

Dabigatran tedavisi sonrası biyoprotez mitral kapakta ciddi tromboz

Severe thrombosis of bioprosthetic mitral valve after dabigatran therapy

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Özet- Kırk bir yaşında kadın hasta hastanemize subfebril ateş, nefes darlığı ve halsizlik yakınmaları ile yatırıldı. Transtorasik ekokardiyografide ciddi mitral yetersizliği ve ileri tetkiklerde transözofajiyal ekokardiyografi ile (TÖE) mitral ön yaprakçığı üzerinde 7 mm boyutunda vejetasyon saptandı. Kan kültürleri negatifti ve 45 günlük 12 gr/gün ampicilin-sulbaktam tedavisi sonrasında vejetasyon kayboldu. Ancak devam eden ciddi mitral yetersizliği ve kapak deformitesi nedeniyle metalik mitral kapak protezi implante edildi. Ameliyat sonrasında subfebril ateş ve nedeniyle TÖE tekrarlandı ancak kapak normaldi ve kan kültürleri negatifti. Enfektif endokarditin tekrarlama olasılığı nedeniyle ameliyat öncesi başlanan antibiyotik tedavisi intravenöz olarak 21 gün, oral olarak da yedi gün sürdürüldü. Daha sonra hasta poliklinikte takip edilmeye başlandı ancak bu dönemde INR düzeyleri oldukça kararsızdı. Yeniden başlayan subfebril ateş nedeniyle hasta tekrar hastaneye yatırıldı ve ekokardiyografisinde vejetasyon saptandı. Kan kültürleri negatifti. Vankomisin-rifampisin-gentamisin tedavisi başlandı ancak bu tedavi altında önce felç, birkaç gün sonrasında da geçici iskemik atak gelişti. Tekrarlanan ekokardiyografide vejetasyonda büyüme saptandı. Acil olarak kapak ameliyatı planlandı ve biyoprotez kapak yerleştirildi. Mikrobiyoloji bölümünün önerisiyle önceki antibiyotik

Summary- A 41-year-old female was admitted to our hospital with subfebrile fever, dyspnea and malaise. Transthoracic echocardiography demonstrated severe mitral valve regurgitation, and further examination with transesophageal echocardiography (TEE) revealed a 7-mm vegetation on the anterior mitral leaflet. Blood cultures were negative, and after 45 days of empirical 12 g/day ampicillin-sulbactam therapy, the vegetation disappeared. However, due to ongoing severe mitral regurgitation and valve deformity, a prosthetic metallic mitral valve was implanted. After the operation, TEE was performed again due to subfebrile fever; however, the valve was normal and blood cultures were negative. Because of the probable relapse risk of infective endocarditis, the preoperative intravenous antibiotherapy was continued for 21 days and then orally for one week. Then, she was followed up by our outpatient clinic. As her INR was highly unstable during this period and she developed new-onset subfebrile fever, she was hospitalized again, and the TEE demonstrated vegetation. Blood cultures were still negative, and a combination of vancomycin-rifampicin-gentamicin therapy was started. While under that therapy, firstly, stroke and after a few days recurrent trans-ischemic attack occurred. Also on repeat echocardiogram an increase in the size of the vegetation was observed. Urgent valve operation was performed using a bioprosthetic mitral

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arejimine ampicilin-sulbaktam eklendi. Üç ay süre ile oral antikoagulan tedavi alması planlandı ancak INR düzeyleri o kadar kararsız seyretti ki takip eden iki gün boyunca bile terapötik düzeyler içerisinde tutulamadı. Kreatinin klirensine göre ayarlanmış günde iki kez 10 mg dabigatran ve 150 mg aspirin kombinasyonu başlandı. Ne var ki bu tedavi altında kapak trombozu ve büyük bir felç gelişti. Tromboz sürekli heparin infüzyonu sonrasında kayboldu ve hasta, son ameliyattan 55 gün sonra 150 mg/gün aspirin tedavisi ile ve nörolojik sekel ile taburcu edildi. Takip eden dört aylık süre içerisinde başka herhangi bir klinik olay yaşanmadı.

Abbreviations:

AF Atrial fibrillation
CRP C-reactive protein
TEE Transesophageal echocardiography

Dabigatran etexilate is an oral thrombin inhibitor which inhibits thrombin formation after conversion to its active form.^[1] Following large scale dose-safety studies, its use in patients with atrial fibrillation (AF) to prevent thromboembolic events has been approved, provided that age, and renal functions are taken into consideration in dosage selection.^[2] Contrary to warfarin, it does not interact with diet, and other drugs. Dabigatran becomes an attractive

valve, and ampicillin-sulbactam therapy was added to her previous antibiotherapy upon the suggestion of the Microbiology Department. Oral anticoagulant therapy was planned for three months. However, during the postoperative period, her INR levels were highly unstable and could not be maintained within therapeutic ranges for even two consecutive days. Adjusted dosage of dabigatran to 110 mg/bid according to renal clearance in combination with 150 mg/day aspirin was started. However, valve thrombosis and a massive stroke developed under this therapy. Thrombosis disappeared after continuous heparin infusion, and she was discharged with neurological sequelae on 150 mg/day aspirin 55 days after her last operation. During the follow-up period of four months, no other clinical events occurred.

alternative in that it is converted to its active form independent from P-450 system without being effected by genetic polymorphism. Dabigatran is more advantageous than warfarin in that it does not require close monitorization of laboratory parameters, and consumption of vitamin K.^[1] Daily use of dabigatran is so practical, and user-friendly, that it attracts the attention of physicians who search the best, and the most comfortable for their patients. However, its dazzling features create an illusion that dabigatran with its prevalent doses can be used in the treatment of conditions apart from available indications.

In this article, we wanted to present, and discuss a patient with acute

valvular thrombosis who had been reoperated, and a bioprosthetic mitral valve was implanted during the course of the treatment of infective endocarditis. Because of a labile INR course, she received acetylsalicylic acid, and dabigatran instead of warfarin on the 10th postoperative day leading to severe morbidity.

CASE PRESENTATION

A 41-year-old female patient was referred to a cardiology clinic because of a mitral murmur, unexplained fever, and shortness of breath lasting for 2 months. Transthoracic echocardiography revealed severe mitral valve regurgitation. Transesophageal echocardiography (TEE) disclosed a 7 mm- vegetation on an aneurysmatic formation located on the anterior mitral leaflet, and severe mitral regurgitation which led to the diagnosis of infective endocarditis. Blood cultures were negative. Then a heart failure therapy including ampicillin-sulbactam (12gr/d), a diuretic, and an angiotensin- converting enzyme inhibitor (ACEI) was initiated. Her shortness of breath alleviated, and her fever was brought under control. Her sedimentation rate decreased from 90 mm/hr to 10 mm/hr, and C-reactive protein (CRP) level dropped from 85 mg/L to normal ranges. On the 20., and 35. days of her treatment TEE was repeated. On her control visits, disappearance of vegetation but persistence of severe mitral regurgitation secondary to valvular aneurysm were noted. Presumptive microbial eradication following treatment of infective endocarditis led us to plan elective valvular surgery at the end of the treatment period as recommended by guidelines because of severe mitral valve deformity, and insufficiency. Her treatment was maintained for 45 days, and

then prosthetic metallic mitral valve replacement was performed. Histopathological examination of the prosthetic valve material revealed diffuse fibrin deposits, and infiltration of inflammatory cells. Bacterial growth was not detected on cultures of the prosthetic material. TEE performed on the 3rd postoperative day, because of higher subfebrile fever, revealed disappearance of the previously detected vegetation. Cultures of blood samples, and specimens of the surgical material were negative for atypical bacterial growth even after a prolonged incubation period. The patient who had been previously treated for culture-negative infective endocarditis was considered to be under the risk of recurrent endocarditis, and antibiotherapy was initiated again. Postoperative antibiotherapy was maintained for three weeks at a daily dose of 12g ampicillin-sulbactam combination. During this period, repeat TEE performed on the afebrile patient with procalcitonin, and CRP values within normal ranges revealed disappearance of vegetation. The treatment regimen of the patient who had been on antibiotherapy because of the suspect relapse of infective endocarditis was consulted to the Department of Microbiology together with her latest culture results, and TEE findings. Prolonged in-patient treatment was deemed to be unnecessary, and she was discharged with oral amoxicillin/clavulanic (1 g bid) therapy to be continued for one week.

During the early postoperative period, she demonstrated labile INR levels, and daily warfarin requirement of the patient ranged between 2.5 mg, and 10 mg. During this period, INR value was occasionally higher than detectable levels or lower than 2. INR value of the patient 2

days after discharge while she was on daily 5 mg warfarin therapy was 1.4, however it was higher than detectable levels when she was receiving daily doses of 7.5 mg warfarin 2 days after the first measurement. Within the same week, her body temperature started to rise, and her sedimentation rate, and CRP values increased again which necessitated a repeat TEE. On repeat TEE, a vegetation measuring 15 mm was detected on the atrial aspect of the prosthetic metallic mitral valve. The patient was rehospitalized, and her blood cultures obtained were again negative for bacterial growth. Since her INR levels were still unstable, her warfarin therapy was stopped, and infusion of unfractionated heparin was initiated so as to maintain aPTT levels 2 times of ULN.

Early onset postoperative infective endocarditis, rather than relapse was considered. Therefore, treatment regimen of the patient was arranged as a combination of appropriate doses of vancomycin, rifampicin, and gentamicin as recommended in the guidelines. However on the 6th day of her hospitalization occlusive type cerebrovascular event developed. The patient was intubated, and transferred into the intensive care unit for further monitorization. One week after the event her general health state was partially improved, so she was extubated.

Control cerebral tomography detected parenchymal bleeding confined around the infarct area. Department of Neurology recommended discontinuation of heparin, however we continued to administer heparin because of risk of thrombosis. A new episode of bleeding did not occur. TEE performed on the patient who had subfebrile fever on the 20th day of

her second hospitalization with persistently higher sedimentation, and CRP values, detected a 20 –mm vegetation on the prosthetic valve. Meanwhile, the patient experienced a transient ischemic attack on the 22th day of her last antibiotherapy, and mitral valve operation was planned for the second time. Replacement of metallic prosthetic valve by bioprosthetic valve in that the latter does not require postoperative life-long warfarin use, and it is relatively more resistant against infiltration of microorganisms.

Absence of bacterial growth in cultures of blood and surgical materials, was thought to be related to suppression of bacterial growth by higher doses of antibiotics or an infection which might develop with an atypical agent. Therefore, pre-, and postoperative antibiotherapy was supplemented with ampicillin/sulbactam therapy (12g/d). The patient under warfarin therapy was followed up for a period of 3 months which was the time interval predicted for the completion of valvular endothelization. The patient was restarted on warfarin therapy. Following the last operation, she was afebrile, and her biochemical, and microbiological markers of infection were negative without any sequelae related to her previously experienced cerebrovascular event. Afterwards, her renal functions deteriorated, and her creatinine clearance regressed to 30 ml/min with resultant discontinuation of gentamicin therapy. Doses of other antibiotics were readjusted based on creatinine clearance. On the 10th day of the follow-up period, upon persistence of unstable INR levels (her INR values increased sharply to undetectably higher levels for a few days while she was receiving daily doses of 2.5-5 mg warfarin, then the next day they

dropped suddenly below the therapeutic levels without any intervention, and couldn't approach to therapeutic levels despite daily doses of 10-15 mg warfarin) her warfarin therapy was discontinued, and instead dabigatran (110 mg bid), and acetylsalicylic acid (150 mg/d) was initiated based on her creatinine clearance. On the 9th day of the this modified therapy, the patient suddenly lost her consciousness without any change in her creatinine clearance. She was transferred into the intensive care unit, and had to be intubated. Her cranial tomography revealed an occlusive type stroke affecting a large area without any finding of bleeding. TEE detected a thrombus on the bioprosthetic mitral valve. A relatively larger thrombus (1.5 cm) isoechogenic with myocardium extended from the posterior aspect of the left atrium into the mitral valve, and its end portion entered partially into the ventricle synchronously with valvular movements. The surface of the thrombus was fragmented, and smooth without any fimbrias, and chaotic movements. The patient was afebrile, and her infection parametres were within normal limits. Unfractionated heparin infusion was initiated for the patient for whom thrombolytic treatment could not be employed, and surgical intervention was considered to be risky because of potential danger of stroke. Control TEE performed 5 days after starting heparin therapy evidenced complete disappearance of the thrombus. General health state of the patient improved, and then she was extubated. Unfortunately, the patient without any motor deficit lost all her intellectual faculties, speech, and communication abilities. Afterwards her renal functions improved. Fifteen days after initiation of unfractionated heparin infusion, and nearly 40 days following operation, we switched to enoxaparin

(6000 IU bid), and acetylsalicylic acid (300 mg/d), and doses of antibiotics were readjusted. This treatment regimen was maintained for an additional 15 days in the hospital. Her antibiotherapy was discontinued 55 days after the last operation, and then she was discharged from the hospital with recommendations of maintaining the same treatment regimen. She was followed up for 3 months while she was on this treatment protocol, then enoxaparin treatment was discontinued, and acetylsalicylic acid therapy was maintained. Subsequently, during a 4-month follow-up period, although a new adverse event did not occur, her neurological health state did not improve.

DISCUSSION

Thrombosis of prosthetic valve is a condition which can cause serious morbidity, and mortality.^[3] Even though thrombosis is more frequently seen in mechanical valves, it can be also seen in bioprosthetic valves especially during the first 3 months after the operation.^[4] Ten days after the compulsory bioprosthetic mitral valve replacement performed for the second time during the course of infective endocarditis, because of persistence of labile INR levels, warfarin therapy was terminated, and we switched to dabigatran and acetylsalicylic combination therapy. Meanwhile, we observed mitral valve thrombosis, and related occlusive type cerebrovascular event with resultant secondary sequelae.

When we reviewed literature data, especially warfarin has an established and prominent superiority in the prevention of valvular thrombosis.^[5] In our patient, discontinuation of an agent with such a higher efficacy, and reliability, and usage of an agent which has not been approved

for this indication seems to be a risky approach. However immunological phenomena emerged secondary to long-term clinical follow-up of the patient with infective endocarditis, drug-drug interactions related to the usage of higher doses of antibiotics, and transient hepatic congestion due to variable need for diuretics might result in labile INR with potential life-threatening consequences which under conditions prevailing at that time, and with an erroneous foresight, led us to discontinue warfarin, and instead initiate dabigatran, and acetylsalicylic acid combination therapy.

In the literature, INR levels above or below the therapeutic range for more than 60 % of the duration of the drug therapy is defined as labile (unstable) INR.^[6] Our decision to stop warfarin therapy was not based only our fear from potential valvular thrombosis in consideration of labile INR. Especially rise in INR values up to undetectably higher levels, and their persistence at that levels, created a risk for recurrent episodes of bleeding in our patient who had previously experienced septic cerebrovascular embolism, and then developed parenchymal bleeding around embolus. Because of deterioration of creatinine clearance of the patient, she was given dabigatran (110 mg bid), and acetylsalicylic acid (150 mg/d). While we were afraid of potential development of hemorrhagic complications, during monitorization of the patient valvular thrombosis, and for the second time, an occlusive type cerebrovascular event with serious sequelae developed. Albeit we can not say that valvular thrombosis developed in our patient was definitely associated with dabigatran use, higher level of clinical suspicion was entertained.

There is a serious illusion of perception in our country that available doses of dabigatran which has been recently introduced into clinical use can be superior or equivalent to warfarin for all indications. When this illusion of perception finds a place in clinical practice, it can unfortunately cause unwanted complications as seen in our case. However, relevant literature data, and indications for use of dabigatran are clear-cut. In the mainstay RE-LY (“Randomized Evaluation of Long-Term Anticoagulation Therapy”) study dabigatran was compared to warfarin in the treatment of patients with non-valvular AF.^[7] In the RE-LY study, the researchers observed that dabigatran at a dose of 110 mg, and warfarin had induced thromboembolic events at comparatively similar rates. However i higher dose (150 mg) dabigatran led to lower rates of thromboembolic events. In the same study, it was reported that twice daily doses of 110 mg dabigatran resulted in lesser amount of bleeding relative to warfarin. However its 150 mg doses had similar rates of bleeding in comparison with warfarin.

In off-label uses of dabigatran selection of doses in the whole world is erroneously based on the abovementioned data related to AF patients. However risks of thrombosis differ dependent on the implantation site of the prosthetic valves (mitral, aortic or both). Still irrespective of the location of implantation, a patient with a prosthetic valve has a higher risk of thrombotic complications when compared with an AF patient. It is possible to give rise to such unwanted results, when doses used in the treatment of AF, are also employed for the patients with prosthetic valves. However, available doses of the

drug are marketed in 110, and 150 mg tablets suitable for the treatment of AF.

At this point, we should indicate lack of clinical data suggesting potentially preventive effect of dabigatran on the development of prosthetic valve thrombosis without inducing hemorrhagic episodes. Similarly, any clinical study cited in the literature has not compared warfarin, and dabigatran with this respect, and has not demonstrated the relative superiority of warfarin. . In the future, different doses of dabigatran may be used for this indication. However, till accumulation of adequate clinical data, use of dabigatran for the prevention of the development of thrombosis at doses prescribed for the treatment of AF might fail to prevent serious thrombotic complications. Physicians who search for more comfortable solutions for their patients can endanger many lives, if they act in a hurry. Clinical suspicion about inadequacy of dabigatran in the prevention of valvular thrombosis when used in conventional doses is globally reinforced with increasing number of case reports^[3,8] Price et al. ^[8] published two case reports about two patients with metallic mitral prosthetic valves in their fifties. Primary care physicians of the patients switched from warfarin to dabigatran (150 mg bid) therapy, and the patients developed serious valvular thrombosis nearly 2 or 3 months from this alteration in the treatment regimen. Clinical Phase 2 RE-ALIGN (NCT01452347) study which might guide future studies, investigated the effects of dabigatran used at twice daily doses ranging between 150 mg and 330 mg in patients with metallic mitral prosthetic valves. ^[8]

In our patient in whom we had to stop ineffective warfarin therapy because

of labile INR levels, the most logical step was to discontinue warfarin, then switch to unfractionated heparin therapy given under aPTT monitoring which should be maintained for 3 months in line with the recommendations of the literature, and the guidelines. The most important mistake at this point, was to off-label use of a new anticoagulant dabigatran whose effectiveness was not previously proved in a dose efficacy, and reliability study. Another clinical use contradicting with literature recommendations is enoxaparin treatment initiated 40 days after the last operation. Literature does not contain any recommendation suggesting safe use of enoxaparin in patients with prosthetic valves. Nevertheless, our patient didn't suffer from any complication related to enoxaparin use.

In cases requiring use of oral anticoagulants, increase in the treatment options is doubtless in favour of both physicians, and the patients. However safe, use of new agents requires adequate clinical experience, and larger scale randomized, and reliable dose- ranging studies. If in patients with prosthetic valves, interruption of warfarin therapy is required, currently, switching to unfractionated heparin therapy seems to be the most suitable, and logical approach.

The authors of this case presentation reported that RE-ALIGN study was continuing actively during medical management of the patient.

Conflict of interest: None declared

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Anahtar sözcükler: Antikoagulan/yan etki; atriyum fibrilasyonu/ilaç tedavisi; dabigatran; emboli; endokardit; inme; kalp kapak protezi; varfarin/yönetim ve dozaj/yan etki.

Key words: Anticoagulants/adverse effects; atrial fibrillation/drug therapy; dabigatran; embolism; endocarditis; stroke; heart valve prosthesis; warfarin/management and dosage/adverse effects.