Performing therapeutic venesection in a doctor’s surgery

Hui Yin Lim, Wai Khoon Ho

Background

Although venesection was widely applied in the past for the treatment of various ailments and diseases, in modern medical practice, it is indicated in very few conditions, namely, hereditary haemochromatosis, polycythaemia and porphyria cutanea tarda.

Objective

This article briefly reviews the pathophysiology of these conditions, and the rationale and goals of therapeutic venesection as a treatment modality. It also summarises the venesection procedure itself and the considerations for setting up a venesection service in a doctor’s surgery.

Discussion

Venesection is generally safe and carries few side effects. Before commencing therapeutic venesection, management goals in terms of laboratory parameters should be set for individual patients. These patients should be monitored regularly so that set targets are met and not overshot as to render them anaemic and acutely symptomatic. Venesections should also be performed by persons familiar with the procedure and management of the attendant complications.

Venesection, historically also known as “bloodletting”, is a longstanding medical procedure with a history spanning at least 3000 years, and was widely practised around the world until the 19th century. While the rationale for bloodletting in ancient medicine was diverse and included reasons such as treatment of inflammation and apoplexy, in modern evidence-based medicine, this practice is now restricted to only a few conditions, including hereditary haemochromatosis, polycythaemia vera (PV) and porphyria cutanea tarda (PCT; Table 1).

Indications for venesection

Haemochromatosis

The aetiology of iron overload is diverse and includes hereditary haemochromatosis (HFE and non-HFE types), secondary causes such as iron-loading anaemias (with or without transfusions) and aceruloplasminemia.

Hereditary haemochromatosis is characterised by genetic mutations that affect various sites of the iron absorption pathway, resulting in excess body iron. Type I hereditary haemochromatosis is by far the most common type in the Australian population. Type I involves the HFE gene on chromosome 6 and is an autosomal recessive disorder. It is most prevalent among people of northern-European origin. Most cases (90%) are due to homozygous carriage of a mutation in the HFE gene resulting in the C282Y protein product. Only a small number of cases are attributable to C282Y/H63D compound heterozygosity, H63D being the protein product of another mutation in HFE.

Clinical penetrance of these mutations is low and variable; this is summarised in Table 2, which also gives the prevalence of these mutations.

The clinical manifestations of haemochromatosis are related to the marked excess of iron (usually indicated by serum ferritin >1000 μg/L) deposited in tissues such as the liver, heart, pancreas, pituitary gland and joints. Cirrhosis, hepatocellular carcinoma, diabetes mellitus and cardiomyopathy are the major causes of morbidity and mortality in symptomatic hereditary
haemochromatosis; these complications depend on the amount and duration of iron excess/overload. Although there are no large randomised controlled studies to address the clinical benefits of venesection in this condition, adequate venesection may reduce mortality, reduce hepatic fibrosis and eliminate the risk of haemochromatosis-related hepatocellular carcinoma if iron removal is achieved prior to the development of cirrhosis. In some patients, venesection may minimise complications, including malaise, fatigue and skin pigmentation. Once established, cirrhosis, diabetes, arthropathy and testicular atrophy are irreversible.

Therapeutic venesection is indicated in patients with symptoms or end-organ manifestations and in those with serum ferritin ≥1000 μg/L. The indication for venesection in asymptomatic patients with elevated serum ferritin (>300 μg/L for men and >200 μg/L for women), but <1000 μg/L is less certain; nevertheless, it should be considered in C282Y homozygotes.

The effectiveness of venesection in reducing body iron is, firstly, through blood loss, which directly reduces the haemoglobin stores of iron; and secondly, by stimulating erythropoiesis to compensate for blood loss, thus mobilising and reducing iron stores. On average, each venesection removes 450–500 mL of blood, which is equivalent to 200–250 mg of iron. The aim is to reduce serum ferritin levels to 50–100 μg/L. The frequency of venesections required to achieve this goal is highly variable and depends on an individual’s iron stores; some authors recommend weekly venesections initially, and spacing the frequency as haemoglobin and/or serum ferritin falls. At the commencement of venesection, an affected individual may hold as much as 10–40 g of iron, and excess iron may take several months to remove. Once the target serum ferritin is achieved, lifelong maintenance venesection is generally required. The frequency of venesections during this phase is again highly variable among individuals, but averages once every three to four months.

While most patients are able to tolerate therapeutic venesection, those who are intolerant can be considered for: iron chelation drugs – these drugs are unavailable on the Pharmaceutical Benefits Scheme (PBS) for the treatment of iron overload from haemochromatosis; erythrocytapheresis – an apheresis technique in which red cells are removed in an isovolaemic manner while sparing plasma proteins, coagulation factors and platelets.

Polycythaemia (erythrocytosis)

Absolute polycythaemia due to increased red blood cell mass may be primary (PV) or secondary to various causes that generally result in elevated serum erythropoietin. The raised red blood cell mass is generally reflected by elevated haematocrit, and in polycythaemic patient populations, there is an association between the resultant increased blood viscosity and both arterial and venous thrombosis.

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Indication</th>
<th>Target laboratory parameter</th>
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<tbody>
<tr>
<td>Hereditary haemochromatosis</td>
<td>Removal of excess body iron to prevent iron overload-related diseases and end-organ complications</td>
<td>Serum ferritin of 50–100 μg/L</td>
</tr>
<tr>
<td>Polycythaemia vera</td>
<td>Reduction of red cell mass to lower arterial and venous thrombotic risk</td>
<td>Haematocrit &lt;45%</td>
</tr>
<tr>
<td>Chronic hypoxic pulmonary disease</td>
<td>Reduction of blood viscosity and improvement in symptoms</td>
<td>Haematocrit 50–52% (consult with specialist unit)</td>
</tr>
<tr>
<td>Post-renal transplant erythrocytosis</td>
<td>Reduction of blood viscosity if not adequately achieved by pharmacological agents alone</td>
<td>Haematocrit 45%</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Reduction of hepatic iron load to decrease uroporphomethene formation, an inhibitor of uroporphorinogen decarboxylase</td>
<td>Serum ferritin at lower limit of normal</td>
</tr>
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<table>
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<tr>
<th>HFE mutation</th>
<th>Prevalence*</th>
<th>Frequency of iron overload-related diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y homozygosity</td>
<td>0.68%*</td>
<td>28.4% of men and 1.2% of women*</td>
</tr>
<tr>
<td>C282Y heterozygosity</td>
<td>11.1%*</td>
<td>Rare*</td>
</tr>
<tr>
<td>H63D homozygosity</td>
<td>3.4%*</td>
<td>Requires additional risk factor(s) for iron overload or liver disease*</td>
</tr>
<tr>
<td>H63D heterozygosity</td>
<td>26.2%*</td>
<td>Requires additional risk factor(s) for iron overload or liver disease*</td>
</tr>
<tr>
<td>C282Y/H63D compound heterozygosity</td>
<td>2.4%*</td>
<td>0.5–2.0%*</td>
</tr>
</tbody>
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*Prevalence in Australians of northern European origin.
Primary polycythaemia (polycythemia vera)

PV is a myeloproliferative neoplasm that is characterised by elevated haemoglobin (>165 g/L in men and >160 g/L in women), raised haematocrit (>49% in men and >48% in women) or increased red cell mass of >25% above the mean normal predicted value. The bone marrow is hypercellular for age with pancytosis. About 95% of patients harbour the Janus kinase 2 (JAK2) V617F mutation, and the remaining 2–4% have mutations in JAK2 exon 12. The serum erythropoietin level is subnormal in PV. The bone marrow is hypercellular for age with panmyelosis. Elevated red cell mass of >25% above the mean normal predicted value. The bone marrow is hypercellular for age with pancytosis. About 95% of patients harbour the Janus kinase 2 (JAK2) V617F mutation, and the remaining 2–4% have mutations in JAK2 exon 12. The serum erythropoietin level is subnormal in PV.11 The bone marrow is hypercellular for age with panmyelosis. Increased red cell mass of >25% above the mean normal predicted value.11 The bone marrow is hypercellular for age with panmyelosis.

Patients with PV have an increased risk of arterial and venous thromboses. Although incidence varies across studies, prospective studies have reported rates of 2.6% and 2.3% per annum for arterial and venous thrombosis, respectively.13,14 Arterial thrombosis (including transient ischaemic attack, thrombotic stroke, angina pectoris, myocardial infarction and peripheral arterial thromboembolism) at diagnosis of PV is an independent predictor of inferior survival.15

A major therapeutic goal in patients with PV is the prevention of thrombosis without increasing bleeding risk while ameliorating symptoms. Treatment therefore aims to reduce abnormal blood viscosity by venesection, pharmacological cytoreduction or by a combination of both. Almost 40 years ago, it was observed that the risk of thrombosis is increased in patients with a haematocrit >45%.16 This finding was confirmed more recently by the CYTOreductive therapy to prevent cardiovascular events in patients with polycythemia vera (CYTO-PV) trial, which involved 365 patients with PV patients: those randomised to achieve a haematocrit target <45% had a significantly lower rate of cardiovascular death and major thrombosis, compared with patients with a target of 45–50%.14 These findings have generally led to the adoption of a target haematocrit <45%. Additionally, low-dose aspirin is part of the cornerstone of therapy in all patients with PV as it lowers thrombotic risk without significantly increased haemorrhagic complications.13

The frequency of venesections to achieve and maintain a haematocrit level <45% is variable, depending on the baseline haematocrit, proliferative activity of the bone marrow and concomitant use of cytoreductive therapy. Pharmacological cytoreduction with hydroxyurea, in addition to venesection, is indicated for patients at high risk of thrombosis (eg aged >60 years, prior thrombosis). With repeated venesections to achieve the target haematocrit <45%, iron deficiency may develop. In patients with PV, iron replacement or supplementation is rarely indicated and, if used, it should be done cautiously, with very low doses and with close monitoring of haematocrit.17

Secondary polycythaemia

Secondary polycythaemia occurs in response to tissue hypoxia (eg pulmonary disease, cyanotic congenital heart disease), renal disease (including post-renal transplant erythrocytosis), erythropoietin-secreting tumours or testosterone/androgen administration (iatrogenic).

Limited venesection may be considered in patients with chronic hypoxic pulmonary disease in order to lower haematocrit to 50–52%, thereby reducing blood viscosity and improving cardiac output, tissue perfusion and exercise tolerance. However, venesection can also render these patients anaemic and iron-deficient, thereby compromising tissue oxygenation. Management of these patients and those with cyanotic congenital heart disease in particular is complex, and venesection should only be undertaken in strict consultation with specialised medical units.

Erythrocytosis following renal transplantation occurs in 10–20% of renal transplant recipients because of a complex interplay of factors, including activation of the renin–angiotensin system, overproduction of erythropoietin by the transplanted kidney and enhanced sensitivity of haemopoietic cells to erythropoietin. This results in hyperviscosity of the blood, which in turn causes thrombosis and hypertension. Treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists can lower haematocrit, but if the response is suboptimal, venesection should be undertaken to achieve a target haematocrit of 45%.18,19

Porphyria cutanea tarda

PCT is a rare metabolic disorder that involves haem biosynthesis. It is due to photoreactive porphyrins being deposited in the dermis and interacting with light, leading to tissue damage. Clinical features of PCT include chronic blistering cutaneous lesions in sun-exposed areas (most commonly on the dorsum of the hands) and skin fragility; hypertrichosis and hyperpigmentation can occur. The condition is caused by deficiency or inhibition of hepatic uroporphyrinogen decarboxylase, ultimately resulting in the release of porphyrins into the plasma, which accumulates in

Box 1. Considerations in the setting up of a venesection service

1. Availability of suitably trained staff who are qualified to perform the procedure
2. Availability of the appropriate equipment for venesection
3. Provision of appropriate protective equipment
4. Clearly written standard operating procedures (SOPs) for each step including:
   - Obtaining consent and preparation of patient
   - Procedure for drawing blood
   - The safe disposal of blood removed and sharps
   - Cleaning and maintenance of equipment
   - Procedures for cleaning up blood spills
5. Continuing education and training for staff including an appreciation of the anatomy, risks from exposure to blood and body fluids, and consequences of poor infection prevention and control
6. Management of adverse events in patients, including an incident reporting system
7. Protocol to follow in the event of accidental staff exposure to blood and other body fluids
the dermis. Inhibition of the enzyme is due to uroporphomethene, the formation of which is dependent on hepatic iron, hence the therapeutic need to reduce iron load in the liver.\textsuperscript{20,21}

A unit of whole blood (approximately 470 mL) can be venesected once fortnightly with the aim of reducing serum ferritin to the lower limit of normal. As iron overload is generally not marked, the target serum ferritin is usually reached after five to six venesections.\textsuperscript{20}

Indeed, haemoglobin levels or haematocrit should be monitored closely to avoid rendering the patient anaemic.

**Venesections in the doctor’s surgery: General considerations**

Venesections are generally well tolerated and can be performed in a doctor’s surgery, blood donation centres or pathology facilities. Patient factors such as age, gender, weight, medical comorbidities and compliance should be taken into account when therapeutic venesection is prescribed. The general considerations for setting up a therapeutic venesection service in a doctor’s surgery is summarised in Box 1.\textsuperscript{22}

**Venesection procedure**

Each venesection procedure takes about 15–30 minutes, and should be preceded by measurement of haemoglobin level and/or haematocrit. The procedure can generally proceed if haemoglobin is >110 g/L and haematocrit within 20% of previous measurement.\textsuperscript{10}

Patients are generally encouraged to maintain hydration and avoid rigorous exercise prior to and after the procedure. Box 2 describes the venesection procedure.\textsuperscript{22,23}

**Box 2. Venesection procedure\textsuperscript{22,23}**

1. Ensure correct patient by cross-checking patient identity and checking the indication for procedure. Explain the procedure to the patient, then obtain and document consent. Ensure that the patient’s haemoglobin level (and/or haematocrit) is of acceptable range – this can be checked with point-of-care testing or full blood examination. The patient should also be adequately hydrated prior to commencement of the procedure.
2. Position the patient in a relaxed sitting or reclining position on the examination chair/couch with arm extended. Take baseline observations. Proceed if vital signs are stable (systolic blood pressure 110–160 mmHg, diastolic blood pressure 60–95 mmHg, stable pulse 50–100/min).
3. Prepare the required equipment and ensure appropriate hand hygiene technique is used. Place a plastic-backed absorbent sheet under the elbow and another one on the electronic scales below the patient’s arm level.
4. Apply tourniquet above the intended venepuncture site and locate a good vein (generally the large vein in the ante-cubital fossa). Swab the site with an alcohol swab and allow to dry. Anchor the vein and insert the needle. Secure the needle and tubing against the patient’s arm with micropore tape.
5. Establish blood flow and place the blood donor bag onto scales. Loosen the tourniquet slightly. Note the weight in grams for the venebag.
6. Monitor the blood flow into the bag throughout the collection, ensuring the flow is continuing evenly and fairly slowly. Monitor the patient at all times during the procedure. The venesection should take 10–20 minutes.
7. Clamp the blood bag tubing and tighten the knots of the tubing when the bag has reached the appropriate weight (weight of venebag (g) + amount of blood needed; note that 500 mL blood weighs approximately 600 g). Release the tourniquet and carefully withdraw the needle. Apply direct pressure to the puncture site with cotton balls.
8. Discard the blood bag according to local policies for blood products (may require incinerating or transportation to the local hospital or pathology provider for disposal).
9. Check patient’s puncture site to ensure bleeding has stopped and apply cotton wool and tape. Apply a firm bandage and instruct patient to remove the bandage in approximately two hours.
10. Instruct the patient to remain lying/sitting down for 15 minutes. Offer the patient a drink and recommend maintenance of good hydration over the next 24 hours. Perform blood pressure check on the contra-lateral arm and, if it is lower than baseline, ask the patient to wait and re-measure again in 15 minutes.
11. Advise the patient to avoid heavy lifting with that arm and strenuous exercise for 24 hours.

**Conclusion**

Therapeutic venesection is indicated in the treatment of selected conditions, namely, hereditary haemochromatosis (removal of excess body iron), polycythaemia/erythrocytosis (reduction of red cell mass) and PCT (reduction of hepatic iron). Venesection is generally well tolerated and reduces morbidity in these conditions. Caution should, however, be exercised to avoid overdoing it and for haemochromatosis, PV or PCT are rebatable on the Medicare Benefits Schedule (MBS; item number 13757).

**Side effects**

Venesection is generally safe and has few side effects. Possible complications include local venepuncture site haematoma, phlebitis, nerve injury, venous scarring, hypovolaemia and vasovagal syncope.\textsuperscript{22,24} The patient should also be warned of feeling lethargic for a few days after the procedure.
there are guidelines on the target laboratory parameters as well as on the performance of the procedure itself in the doctor’s surgery.

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