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Anesthetic and Perioperative Management of Patient with Paroxysmal Nocturnal Hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disorder. Surgery, anesthesia, infection, trauma, and pregnancy can exacerbate hemolysis and thrombotic risk by increasing complement activity. However, perioperative treatment of eculizumab can reduce risk of hemolytic event by surgical stress. Here, we present the perioperative clinical course and adequate anesthetic management of PNH complicated by spine surgery under general anesthesia. We also describe a possible role of eculizumab for PNH patients with anticipated high risks.

Keywords: Hemoglobinuria, Hemolysis, Paroxysmal, Thrombosis

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disorder for biosiynthesis of glycosyl phosphatidylinositol (GPI) caused by a somatic mutation of the PIGA gene [1]. Clinical manifestations such as hemolytic anemia, bone marrow failure and thrombosis depend on uncontrolled complement activation by GPI anchor protein deficiency [2]. Surgery, anesthesia, infection, trauma, and pregnancy can exacerbate hemolysis and thrombosis risk by increasing complement activity [3]. Eculizumab, which is a humanized monoclonal antibody against C5 for inhibiting complement activation, can reduce intravascular hemolysis and the need for red blood cell transfusion [4]. Kurita et al. showed that perioperative induction of eculizumab inhibited any significant

complications of PNH complicated by gastrectomy [5].

Here, we present the perioperative clinical course and adequate anesthetic management of PNH patient undergoing spine surgery under general anesthesia. We also describe a possible role of eculizumab for PNH patients with anticipated high risks.

Case

A 65-year-old man (64 kg, 164 cm) was scheduled for elective spine surgery by low back pain. He was diagnosed PNH with peripheral blood morphology study and flow cytometry for CD55 and CD59 10 years ago. He presented with dyspnea on exertion and general fatigue. Preoperative transthoracic echocardiogram showed pulmonary hypertension (Right ventricular systolic pressure = 37 mmHg). Treatment changed from pack RBC transfusion and iron loading to eculizumab 900 mg every 2 weeks from 3 years ago. After eculizumab treatment, his lactate dehydrogenase (LDH) level was significantly reduced from 5000~7000 IU/L to 500~700 IU/L and the frequency of transfusions was also reduced. Before one week surgery, he underwent a routine eculizumab treatment and pack RBC two units of transfusion because his hemoglobin was 8.6 g/dL.

In the operating room, noninvasive blood pressure, electrocardiogram, oxygen saturation (SpO_2), bispectral index (BIS), esophageal temperature and urine output monitoring were initiated. General anesthesia was induced with propofol (1.5 mg/kg), rocuronium (0.8 mg/kg), and a continuous infusion of remifentanil (1 μg/kg/h). After tracheal intubation, anesthesia was maintained with sevoflurane in 50% oxygen and remifentanil (0.1 - 0.5 μg/kg/h) to maintain BIS 40 to 60. Continuous infusion of rocuronium was also used for preventing unexpected movement during microscopic surgery. Because operation was expected a large amount of bleeding, a vascular catheter was inserted into the right radial artery and left femoral vein.

Despite the blood loss was more than 500 mL during the operation, the vital sign remained mean arterial pressure 80~90 mmHg and heart rate 70~80 bpm. Because hemoglobin in laboratory blood test was 7.5 g/dL, two units of pack RBC were transfused. At the end of surgery, he was extubated after the return of neuromuscular block and consciousness. Intravenous self controlled analgesia with fentanyl and oral oxycodone 5 mg was performed for postoperative analgesia.

Hemoglobin was 9.4 g/dL on the first postoperative day (POD) laboratory finding, so he didn't need to transfusion during hospitalization. We could not find thrombotic event such as deep vein thrombosis, pulmonary embolism and portal vein thrombosis. He was administered a routine eculizumab on the eighth POD and discharged on the ninth POD. Laboratory finding performed 3 weeks after surgery was no meaningful difference between preoperative and postoperative state (Table. 1).

Discussion

Surgical procedures and anesthesia is the major risk factors triggering hemolysis and thrombosis in a PNH patient via complement activation [3]. During perioperative setting, various inflammatory cytokines response to surgical procedures and acidotic environment caused by hypoperfusion, hypoxemia, and hypercapnia can aggravate complement-mediated intravascular hemolysis of PNH [6,7]. Moreover, prophylactic administration of antibiotics for surgery can trigger hemolysis, especially in PNH patients with bone marrow aplasia [8]. Therefore, it is important to stabilize patient and to avoid complement activation in perioperative period. In this case, we carefully monitored to avoid hypoxemia, hypercapnea and

Table 1. Serial laboratory data around surgery

	Before surgery		After surgery	
	1 week	1 day	1 day	3 weeks
RBC (M/uL)	2.57	2.96	3.14	2.87
WBC (K/uL)	4.07	3.51	5.42	3.93
Hemoglobin (g/dL)	9.6	10.6	10.4	9.3
Hematocrit (%)	29.9	31.2	32.2	29.7
LDH (IU/L)	647	-	-	713
Total bilirubin (mg/dL)	6.52		5.18	2.23
Reticulocyte count (%)	14.66	-	-	10.54

RBC: red blood cell counts, WBC: White blood cell counts, LDH: lactate dehydrogenase.

acidosis in perioperative period by maintaining of oxygen saturation, end tidal CO_2 and blood pH within normal range [9]. Furthermore, maintaining proper anesthetic depth is also essential to avoid exacerbation by uncontrolled complement activation due to surgical stress. He was maintained with 30-50 of BIS level during surgery.

In terms with anesthetics, volatile agent like sevoflurane can reduce complement activation by decreasing C3 and C4 levels up to 70% [10]. However, N2O should be avoided in a case of PNH because of its myelodepressant effects [11]. Propofol does not produce anaphylactoid reaction by activation of complement, immunoglobulin level, and plasma histamine concentration [12]. Sufficient analgesia during surgery is also needed to prevent complement activation due to surgical stress. In particular, remifentanil infusion is more effective in inhibiting the endocrine stress response than intermittent fentanyl administration [13]. In addition to, adequate analgesic control in the recovery room is as important as in the operating room. In this case, we used propofol for induction and balanced anesthesia with sevoflurane and remifentanil. Moreover, we used intravenous PCA for management of postoperative pain.

Pulmonary hypertension is one of the complications by chronic hemolysis of PNH [14]. Intravascular hemolysis can lead to increase free hemoglobin in the plasma and consumption of endogenous nitric oxide. Decreased nitric oxide results in endothelial dysfunction, smooth muscle constriction, and increased peripheral resistance in the pulmonary vessels [15]. Preoperative pro-brain natriuretic peptide (proBNP) test, electrocardio-graphy, echocardiography, and chest radiography are needed for evaluation of perioperative risk. In the intraoperative period, it is need to choice anesthetics with little effect on pulmonary circulation and right ventricle. Preventing hypoxemia, hypercapnea, and hypothermia is also important to management of pulmonary hypertension [16]. In addition to eculizumab, a humanized monoclonal antibody against C5, which blocks the terminal complement cascade, can reduce signs of pulmonary hypertension such as proBNP and dyspnea by preventing depletion of nitric oxide [17,18].

Administration of eculizumab can reduce transfusion requirements and quality of life by improving symptoms of intravascular hemolysis [17]. Even in cases using eculizumab for a limited period of time, surgical related hemolysis could be prevented [5]. Moreover, discontinuation of eculizumab may result in critical hemolytic complications. In this case, the

perioperative eculizumab may help the successful management of a patient who underwent spine surgery without any catastrophic complications.

In conclusion, the goal of anesthetic management for PNH patients is reducing of complement activation for preventing intravascular hemolysis. For this reason, there is a need for a strategy to avoid drugs and anesthetic techniques that promote complement activation. Perioperative treatment of eculizumab can reduce risk of hemolytic event by surgical stress in the operating room and signs of pulmonary hypertension.

References

1. Takeda J, Miyata T, Kawagoe K, Iida Y, Endo Y, Fujita T, *et al*. Deficiency of the GPI anchor caused by a somatic mutation of the PIG-A gene in paroxysmal nocturnal hemoglobinuria. *Cell* 1993;**73**:703–11.
2. Brodsky RA. Narrative review: paroxysmal nocturnal hemoglobinuria: the physiology of complement-related hemolytic anemia. *Ann Intern Med* 2008;**148**:587-95.
3. Röth A, Dührsen U. Treatment of paroxysmal nocturnal hemoglobinuria in the era of eculizumab. *Eur J Haematol* 2011;**87**:473–9.
4. Vargas M, Lallo C, Marra A, Servillo G. Anaesthesia and orphan disease: laparoscopic cholecystectomy with paroxysmal nocturnal haemoglobinuria and human mAb therapy. *Eur J Anaesthesiol* 2013;**30**:770-2.
5. Kurita N, Obara N, Fukuda K, Nishikii H, Sato S, Inagawa S, *et al*. Perisurgical induction of eculizumab in a patient with paroxysmal nocturnal hemoglobinuria: its inhibition of surgery-triggered hemolysis and the consequence of subsequent discontinuation. *Blood Coagul Fibrinolysis* 2013;**24**:658-62.
6. Naito Y, Nakajima M, Inoue H, Tsuchiya K. Successful CABG in a patient with paroxysmal nocturnal hemoglobinuria. *Eur J Cardiothorac Surg* 2004;**25**:468–70.
7. Kathirvel S, Prakash A, Lokesh BN, Sujatha P. The anesthetic management of a patient with paroxysmal nocturnal hemoglobinuria. *Anesth Analg* 2000;**91**:1029–31.
8. Ghoreishi M, Baer MR, Bhargava R, Stauffer CE, Griffith BP, Gammie JS. Aortic valve bypass for aortic stenosis in a patient with paroxysmal nocturnal hemoglobinuria. *Ann Thorac Surg* 2010;**90**:279–81.
9. Vargas M, Lallo C, Marra A, Servillo G. Anaesthesia and orphan disease: laparoscopic cholecystectomy with paroxysmal nocturnal haemoglobinuria and human mAb therapy. *Eur J Anaesthesiol* 2013;**30**:770-2.
10. Lewis RE, Jr., Cruse JM, Richey JV. Effects of anesthesia and operation on the classical pathway of complement activation. *Clin Immunol Immunopathol* 1982;**23**:666-71.
11. Taylor MB, Whitewam JG, Worsley A. Paroxysmal nocturnal haemoglobinuria. Peri-operative management of a patient with Budd-Chiari syndrome. *Anaesthesia* 1987;**42**:639-42.
12. Doenicke A, Lorenz W, Stanworth D, Duka T, Glen JB. Effects of propofol ('Diprivan') on histamine release, immunoglobulin levels and activation of complement in healthy volunteers. *Postgrad Med J* 1985;**61**(Suppl.3):15-20.
13. Winterhalter M, Brandl K, Rahe-Meyer N, Osthaus A, Hecker H, Hagl C, *et al*. Endocrine stress response and inflammatory activation during CABG surgery. A randomized trial comparing remifentanil infusion to intermittent fentanyl. *Eur J Anaesthesiol* 2008;**25**:326-35.
14. Hill A, Sapsford RJ, Scally A, Kelly R, Richards ST, Khurisgara G, *et al*. Under-recognized complications in patients with paroxysmal nocturnal haemoglobinuria: raised pulmonary pressure and reduced right ventricular function. *Br J Haematol* 2012;**158**:409–14
15. Machado RF, Gladwin MT. Chronic sickle cell lung disease: new insights into the diagnosis, pathogenesis and treatment of pulmonary hypertension. *Br J Haematol* 2005;**129**:449-64.
16. Pilkington SA, Taboada D, Martinez G. Pulmonary hypertension and its management in patients

undergoing non-cardiac surgery. *Anaesthesia* 2015;**70**:56-70.
17. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Educ Program* 2016;**2016**:208-16.
18. Hill A, Rother RP, Wang X, Morris SM Jr, Quinn-Senger K, Kelly R, *et al*. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol* 2010;**149**:414-25.