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RESEARCH

Anaesthesia for a patient with beta thalassaemia major

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While beta thalassaemia is not a common disorder with an estimated 100 000 severely affected individuals worldwide, improved survival rates and increased global migration means an increased frequency of such patients being seen for various surgeries. The different aspects of this disorder have wide-ranging implications for anaesthesia. Thus, for safe anaesthetic care, the anaesthetist needs to have a good understanding of beta thalassaemia. Presented here is a case report of a 32-year-old gentleman with beta thalassaemia major presenting for elective laparoscopic cholecystectomy and splenectomy, followed by a discussion of the literature.

Keywords: anaemia, anaesthesia, beta thalassaemia, iron overload, laparoscopic cholecystectomy, splenectomy

Case report

In August 2014 Mr C, known to have beta thalassaemia major, presented for elective laparoscopic cholecystectomy and splenectomy. He had an eight-month history of gallstone-related symptoms progressing to two attacks of cholecystitis, worsening anaemia and jaundice.

Further questioning about his family history revealed that both his parents and three of his four siblings have beta thalassaemia minor. Mr C was diagnosed with beta thalassaemia major at around four months of age, after being noted with pallor by a family physician. He has required lifelong regular blood transfusions, receiving four units of washed red blood cell units every three weeks. He was also on lifelong iron chelation therapy, desferrioxamine and deferiprone. He had no cardiac or respiratory complications, and no history of endocrine or renal aberration attributable to iron overload. Prior to December 2013, he had no symptoms of liver dysfunction. A MRI done in December 2013 showed a normal heart, but moderate iron deposition in the liver. He had only one known adverse reaction to blood transfusion, and had no history of blood-borne infections and nothing else of note on history.

Mr C was thin and of short stature (weight 49 kg and height 153 cm), likely due to growth insufficiency from the disorder itself. No other skeletal abnormalities were evident. On general examination, he had pallor and jaundice. His cardiac assessment revealed a hyperdynamic circulation with elevated heart rate, but no other abnormalities. His respiratory examination was unremarkable. His abdominal examination revealed hepatomegaly and splenomegaly. Airway assessment showed no facial deformities, with Mallampatti grade 2 and normal range of movements at cervical spine and temporomandibular joints.

Preoperative blood investigations showed an anaemia with a haemoglobin of 10.1 g/dl, and elevated AST and ALT. Chest radiography, electrocardiography and lung function tests did not yield additional information. He had already been vaccinated in anticipation of the splenectomy.

In theatre, consent was checked, standard ASA monitors were placed, and a 16-G intravenous cannula was inserted. Elective sequence induction was performed with fentanyl, propofol and rocuronium. Intubation was achieved easily. Anaesthesia was maintained with a balanced mixture of oxygen, air and isoflurane. In preparation for the possibility of significant haemorrhage, a second 16-G intravenous line and arterial line were inserted. Aseptic technique was adhered to, and antibiotic prophylaxis administered. Pressure points were protected, and temperature monitoring and management instituted. The first arterial blood gas sample prior to surgery starting was within normal limits, except for a low haemoglobin of 7.6 g/dl. Blood was ordered to theatre; however, incorrectly only normal red packed cell units were received. In discussion with the blood bank and the patient's haematologist, it was decided to utilise these units. Graduated compression stockings were placed on the patient's legs, he was cleaned and draped, and surgery commenced. Ventilation was adjusted during peritoneal insufflation to keep the $ETC0_2$ within normal limits, and airway pressures were monitored. Vitals were consistently stable, and on serial arterial blood gas samples the haemoglobin remained above 7.5 g/dl. Due to the risk of alloimmunisation, blood transfusion of one unit was only initiated at the end of the procedure, titrated to observed blood loss. Analgesia was multimodal, including intravenous opioids and local blocks done under direct vision by the surgeon. At the end of the procedure of four hours' duration, neuromuscular blockade was reversed after checking the train-of-four count. The patient was successfully extubated, and transferred to the high-dependency unit awake and pain free. Postoperatively, he was placed on prophylactic low molecular weight heparin with early mobilisation. He received his standard washed red blood cell units and his further postoperative course was uncomplicated.

Discussion

Pathophysiology

Haemoglobin contains two alpha, and two non-alpha, globin chains attached to four iron-containing heme complexes.[1] Beta thalassaemia is a defect of the beta globin chains of the haemoglobin A molecule. The clinical presentation typically manifests at approximately four to six months of age, as during this time period haemoglobin F falls significantly to be replaced by haemoglobin A.[2] This genetic disorder is transmitted by autosomal recessive inheritance.[3] A defect in one beta globin

allele will result in beta thalassaemia minor. This is effectively a carrier state, and individuals are usually asymptomatic or present with anaemia. Defects in both alleles result in beta thalassaemia major, which results in a severe clinical picture requiring lifelong blood transfusions. A more moderate phenotype presenting with less blood transfusion dependence is called beta thalassaemia intermedia.[1] The cause behind this differing severity of disease from the same genotype is unknown. However, the type of mutation and gene interactions are thought to play key roles.[4]

Epidemiology

According to a WHO review in 2008, the disorder is most prevalent in the Asian and Mediterranean regions.[5] Theories to explain the higher numbers in these areas include protection against malaria and consanguinity.[6] Due to global migration of people, beta thalassaemia is being seen more frequently in other countries of the world.[6] About 1.5% of the world's population are carriers for beta thalassaemia, with an estimated 100 000 transfusion-dependent individuals living worldwide.[5,6]

Presentation and management

Due to this genetic abnormality, an excess of alpha chains is produced in the haemoglobin molecule. This creates an unstable profile, with precipitation of the alpha globins and resultant haemolysis of the red blood cell. As a result, there is increased but ineffective erythropoiesis.[4] This leads to multiple systemic manifestations as outlined in Table 1.

The cornerstone of treatment is blood transfusions.[7] Many specialised centres have 2–4-weekly transfusion programmes. Blood used is leucocyte-deplete with extended antibody typing that has been washed to reduce the risk of alloimunisation.[2,8] Patients who receive no or minimal blood transfusion in their lifetime generally only survive to the first/second decade of life.[6] However, this essential form of treatment comes with its own detrimental effects, including: worsening of iron overload; potential for adverse blood transfusion reactions; potential for transmission of blood-borne infections.[2] Iron overload is a significant complication, and without treatment results in mortality in the second/third decade of life.[3] Iron overload is due to chronic haemolysis, compensatory increased iron absorption from the gut, and frequent blood transfusions.[4] The adverse organ effects of iron overload are summarised in Table 2.

Iron overload is countered by iron chelation therapy with the current frequently used drugs being desferrioxamine, deferiprone and deferisarox. These do have potential side effects

Table 1: Systemic manifestations of the beta thalassaemia disorder[1,3,6,9,10,16]

Organ system	Defects	Pathophysiological mechanisms
Cardiac	Cardiomegaly, dilated cardiomyopathy, congestive cardiac failure	High output state due to chronic anaemia, and hypervolemia from plasma expansion due to shunting of blood through the expanded marrow
	Electrophysiological abnormalities including repolarisation irregularities with increased risk of Torsade de Pointes, and ventricular tachycardia	
Respiratory	Restrictive lung disease	Thoracic cage and spinal deformities
Muscle	Decreased muscle development and weight gain leading to growth retardation and small stature	Increased metabolic demand
		Decreased supply due to anaemia, chronic infections and frequent hospitalisations
Skeletal	Craniofacial deformities (frontoparietal bossing, prominent zygomatic bones, nasal bridge depression, maxillary prominence, dental abnormalities)	Expansion of ineffective extramedullary erythroid tissue
	Compression of neural structures (spinal cord, optic nerve in optic canal)	
	Middle-ear occlusion with conductive hearing loss	
	Osteopenia leading to pathological fractures	
Haematology	Severe hypochromic microcytic anaemia	Abnormal erythrocyte membranes leading to chronic haemolysis and sequestration by worsening splenomegaly
	Haemodilution coagulopathy	Large-volume blood transfusions
	Hypercoagulable state leading to increased risk of thrombosis (arterial thrombosis predominant in beta thalassaemia major and venous thrombosis in beta thalassaemia intermedia)	Reduced nitric oxide as haemolysis increases the amount of free haemoglobin and arginine, which leads to increased nitric oxide scavenging and decreased bioavailability respectively
		Erythrocyte membrane aberrations
		Platelet and endothelial activation due to free haemoglobin
		Low levels of antithrombin III, protein C and S
Vascular	Vasculopathy including pulmonary hypertension and silent cerebral infarctions	Reduced nitric oxide carriage
		Ischaemia-reperfusion injury
		Endothelial activation
Immunology	Immunosuppression, increased incidence of opportunistic infections	Chronic anaemia
		Nutritional deficiencies
	Risk of transmission of blood-borne infections	Frequent blood transfusions
		Iron overload
		Splenectomy
Hepatic	Increased incidence of gallstones	Chronic haemolysis
Neurology	Higher incidence of cognitive defects and impairment of neuropsychological tests	Chronicity of disease with emotional, psychosocial and financial burdens
	Increased incidence of depressive symptoms	Varying limitations on quality of life

Table 2: Adverse organ effects of iron overload[4,7,9,18]

Organ system	Clinical feature
Cardiac	Cardiac hypertrophy, chamber enlargement, cardiomyopathy, subpericardial deposits leading to myocarditis and pericarditis
Endocrine	Endocrinopathies (particularly diabetes mellitus, hypogonadism, hypoparathyroidism, hypothyroidism) caused by iron toxicity in the anterior pituitary gland, pancreas and thyroid
Hepatic	Fibrosis leading to cirrhosis, liver failure, and increased risk of hepatocellular carcinoma
Renal	Nephrotoxicity compounded by anaemia, rapid correction of iron overload, and nephrotoxic iron chelating agents
	Tubular dysfunction with hyperfiltration and reduced concentrating ability leading to: proteinuria; aminoaciduria; increased excretion of calcium, magnesium, and phosphate
	Glomerular dysfunction with increased glomerular filtration and creatine clearance
Immune system	Immunosuppression
	Increased risk of bacterial infections, especially *Yersinia* and *Klebsiella* species
Respiratory	Lung fibrosis with or without interstitial oedema leading to restrictive lung disease (compounded by thoracic cage skeletal abnormalities)

such as: sensorineural deafness, visual disturbances, vertebral dysplasia, growth retardation (desferrioxamine); agranulocytosis (deferiprone); transient deterioration in renal function, skin rashes, and gastrointestinal upset (desferasirox).[3] Splenectomy has been shown to be effective in reducing transfusion requirements and improving morbidity.[2,4] However, a splenectomy has its own host of complications, including increased risk of postoperative infections and thrombotic events.[9] More novel treatment modalities include: stem cell transplantation; foetal haemoglobin inducers; gene therapy.[2]

Anaesthesia

The cardiovascular system should be carefully evaluated with particular attention to a history of poor exercise tolerance and dyspnoea.[9] Preoperative evaluation will guide investigations such as electrocardiogram, echocardiography and cardiac catheterisation.[2,10] If cardiac involvement is suspected, caution is warranted with cardiac suppressant agents intraoperatively and with the use of neuroaxial techniques to avoid depression of high cardiac output state.[11] Depending on the operation, close haemodynamic monitoring should be considered with modalities such as an arterial line, minimally invasive cardiac output monitors, and transoesophageal echocardiography.[10]

Patients may present with asymptomatic restrictive lung disease, although occasionally an obstructive respiratory picture may be seen.[12] Lung function tests are useful for diagnosis of this condition, and for quantification of severity. It must also be borne in mind that these patients may present with pulmonary hypertension.[13] Thus it is prudent intraoperatively to avoid conditions that will worsen pulmonary hypertension such as acidosis, hypoxia and hypercarbia. Ventilatory strategies will need to be tailored to the patient's underlying respiratory pathology.

A full blood count should be done preoperatively. There is no standardised haemoglobin for surgery, but a baseline level of 10 g/dl or above is generally recommended.[2,14] Patents with low haemoglobin should be transfused preoperatively.[11] Leucodepleted blood is generally used to reduce the risk of alloimunisation.[8,11] Blood-conserving strategies should be considered in high-risk procedures, due to a low tolerance for bleeding.[14] Blood salvage is controversial due to increased risk of haemolysis, but has been used safely with low suction pressures and leucocyte depletion filters.[1,14] There are no standardised anaesthesia guidelines for intraoperative blood transfusion triggers for patients with beta thalassaemia. However, taking into account the recommended baseline trigger of 10 g/dl, it would be reasonable to continue this recommendation intraoperatively. Due to increased incidence of blood-borne infections in these patients, caution must be exercised by staff in exposure to the patient's blood.[11]

Iron chelation therapy should be optimised with the patient's attending physician.[2] Both complications of iron overload and adverse effects of iron chelation therapy need to be borne in mind.[3,7] Iron studies are usually routinely monitored in these patients, although MRI studies tend to give a more accurate reflection of target organ damage.[7]

The coagulation profile will need to be checked due to the hypercoaguable milieu. However, normal results do not exclude a potential for thrombosis. Thus measures still need to be taken perioperatively to reduce this risk, for example: compression stockings; low molecular heparin; mobilisation.[13] The risk of thromboembolism is increased in: beta thalassaemia intermedia; post-splenectomy; advancing age; transfusion independence; personal or family history of thromboembolic events.[13]

Due to possible renal damage, electrolytes should be checked preoperatively and corrected as required, preoperative renal function assessed, and renal-protective measures taken as appropriate.[15] Liver function tests should also be assessed preoperatively.[3] To minimise further injury, hepatotoxic medications should be avoided.[3] Endocrine abnormalities should be looked for preoperatively and optimised accordingly.[3] Glucose tolerance tests or thyroid function tests may be indicated, guided by clinical assessment.[2]

These patents are immunosuppressed, thus aseptic vigilance must be maintained at all times. Prior to a splenectomy, pneumococcal, meningococcal and H influenza type B immunisations are recommended.[16] Appropriate antibiotic prophylaxis should be administered.[6] In these patients, there is an increased risk of poor wound healing postoperatively.[10]

Both general anaesthesia and neuroaxial techniques have been reported as being used safely.[9] The technique used must be tailored according to the patient and surgery involved. Osteopenia and micro-fractures necessitate careful transfers and positioning.[9] Skin ulcerations if found should be noted, and careful padding is required.[9] Additional factors to note are

potentially difficult intravenous access, sizing of monitors due to small stature, and effect of severe anaemia on pulse oximetry readings.[17] No specific anaesthesia agents are dictated, but rather the choice of agents to be used will be decided by the patient's clinical condition and the surgery planned. These patients are at high risk for difficult airway management due to facial skeletal deformities.[1,11] If a neuroaxial technique is to be done, skeletal deformities, pre-existing neurological deficits and a hypercoaguable profile must all be taken into consideration.[9]

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