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Case Report

Long-term thromboprophylaxis in metallic aortic valve prosthesis using oral nattokinase-A case report

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ABSTRACT

Background: Oral anticoagulation with a vitamin K antagonist like warfarin is the standard of care for thromboprophylaxis after cardiac valve replacement. However warfarin requires strict monitoring of INR to avoid bleeding.[1] Bleeding is a major concern with warfarin, particularly in those at high risk.[2]
Nattokinase is an enzyme obtained from natto, a cheese-like food made of soybeans fermented with Bacillus subtilis, which has been consumed as a traditional food in certain Asian countries for more than 2000 years.Recent research has demonstrated that nattokinase has potent fibrinolytic activity and antithrombotic action.[3]
Case Summary: We present a case of a 37-year-old male who had undergone aortic valve replacement using a metallic prosthetic valve for rheumatic heart disease associated severe aortic regurgitation and has been maintained on oral nattokinase therapy for prophylaxis against thromboembolic complications post cardiac wall replacement since the last 12 years.
Discussion: This case highlights the role of oral nattokinase for thromboprophylaxis in valve prosthesis and other prothrombotic states. This case report presents the first documented case where oral nattokinase has been successfully used for long-term thromboprophylaxis in metallic aortic valve prosthesis.
Key Messages: We present a case of a 37-year-old male who had undergone aortic valve replacement using a metallic prosthetic valve for rheumatic heart disease associated severe aortic regurgitation and has been maintained on oral nattokinase therapy for prophylaxis against thromboembolic complications post cardiac wall replacement since the last 12 years.
This case highlights the role of oral nattokinase for thromboprophylaxis in valve prosthesis and other prothrombotic states. This case report presents the first documented case where oral nattokinase has been successfully used for long-term thromboprophylaxis in metallic aortic valve prosthesis.

1. Introduction

Oral anticoagulation with a vitamin K antagonist like warfarin is the standard of care for thromboprophylaxis after cardiac valve replacement. However warfarin requires strict monitoring of INR to avoid bleeding.[1] Bleeding is a major concern with warfarin, particularly in those at high risk.[2]

Nattokinase is an enzyme obtained from natto, a cheese-like food made of soybeans fermented with Bacillus subtilis, which has been consumed as a traditional food in certain Asian countries for more than 2000 years.Recent research has demonstrated that nattokinase has potent fibrinolytic activity and antithrombotic action.[3]

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2. Case History

A 37-year-old male had undergone aortic valve replacement using a metallic prosthetic valve for rheumatic heart disease-associated severe aortic regurgitation 12 years ago at the age of 25 years. Post valve replacement the patient was started on lifelong oral warfarin 5 mg daily (with additional 2.5 mg doses twice per week) for prophylaxis against thromboembolism as standard of care. Other concomitant medications started were inj. penicillin 1.2 million units every 21 days, tablet digoxin 0.25 mg once daily (five days a week), tablet Furosemide 40 mg once daily and tablet ranitidine 150 mg twice daily. However within a week of initiating warfarin the patient developed significant nasal bleeding causing severe emotional distress and fear to the patient. The patient sought other treatment options with low bleeding risk. Hence the patient was shifted to tablet nattokinase 2000 fibrinolytic units (FU) twice daily, 1 week post aortic valve replacement, which he is continuing till date.

The patient was followed up annually thereafter. Echocardiography performed 10 months post valve replacement shows metallo-prosthetic aortic cusps with normal opening, absence of aortic regurgitation, mild mitral regurgitation, absence of mitral stenosis, no perivalvular/paravalvular leakage at an aortic level and no clot or vegetation with a LVEF of 55%. The patient gives a history of good compliance with oral nattokinase throughout for 12 years. The patient does not give any history of bleeding manifestations or other side effects since starting oral nattokinase.

The patient hasa history of juvenile rheumatoid arthritis since the age of 14. The patient also has a history of ankylosing spondylitis since the age of 23. The HLAB27 marker was positive. However he is currently not on any medication for the same. The patient underwent right total hip replacement 16 months ago for severe hip ankylosis. His PT and INR before surgery were 11.7 seconds and 0.96 respectively. Nattokinase was withheld 7 days prior to surgery and the patient was put on subcutaneous LMWH. Oral Nattokinase was restarted on the 4th day post-surgery after stopping LMWH.

Echocardiography done 12 years after aortic valve replacement shows a normally functioning aortic prosthesis in situ position with no peri/para valvular leak, grade 2 mitral regurgitation with no mitral stenosis, mild pulmonary hypertension, and a left ventricular ejection fraction of 60%. There was no evidence of vegetations, clots or pericardial effusion. Repeat echocardiography done 8 months later shows the same findings and no pulmonary hypertension.

Recent blood investigations show a normal hemogram with a hemoglobin level of 14.6 gm%. His renal function and liver function tests were normal with a creatinine level of 0.6 mg/dl and SGOT, SGPT levels of 23 U/L and 15 U/L, respectively. The Lipid profile shows a total cholesterol level of 185 mg/dl, HDL cholesterol 44 mg/dl, LDL cholesterol 121 mg/dl, VLDL cholesterol 20 mg/dl and triglyceride 100 mg/dl. Urine and Stool analysis do not show any occult bleeding. At the time of writing this report, the patient did not have any symptoms or signs of bleeding manifestations or any symptoms of thrombosis.

The recent coagulation profile of the patient along with the reference values has been summarised in Table 1.

Table 1: Coagulation profile of the patient

Parameter	Patient value	Normal reference value
Bleeding time	2 minutes 20 seconds	2-6 minutes
Clotting time	6 minutes 30 seconds	3-9 minutes
Partial thromboplastin time	29.8 seconds	24.7-26.22 seconds
Prothrombin time	11.5 seconds	11.3-12.3 seconds
INR	1.03	0.8-1.2
D-dimer level	0.28 μg/ml	<0.5 μg/ml
Plasma Factor VII activity	76.10%	70.0-120.0
Plasma Factor VIII activity	88%	60-150%
Plasma Antithrombin activity	91%	70-122%
Plasma Fibrinogen level	467 mg/dl	200-400 mg/dl
Plasminogen activator inhibitor-1 antigen level	26.7 ng/ml	4-43 ng/ml

Oral anticoagulation with a vitamin K antagonist like warfarin is the standard of care after cardiac valve replacement. However warfarin requires strict monitoring of INR to avoid bleeding.[1] The initial dosing of warfarin varies widely for different patients and is influenced by factors including age, race, body weight, sex, concomitant medications, comorbidities and genetic factors (CYP2C9 and VKORC1 genotypes). Bleeding is a major concern with warfarin, particularly in those at high risk.[2]

To the best of our knowledge, the long term use of Nattokinase for thromboprophylaxis in metallic valve prosthesis, even though off label indication, has not been reported till date. Nattokinase is an enzyme obtained from Natto, a cheese-like food made of soybeans fermented with bacillus subtilis, which has been consumed as a traditional food in certain Asian countries for more than 2000 years. Nattokinase is considered to be a relatively safe, low cost, and natural supplement for the treatment of cardiovascular diseases.[3] Animal[4,5] and human[6–8] trials have demonstrated that Nattokinase provides support to the cardiovascular system through its anticoagulant and fibrinolytic property.

Nattokinase is known to degrade fibrin directly and also increase the release of tissue plasminogen activator

(tPA) with a subsequent increase in the formation of plasmin. Plasminogen activator inhibitor 1 (PAI-1) is the primary inhibitor of tPA and regulates fibrinolytic activity. Nattokinase is known to enhance fibrinolysis through cleavage and inactivation of PAI-1 and thus enhance t-fibrin clot lysis. Nattokinase also enhances the production of thrombolytic agents such as urokinase through the conversion of prourokinase to urokinase. Additionally, Nattokinase is known to be capable of blocking thromboxane formation resulting in an inhibition of platelet aggregation.[3] The mechanism of action has been summarised in Figure 1.

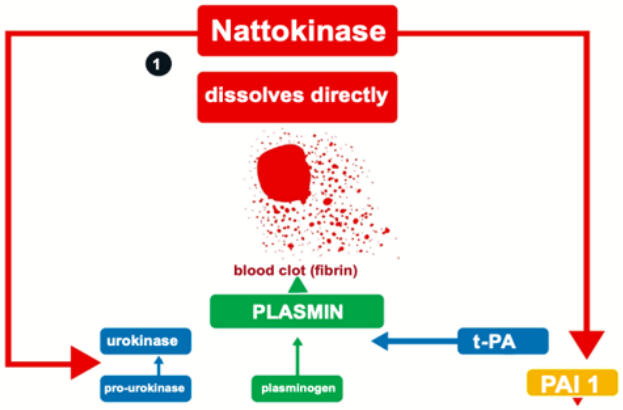

Fig. 1: Mechanism of action of Nattokinase. Nattokinase dissolves blood clots by directly hydrolyzing fibrin and plasmin. It converts endogenous prourokinase to urokinase (uPA). Additionally, it degrades plasminogen activator inhibitor (PAI-1) and increases the level of tissue plasminogen activator (t-PA). *(Adopted from Selvarajan E, Bhatnagar N. Nattokinase: an updated critical review on challenges and perspectives. Cardiovasc Hematol Agents Med Chem. 2017 Dec 7.)*[9]

Elevated levels of factor VII and VIII are associated with atheir potential to trigger a blood coagulation cascade. In a human trial, 45 subjects consisting of three groups (healthy volunteers, patients with cardiovascular risk factors, and patients undergoing dialysis) were orally administered two capsules of nattokinase (2000 FU/capsule) daily. After two months, a significant decrease in factor VII, factor VIII, and fibrinogen was observed in all of the groups. No notable adverse effects were detected during the two-month trial.[10]

A Japanese study examined the efficacy of Nattokinase as an to low molecular weight heparin & antiplatelet agents in the prevention of stroke progression in 24 patients with acute ischaemic stroke and showed beneficial effects in these patients after oral administration.[11]

The above clinical studies highlight the antithrombotic, fibrinolytic/anticoagulant properties of nattokinase, which has also been seen in this case report. Apart from this, clinical evidence suggests that nattokinase has also been found to have antihypertensive,[12] antihyperlipidemic[13] and antiatherosclerotic[13] properties.

3. Conclusion

This case report presents the first documented case where oral nattokinase has been used successfully for thromboprophylaxis in metallic aortic valve prosthesis for a period of 12 long years. Even though this isolated case report may not provide enough evidence, 12 years of uneventful thromboprophylaxis for metallic valve prosthesis, certainly merits deeper considerations and research by investigators for exploring the efficacy of nattokinase for similar conditions and other prothrombotic states.

4. Source of Funding

None.

5. Conflict of Interest

None.

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