orphanaesthesia

Anaesthesia recommendations for patients suffering from

Paroxysmal nocturnal haemoglobinuria (PNH)

Disease name: Paroxysmal nocturnal haemoglobinuria (PNH)

ICD 10: D59.6

Synonyms: Marchiafava-Micheli disease; PNH

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disease caused by somatic mutations in the PIGA gene (Xp22.1), encoding a protein involved in the biosynthesis of the glycosylphosphatidylinositol (GPI) anchor. The mutation occurs in one or several hematopoietic cells and leads to a lack (total or partial) of all GPI-anchored cell membrane proteins (the most important being CD55 and CD59). PNH had a prevalence of up to 1.6/100,000, a 5-years mortality about 35% and a median survival of 10-15 years. After bone marrow transplant, the majority of deaths occur within the first years of transplantations while the probability to survive at 2 years is 56%. Symptoms and complications of PNH are caused by the deficiency of CD55 and CD59, proteins regulating and stabilizing the complements cascade, on PNH erythrocytes. The lack of CD55 and CD59 is responsible for a complement mediated intravascular hemolysis mainly associated to hemoglobinuria, thrombosis and bone marrow failure. Furthermore, cell-free plasma hemoglobin in PNH leads to depletion of nitric oxide causing smooth muscle dystonia and altering the vascular tone. For these reasons in a clinical context, hemolysis of PNH is associated with anemia, weakness, dyspnea, fatigue, renal impairment, need for transfusions, pulmonary hypertension, abdominal pain and thromboembolic complications.

Medicine in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Disease summary

The main anaesthetic concerns in PNH consist in preventing the activation of complement cascade during the perioperative period. Any stressful situations may activate or exacerbate the complement cascade.

An optimal perioperative management of patients with PNH includes the use of eculizumab, a novel antibody blocking the terminal complement cascade, blood cells transfusion and antibiotic prophylaxis, the avoidance of hypoxemia, acidosis, dehydration and drugs known to activate complement cascade.

Typical surgery

Literature review is limited to case reports of PNH patients presenting cholecystectomy, caesarean section, coronary artery bypass, cardiac valve repair and peripheral vascular surgery.

PNH patients have an increased risk of venous and arterial thromboembolic complications or haemorrhages in different organs and system of the body, so surgical and/or invasive procedure may take place in these situations.

Type of anaesthesia

There is no definite recommendation for general and regional anaesthesia.

Literature reported case reports about the use of general anaesthesia for different surgical procedure in PNH patients. General anaesthesia in PNH patients must eliminate the stress response to surgical stimuli, achieving a deep anaesthetic and analgesic level.

General anaesthesia in PNH patients should avoid or minimize:

1) complement activation
2) hypoxemia
3) acidosis
4) dehydration

Regional anaesthesia may be difficult to apply in PNH patients depending on their degree of thrombocytopenia and their need of immediate anticoagulation in case of acute exacerbation of this disease or thromboembolic complications.

Necessary additional diagnostic procedures (preoperative)

PNH is associated to aplastic and/or iron-deficiency anaemia, haemolysis and thrombosis. Patients should have full blood count, coagulation screening including d-dimeres, blood chemistry test including LDH, electrolytes, kidney and liver function. LDH is a very good parameter to estimate the ongoing haemolytic activity. Urine test is helpful to assess the presence of an active haemoglobinuria. Analysis of complement components, as C3 and C4, might be useful to evaluate the basal complement activity before the surgical procedure.

PNH is associated to cerebral, abdominal, pulmonary and liver complications due to its pathogenesis. So, in case of previous complications or focused symptoms, further investigations are needed. For example, in case of recurrent abdominal pain or thrombosis of abdominal vessels, an (duplex-)ultrasound evaluation of the site should be done. In case of suspected or confirmed pulmonary hypertension, more specific test to assess functional or hemodynamic impairment is required (BNP, echocardiograph).

Particular preparation for airway management

Difficult swallowing and breathing may appear during haemolytic crisis in PNH patients.

Literature has not reported cases of difficult airway management in PNH.

The main concern about the airway management in PNH patients is to apply a good analgesia to prevent the stress response to endotracheal intubations.

However, if a difficult airway is suspected, a protocol according to national and international guidelines should be applied.

Particular preparation for transfusion or administration of blood products

PNH patients required blood transfusions due their state of anaemia. Post transfusions haemolysis may occur in PNH patients while using ABO incompatible plasma or prolonged storage blood cells, even if with lower incidence.

Washing blood transfusion could be avoided using group specific fresh blood and blood products. However, if patients need large volume of blood in a short period of time, as acute bleeding or emergency situations, the role of washed red cells needs to be taken into account.

Particular preparation for anticoagulation

Prophylaxis with heparin or LMWH should be used during the perioperative period. Aggressive anticoagulation with heparin or LMWH in combination with eculizumab should be used in acute thrombotic episode. However when platelet count is less $10x10^9$/L anticoagulation is contraindicated while it should be used with a platelet count greater then 50 $x10^9$/L. In patients with platelet counts between 30 and 50 $x10^9$/L, a reduced dose of LMWH is probably appropriate.

Particular precautions for positioning, transport or mobilisation

Not reported.

Probable interaction between anaesthetic agents and patient's long-term medication

Eculizumab, a human monoclonal antibody approved by the US Food and Drug Administration and EMA, which binds C5 preventing its activation to C5b and thereby inhibiting MAC formation, is used as standard treatment of symptomatic PNH.

For PNH patients chronically treated with eculizumab, surgery should be planned right after the last infusion of eculizumab (e.g. next day). Eculizumab administration during perioperative period may give a better control on complement activity. This monoclonal antibody may have synergic activity on complement regulation but has no direct effect on the pharmacokinetics and pharmacodynamics of anaesthetic drugs. It is suggested that the reduction of complement levels in the perioperative period may be due to a synergistic effect of anaesthetic management and monoclonal antibody therapy. Extra dosing of eculizumab should be considered for PNH patients with breakthrough hemolysis/uncontrolled hemolysis.

Anaesthesiologic procedure

Antibiotic prophylaxis could be administered before starting surgery. For general anaesthesia, propofol in lipid emulsion is suitable for induction because it is not associated to complement activation. Since haemoglobinuria is frequently associated to dark colour urine, long-time infusion of propofol causing urine discoloration should be discouraged in PNH patients. Sevoflourane should be suitable for anaesthesia maintenance because it is showed that this volatile anaesthetic significantly reduces the complement activation and the levels of complement fragment. N_2O should be avoided because of its myelodepressant effects. Analgesia during surgery may be obtained with remifentanil TCI or intermittent fentanyl with the aim to firmly reduce the stress response to surgical stimuli. Neuromuscular blockade should be considered using drugs with lower rate of cross-reactivity and anaphylaxis. Accurate fluid management should be obtained with crystalloids avoiding colloids for its effects on complement activation.

Particular or additional monitoring

Bispectral index or other non-invasive cerebral monitoring may be useful to assess the level of anaesthesia.

Neuromuscular relaxation monitoring using patterns of electrical nerve stimulation as train-of-four, tetanic or post-tetanic count, double burst stimulation, are controversial in PNH because their continuous or alternate stimulation may trigger the complement activation. Furthermore, it is better to evaluate the neuromuscular relaxation by clinical or capnographic curve.

When needed according to the level of surgical risks, it is better to use non-invasive monitoring then invasive monitoring to avoid further complication from complement and coagulation activation.

Analysis of parameters of haemolysis especially LDH-levels and haemoglobin are useful to evaluate the hemolytic and complement activity during the surgery.

Possible complications

Haemolytic crisis and -aemia, haemoglobinuria, infection, thromboembolic complication, acute bleeding may complicate the postoperative period.

Postoperative care

Postoperative analgesia is needed to avoid postoperative pain. Pain may be treated with NSAIDs and opioids according to pain levels and patient characteristics.

Urine test after surgery is needed to assess possible haemoglobinuria.

Analysis of LDH-levels are useful to evaluate the level of hemolysis and complement activity after the surgical procedure.

Full blood count and coagulation screening including d-dimers are useful to check possible exacerbation of anaemia, infection and thrombosis.

Information about emergency-like situations / Differential diagnostics

caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the disease

Fulminant haemolysis, thrombosis of abdominal vessels, deep vein thrombosis, pulmonary embolism, sinus-vein thrombosis, meningogoccal infection during eculizumab treatment.

Ambulatory anaesthesia

Ambulatory anaesthesia should be done in non-symptomatic and well-controlled PNH patients in low risk surgery, in spite of which, the patients should be protected against all causes of complement activation as, pain, anxiety, infection, radiocontrast agents etc.

Obstetrical anaesthesia

Pregnancy is possible for women with PNH, but it is potentially hazardous for mother and infant. Pregnancy in PNH patients is risky and leads to complications as cytopenia, transfusion dependency, thrombosis, need of anticoagulation, eculizumab treatment and immunosuppressant (for cytopenia due to bone marrow failure).

Literature reported cases of caesarean section in PNH patients treated with general or regional anaesthesia. The choice of the type of anaesthesia must take into account the risk

of acute bleeding, coagulation disorders and the need of high dose of anticoagulation in PNH thrombocytopenic patients.

Vaginal delivery is still possible in PNH patients but the analgesic administration through epidural catheter must consider the risk of anticoagulation dosage and coagulation disorders. Literature reported a case of vaginal delivery using a regimen of regular pethidine injections to minimize the labour stress.

Blood transfusion, anticoagulation and eculizumab may reduce the risk and complications of fulminant haemolysis and thrombosis.

A close control of blood count, coagulations screening including d-dimers and clinical evaluation should be performed after the delivery to reduce and prevent further complications. Need for anticoagulation is recommended during pregnancy and at least 6 weeks postpartal.

Literature and internet links

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Please note that this guideline has not been reviewed by an anaesthesiologist but by two disease experts instead.