CASE REPORT

Warfarin-related recurrent knee haemarthrosis treated with arterial embolisation and intra-articular injection of tranexamic acid

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Accepted 14 June 2015

SUMMARY

Haemarthrosis is an uncommon complication of anticoagulation therapy. Tranexamic acid (TXA) has a high clinical value for the treatment of bleeding due to fibrinolysis. We describe a case of a 61-year-old woman with a mechanical heart valve who presented with warfarin-related recurrent haemarthrosis of her right knee, which recurred after transarterial embolisation. Intra-articular injection of TXA led to a cessation of haemarthrosis without any adverse event for 1 year. Intra-articular injection of TXA may be an effective treatment for warfarin-related haemarthrosis.

BACKGROUND

Haemarthrosis is an uncommon complication of anticoagulation therapy. Joint bleeding causes inflammatory changes in the synovium and subsequent articular cartilage damage. Intra-articular blood exerts a preliminary direct effect on the articular cartilage as a result of the iron-catalysed formation of destructive oxygen metabolites and subsequently affects the synovium, triggering a haemosiderin-induced inflammatory response.¹

Tranexamic acid (TXA) inhibits fibrinolysis by blocking the lysine-binding sites of plasminogen and has high clinical value for the treatment of bleeding due to fibrinolysis.² We report the case of a woman who presented with recurrent warfarin-related knee haemarthrosis, which was successfully treated with direct intra-articular injection of TXA.

CASE PRESENTATION

The patient was a 61-year-old woman with a history of aortic and mitral regurgitation related to childhood rheumatic fever. She underwent surgical repair of aortic and mitral valves when she was 28 years old. The aortic and mitral valves were replaced with mechanical heart valves and a pacemaker was implanted when she was 51 years old. Following these surgeries, she started taking warfarin for the prevention of embolisation. Her attending doctor had controlled her international normalised ratio (INR) at 1.8–2.0. When she was 60 years old, she presented with symptoms of haemarthrosis in the right knee without any trauma or knee injury. She consulted the attending doctor; knee aspiration yielded 50 mL of bloody joint fluid. Her INR was 2.4. After 3 days of cessation of warfarin therapy and 1 month of rest, the haemorrhaging of her right knee stopped. Three months later, she presented with haemarthrosis in the right knee

Figure 1 A skyline view of the patella showing a large effusion in the knee joint.

after mild exercise consisting of quadriceps training and consulted our hospital. Physical examination revealed swelling in the right knee with a tense suprapatellar knee effusion. A skyline view of the patella demonstrated a large joint effusion, as marked by the arrow in [figure 1](#). Laboratory analysis revealed a haemoglobin level of 9.9 g/dL (normal range (NR) 11.5–15 g/dL), total white cell count of $11.52 \times 10^9/L$ (NR $4\text{--}10 \times 10^9/L$) with slight neutrophilia of 82% (NR 40–75%) and a normal platelet count of $177 \times 10^9/L$ (NR $140\text{--}440 \times 10^9/L$). The patient's INR was 3.34. Knee aspiration yielded 23 mL of bloody joint fluid.

TREATMENT

After 3 days of cessation of warfarin therapy and 1 week of rest and cooling of the knee, the haemarthrosis persisted. Transcatheter arterial embolisation was performed by the radiologist. First, non-selective angiography of the femoral artery was performed to identify the areas of bleeding within the knee joint. Angiography ([figure 2A](#)) demonstrated geniculate artery hypertrophy and synovial hypervascularity with no tumorous stain. Microcatheter selection of geniculate arterial branches that exhibited no tumorous stain was performed. Embolisation was performed with spherical embolic 1 mm gel particles (Nippon Kayaku Co Ltd, Tokyo, Japan; [figure 2B](#)). The haemorrhage in the right knee stopped following the procedure, and the patient was discharged from the hospital. Five days later, the patient visited the hospital for pain and swelling caused by subcutaneous haemorrhage in the anterior right thigh. She was readmitted to the hospital; warfarin therapy was ceased for 2 days and the affected area was kept at rest and cooled for

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To cite: Kunugiza Y, Nakamura Y, Mikami K, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-210203

Figure 2 (A) Popliteal angiography demonstrates abnormal blush of vessels fed by the lateral inferior genicular artery (arrow A) and medial inferior genicular artery (arrow B). (B) Popliteal angiography following embolisation showing no blush in the vessels.

2 weeks. Her symptoms of pain and subcutaneous haemorrhage were relieved but the haemorrhage in the right knee recurred once walking rehabilitation was initiated. The patient's INR was 1.98. After 3 days of cessation of warfarin therapy, knee aspiration yielded 43 mL of bloody joint fluid, and bleeding at the puncture site persisted. Intra-articular injection of a mixture of TXA (4 mL, 400 mg) and saline (16 mL) into the right knee was performed. The patient's INR was 1.87 prior to intra-articular TXA injection.

OUTCOME AND FOLLOW-UP

Soon after intra-articular injection of a mixture of TXA and saline, bleeding from the right knee joint stopped. On the day following the injection of TXA, the patient started taking warfarin again and her INR was controlled at 1.5–1.6 following her attending doctor's advice. The patient was free of relapse without any adverse event for 1 year. At present, she can walk with a single cane.

DISCUSSION

Oral anticoagulants such as warfarin have long been recognised as highly effective drugs for the prevention and treatment of numerous thromboembolic events.³ Warfarin inhibits the production of functional vitamin K-dependent blood procoagulant factors as well as inhibiting the production of the physiological anticoagulant proteins C and S. At therapeutic dosages, warfarin administration results in reduced thrombin generation, as indicated by the reduction of plasma levels of prothrombin fragment 1+2 and the thrombin–antithrombin complex.^{4 5} Patients with mechanical heart valves are considered to be at a higher risk for thromboembolic events, and vitamin K antagonists are the only approved agents for thromboprophylaxis at present.^{6 7} However, as with anticoagulation therapy, there remains a chance of bleeding complications. The frequency of major bleeding related to warfarin treatment is reported to be 1.6% per patient-year.⁸ The patient in this report took warfarin following mechanical aortic and mitral valve replacement, and the haemarthrosis was thought to be related to the warfarin use. We ceased the use of warfarin for 3 days, and her knee was kept at

rest and cooled. Rest, ice, compression and elevation (RICE) together or alone is commonly recommended as an adjunct treatment for the treatment of haemarthrosis, to decrease bleeding and pain.⁹ Haemarthrosis of the knee continued in this patient following this routine treatment. Transarterial embolisation¹⁰ and radiosynovectomy¹¹ are reported as other treatment options for haemarthrosis. We performed transarterial embolisation because radiosynovectomy was not an available treatment option for us locally; however, haemarthrosis relapsed 3 weeks later. Following this, we tried intra-articular injection of a mixture of TXA and saline into the right knee as a local treatment; this successfully stopped the bleeding without any adverse event. TXA inhibits fibrinolysis by blocking the lysine-binding sites of plasminogen and has a high clinical value for the treatment of bleeding due to fibrinolysis.² The administration of TXA by either intravenous injection¹² or intra-articular injection¹³ inhibits blood loss after total knee replacement. The risk of thromboembolic complications is reported to be low with the use of TXA after primary total hip and knee arthroplasty.¹⁴ TXA mouthwash is used for local delivery of TXA in patients anticoagulated with warfarin who require dental extractions.¹⁵ Local administration of TXA in patients undergoing off-pump coronary artery bypass is also reported.¹⁶ In both these reports, the administration of TXA was effective in controlling bleeding, and no thromboembolic events were observed.

We directly injected TXA (20 mg/mL) into the knee joint, and shortly thereafter, the haemorrhage stopped. In an in vitro experiment, 100 µg/mL of TXA was necessary to inhibit fibrinolytic activity in a reference solution of pig heart tissue activators.¹⁷ In our case, the high concentration of TXA would have been effective for inhibiting bleeding in the joint space. A recent report showed that warfarin treatment not only inhibits fibrin formation but also promotes fibrinolysis by reducing clot resistance to lysis.¹⁸ Fibrinolysis may have been activated in our patient's knee, and TXA may have likely stopped the bleeding by local inhibition of fibrinolysis. The local inhibition of fibrinolysis by intra-articular injection of TXA may be a simple and effective treatment method for warfarin-related haemarthrosis, with minimal side effects. As far as we know, this is the first

report of intra-articular TXA being successfully used for the treatment of recurrent warfarin-related native joint bleeding. As therapeutic options for this complication are scarce, this case report may be of major interest to those specialists who face similar issues.

In conclusion, intra-articular injection of TXA may be an effective treatment for warfarin-related haemarthrosis.

Learning points

- ▶ Haemarthrosis is an uncommon complication of anticoagulation therapy, and joint bleeding causes inflammatory changes in the synovium and subsequent articular cartilage damage.
- ▶ Short-term cessation of anticoagulant therapy, and rest, ice, compression and elevation (RICE), are recommended for first-line treatment of warfarin-related haemarthrosis.
- ▶ In this case, symptoms completely resolved soon after intra-articular injection of tranexamic acid.

Contributors YK was involved in the treatment of the patient, acquisition of the data, and drafting and multiple revisions of the work. YN was involved in proposal of treatment method and conception of the study. KM was involved in the arterial embolisation procedure. SS was involved in the conception of the study, and drafting and multiple revisions of the work, as well as approval of the final version of the study for submission.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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