Clinical Medicine 2013, Vol 13, No 2: 211–12

lesson of the month (2)

Recurrent thrombosis despite a therapeutic international normalised ratio

There has been significant progress in the management of venous thromboembolism in recent years, with increased awareness and adequate thromboprophylaxis proving successful in reducing the morbidity and mortality associated with this condition. Most hospitals in the UK have specialists who run an anticoagulation clinic and ensure the adequate monitoring of, and compliance with, agents such as warfarin. In this Lesson of the Month, we describe an individual with treated congenital heart disease who developed extensive thrombosis while his warfarin control was considered to be in the therapeutic range.

Case study

A 36-year-old Caucasian male presented who had been anticoagulated since a young age for surgically treated cyanotic congenital heart disease (tricuspid atresia, septal defects and patent ductus arteriosus). A modified Fontan operation had been performed in 2010, 20 years after the original procedure, for conversion to total cavopulmonary connection. Postoperatively, the patient had remained stable and wished to discontinue warfarin, which he had been treated with for 20 years. However, increasing breathless over the next six months prompted radiology examination, which demonstrated embolism in the inferior vena cava and right pulmonary arterial conduit. The patient was re-anticoagulated in the tertiary centre with the original target range of 3.0 to 3.5 for his international normalised ratio (INR).

Three months after discharge, the patient presented to a local emergency department with a history of palpitations of sudden onset. Similar episodes had occurred over previous weeks, but had spontaneously resolved. Electrocardiogram showed supraventricular tachycardia. Although his oxygen saturations were between 85% and 88% (normal for the patient), arterial blood gas demonstrated severe hypoxia (5.99 kPa) with hypocarbia (3.28 kPa) and acidosis (bicarbonate 17.5 mEq/l). A full blood count showed haemoglobin of 197 g/l (haematocrit of 59.1), with the rest of the count being normal. His INR was 6.1. Given that anticoagulation was considered excessive, his warfarin dose was omitted. The following day, his INR was closer to the target range (3.0–3.5) at 3.7 and warfarin was restarted. Of note, his three previous INR checks at the local anticoagulation service had noted a higher value and the dose of warfarin had been reduced accordingly.

On transfer to the tertiary centre, repeat INR was found to be below his target range at 1.8. In the tertiary centre, the routine practice in individuals with a raised haematocrit from cyanotic heart disease, is to adjust the quantity of citrate in the coagulation tubes. The INR discrepancy arose because this practice was not followed in the local hospital. Further investigations revealed absent flow velocity across the Fontan tunnel on echocardiogram. A computerised tomography (CT) scan demonstrated widespread pulmonary emboli and an inferior vena caval clot. Owing to the widespread thrombosis, the patient underwent thrombolysis followed by an infusion of unfractionated heparin. Despite this, further complications emerged, with emboli into his brachial artery. Continuous heparin infusions over the next two weeks led to improvement in his symptoms. Angiography was performed to check the patency of the Fontan conduit and confirmed that flow had been re-established in the vena cava. Upon discharge, the patient was referred to the local anticoagulation clinic, which was made aware of the requirement for corrected citrate samples. It was also planned that the results be reviewed and directed by the adult congenital heart disease team.

Discussion

There is a high incidence of thrombus formation in patients who have undergone the Fontan operation owing to low cardiac output and venous stasis, reduced contractility of an enlarged left atrium, atrial arrhythmias, slow flow through the tunnel and valve regurgitation.[1] Cyanosis-induced polycythaemia and

Key points

- Recurrent thrombosis while receiving therapeutic anticoagulation is rare
- Patients with congenital heart disease are at an increased risk of thrombosis
- Coagulation results can be affected by high haematocrit
- Correction of the citrate content of the coagulation tube is necessary in individuals with high haematocrit to obtain accurate results and avoid under-anticoagulation

Amy Carroll,[1] medical student; **Linda Griffiths,**[2] specialist nurse in adult congenital heart disease service; **Vaikom Mahadevan,**[2] consultant cardiologist in adult congenital heart disease service; **Jaspal Dua,**[2] consultant cardiologist in adult congenital heart disease service; **Jecko Thachil,**[3] consultant haematologist

[1]School of Medicine, Manchester Royal Infirmary; [2]Department of Cardiology, Manchester Royal Infirmary; [3]Department of Haematology, Manchester Royal Infirmary

clotting abnormalities further increase thromboembolic risk.[2,3] Intracardiac thrombi can manifest clinically as pulmonary embolism if formed on the right side of the heart, or ischaemic stroke if on the left side.[2] Massive pulmonary embolism accounts for the majority of sudden out-of-hospital death in patients with a Fontan circuit.[3]

Correct sample preparation is paramount if laboratory results are to be accurate.[4,5] Perhaps this is nowhere more relevant than in coagulation testing, where inaccuracies can significantly affect patient outcome and, as demonstrated by this case, cause life-threatening complications.[4,5] Standardisation (where possible) of pre-analytical variables minimises this risk. Such variables include the length of time and temperature at which the sample is stored, underfilling of the tube and a raised haematocrit.[4,5]

Sodium citrate, present in coagulation tubes, works as an anticoagulant by removing the calcium ions that are crucial for coagulation reactions.[6] Different citrate concentrations in the tubes can affect coagulation screen results, with a higher citrate concentration prolonging the prothrombin time (PT) and activated partial thromboplastin time (APTT) as the ratio of citrate to calcium is increased.[4,6] An elevated haematocrit, as in patients with cyanotic heart disease,[3] causes an increased proportion of red cells and a reduced amount of plasma in the collected sample. Excess citrate in these cases binds a considerable amount of the newly added calcium that is in the PT or APTT reagent, causing an artifactually prolonged clotting time and, thus, a raised INR.[6] Therefore, it is imperative that patients with high haematocrit values (>0.55) have the citrate concentration decreased to compensate for the reduced amount of plasma in the collected sample.[6] Specially prepared tubes are advised or the removal of 0.1 ml of sodium citrate can be done because most high haematocrits fall between 0.55 and 0.65.

A high haematocrit is not unique to individuals with congenital heart disease. With advances in treatment, an increasing number of patients with chronic obstructive airways disease and heart failure have been noted to have secondary polycythaemia owing to chronic hypoxaemia.[7] Such patients often have comorbid disorders, such as atrial fibrillation, thromboembolic disease and artificial heart valves, which require anticoagulation. As in the case described, there is also potential for erroneous INR results if the citrate concentration is not appropriately adjusted (especially if the haematocrit is >0.55) in this group of patients.[6] Subsequent underdosing of warfarin puts the patient at risk of thromboembolic events.[5]

There has been a recent move towards monitoring anticoagulation in the community rather than at hospital-based clinics. Anticoagulation clinics in primary care are often provided by nurses and utilise a computer program that gives warfarin-dosing guidance. Obvious benefits include improved efficiency, reduced costs and convenience for patients. However, with this shifting focus, patients might fall into less experienced hands, inferring a greater risk to patients with haemostatic abnormalities whose requirements are often complex. In addition, we question whether such patients would be more suited to therapy with new oral anticoagulant drugs, which do not require frequent INR testing. This could reduce the incidence of thromboembolic events in association with false INR results, but requires controlled trials before widespread acceptance.

References

1 Balling G, Vogt M, Kaemmerer H *et al.* Intracardiac thrombus formation after the Fontan operation. *J Thorac Cardiovasc Surg* 2000;119:745–52.
2 Coon PD, Rychik J, Novello RT *et al.* Thrombus formation after the Fontan operation. *Ann Thorac Surg* 2001;71:1990–4.
3 Fredenburg TB, Johnson TR, Cohen MD. The Fontan Procedure: anatomy, complications, and manifestations of failure. *Radiographics* 2011;31:453–63.
4 McCraw A, Hillarp A, Echenagucia M. Considerations in the laboratory assessment of haemostasis. *Haemophilia* 2010;16:74–8.
5 Smythe MA, Caffee A. Anticoagulation monitoring. *J Pharm Pract* 2004;17:317–26.
6 Marlar RA, Potts RM, Marlar AA. Effect on routine and special coagulation testing values of citrate anticoagulant adjustment in patients with high hematocrit values. *Am J Clin Pathol* 2006;126:400–5.
7 DeFilippis AP, Law K, Curtin S, Eckman JR. Blood is thicker than water. *Cardiol Rev* 2007;15:31–4.

Address for correspondence: Dr J Thachil, Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.
Email: jecko.thachil@cmft.nhs.uk