mobile thrombus on the prosthetic heart valve and a coexisting left atrial thrombosis were accepted as contraindications for fibrinolysis because of the higher embolization risk [Ozkan 2000; Tong 2004]. NYHA functional class has not been accepted in most studies as a predictor for complications and/or success for fibrinolysis, whereas it is an important factor in the surgical treatment of prosthetic valve endocarditis [Ozkan 2000; Tong 2004]. Our results were also in agreement with these reports. Rethrombosis of prosthetic heart valves after fibrinolytic therapy (frequency range, 11.1%-27.8%) may be another problem, and success rates for retreatment with fibrinolysis range from 70% to 91% [Reddy 1994; Gupta 2000; Ozkan 2000; Kumar 2001; Lengyel 2001; Roudaut 2003a; Cáceres-Lóriga 2006a]. In our study, rethrombosis occurred in 1 patient after fibrinolytic therapy, and it was successfully treated with repeat fibrinolytic therapy.

There are limited data regarding the comparison of outcomes after fibrinolytic therapy versus surgical therapy for the treatment of PVT. Azpitarte et al [2001] reported complete success with fibrinolytic treatment in 19 PVT patients, whereas 5 of 14 patients died in the surgery group. In a registry of 59 patients with prosthetic valve endocarditis, Lengyel and Vandor [2001] reported high success and low mortality rates with fibrinolysis (84.4% and 6.2%, respectively), compared with the success and mortality rates after surgery (66.7% and 33.3%, respectively). In that study, fibrinolysis was shown to be superior to surgery for obstructive PVT, especially for patients in NYHA class IV. Although these 2 small studies indicated higher success rates with fibrinolysis than with surgical therapy, we observed the 2 groups to have similar success and complication rates. The accumulating evidence suggests that surgery should be considered, especially in patients with an accompanying left atrial thrombus, active bleeding, a history of intracranial bleeding, or any evidence of ischemic stroke within the previous 4 hours to 6 weeks or during the early postoperative period after valve replacement [Cevik 2010].

Limitations

The small sample size and the retrospective design are the main limitations of our study. In addition, the selection criteria for fibrinolysis therapy were based on the clinical judgment of the physicians and the availability of a cardiac surgery team.

CONCLUSION

Although fibrinolytic therapy is generally applied to critically ill patients with comorbidities, severely impaired cardiac function, and right-sided PVT, our results suggest that fibrinolytic therapy may be as efficacious and safe as surgery, depending on patient selection. In selected cases, this treatment strategy could be preferred, owing to low complication and high success rates. Therefore, the treatment strategy for PVT should be individualized; however, further large-scale studies and experience are needed to clearly define the best therapeutic option.

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