


Propofol-Related Infusion Syndrome: Diagnosis and Management

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ABSTRACT

Propofol-related infusion syndrome (PRIS), first described in 1990, is a rare and dangerous condition caused by high-dose (> 4 mg/kg/hour) and prolonged (> 48 hours) administration of propofol in mechanically ventilated patients. This condition is characterized by a progressive constellation of multi-organ failure. The main clinical presentations include severe metabolic and lactic acidosis, rhabdomyolysis, acute liver failure, lipemic blood, hyperkalemia, and cardiovascular impairment or marked bradycardia, which can lead to cardiac arrest. The mechanism of PRIS remains unclear and is likely controversial. The most effective way to prevent PRIS is to remain vigilant and maintain a high level of suspicion during prolonged propofol administration. Early recognition of clinical manifestations, prompt discontinuation of propofol infusion, and timely initiation of supportive management are essential to reduce morbidity and mortality associated with PRIS. Understanding the underlying pathophysiology and identifying patients at high risk may improve preventive strategies and optimize outcomes in critically ill patients receiving prolonged propofol infusion.

Keywords: Management PRIS, propofol, propofol-related infusion syndrome, severe lactic acidosis, severe metabolic acidosis.

ABSTRAK

Sindrom terkait infus *propofol* (PRIS), pertama kali dikenalkan pada tahun 1990, merupakan kondisi langka dan berbahaya disebabkan oleh pemberian *propofol* dosis tinggi (> 4 mg/kg/jam) yang berkepanjangan (> 48 jam) pada pasien yang menggunakan ventilasi mekanis. Kondisi ini ditandai dengan konstelasi gejala progresif yang melibatkan kegagalan multi-organ. Presentasi klinis utama meliputi asidosis metabolik dan laktat berat, rabdomiolisis, gagal hepar akut, darah lipemik, hiperkalemia, dan gangguan kardiovaskular atau bradikardia, yang dapat menyebabkan henti jantung. Mekanisme PRIS masih belum jelas dan kontroversial. Cara paling efektif untuk mencegah PRIS adalah dengan tetap waspada dan mempertahankan tingkat kecurigaan yang tinggi selama pemberian *propofol* dalam jangka waktu lama. Pengenalan dini terhadap manifestasi klinis PRIS, penghentian segera pemberian *propofol*, serta pemberian terapi suportif yang tepat sangat penting untuk menurunkan morbiditas dan mortalitas. Pemahaman mengenai faktor risiko serta mekanisme patofisiologi PRIS diharapkan dapat membantu klinisi dalam melakukan deteksi dini dan pencegahan komplikasi pada pasien kritis yang mendapatkan infus *propofol* berkepanjangan. **Hori Hariyanto, Carla Oktaviani Pandrya, Kevin Anderson Surya. *Propofol-Related Infusion Syndrome*: Diagnosis dan Tata Laksana.**

Kata Kunci: Tata laksana PRIS, *propofol*, sindrom terkait infus *propofol*, asidosis laktat berat, asidosis metabolik berat.

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INTRODUCTION

Propofol-related infusion syndrome (PRIS) is a rare and potentially fatal condition that was first described in 1990. This adverse body reaction to propofol first occurred in a 3-year-old girl from Denmark,[1] characterized by severe metabolic acidosis and bradycardia, which progressed to asystole (cardiac arrest). Five children were also reported to have died following continuous administration of propofol in 1992.[2] PRIS primarily affects the pediatric population and causes severe neurodevelopmental damage in children under the age of three.[3,4]

Recently, this condition was found in adults receiving prolonged (> 48 hours) and high-dose (> 4 mg/kg/hour) administration of propofol infusion. The first adult death from PRIS occurred in an asthmatic patient in 1998, whose condition deteriorated due to prolonged propofol sedation for mechanical ventilation.[3,5]

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The pathophysiology remains unknown due to its complex nature, but recent experimental and clinical research has concentrated on the mitochondrial respiratory chain dysfunction caused by propofol.[6] Although difficult to quantify, the incidence of PRIS likely affects less than 2% of patients treated with propofol. However, it is associated with high mortality (up to 80%).[5]

The definition of PRIS is still unclear and difficult to determine; there are too many case variations, and it can resemble other conditions. It is characterized by a progressive constellation of symptoms involving multi-organ failure. The main clinical presentations include severe metabolic and lactic acidosis with no apparent cause, rhabdomyolysis, hyperlipidemia, hepatomegaly, acute liver failure, lipemic blood, hyperkalemia, and cardiovascular impairment or marked bradycardia, which can lead to cardiac arrest.[4,7]

MAIN REVIEW

Clinical Pharmacology of Propofol (Mechanism of Action)

Propofol (2,6-diisopropylphenol), initially developed in 1973 in London, is an intravenous anesthesia agent. It is most frequently used for procedural sedation, as an induction agent for general anesthesia, or for maintenance of anesthesia care.[8] It has a rapid onset of action and a short half-life, which allows for quicker awakening after discontinuation of the infusion, and the dosage can be easily adjusted to maintain the desired level of sedation.[4]

Although the mechanism of action for propofol is still poorly understood, it is believed that propofol exerts its effect by enhancing the activity of GABAergic neurons in the central nervous system (ventrolateral preoptic area/VLPO) **(Figure 1)**.[11] It acts on the GABA-A receptor and binds to these receptors, extending the frequency and duration of the opening of chloride channels. This causes hyperpolarization of the postsynaptic neuronal membrane, and excitatory inputs are indirectly promoted to GABAergic neurons, leading to inhibition, increasing glutamate release, and subsequent sedation.[4,9,10]

Pathophysiology

The complicated process of PRIS makes its pathophysiology remain unknown. Under physiological conditions, glucose serves as the primary energy source for various body systems. However, the body shifts toward using free fatty acids (FFA) as the primary energy source for most biological tissues during stress. The shift is driven by the activation of stress hormones (epinephrine, cortisol, *etc*), which regulate hormone-sensitive lipase activity in adipose tissue. Lipase activity breaks down triglycerides into glycerol and FFA; glycerol serves as a source for glucose synthesis, and FFA undergo mitochondrial beta-oxidation.[10]

There are two possible pathophysiological theories why propofol can inhibit the energy sources and cause PRIS: (1) Blocking the transport of FFA and (2) Inhibiting the mitochondrial electron transport chain.[7]

Lipase activity breaks down triglycerides into

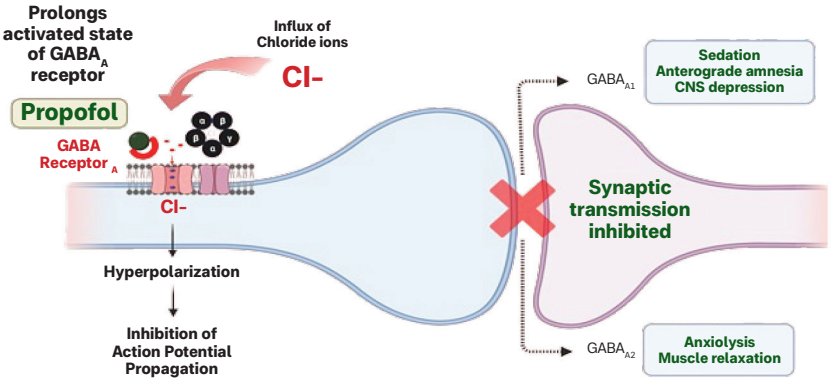

Figure 1. Propofol mechanism of action.[9]
Abbreviations: GABA: Gamma-aminobutyric acid, Cl: Chloride.

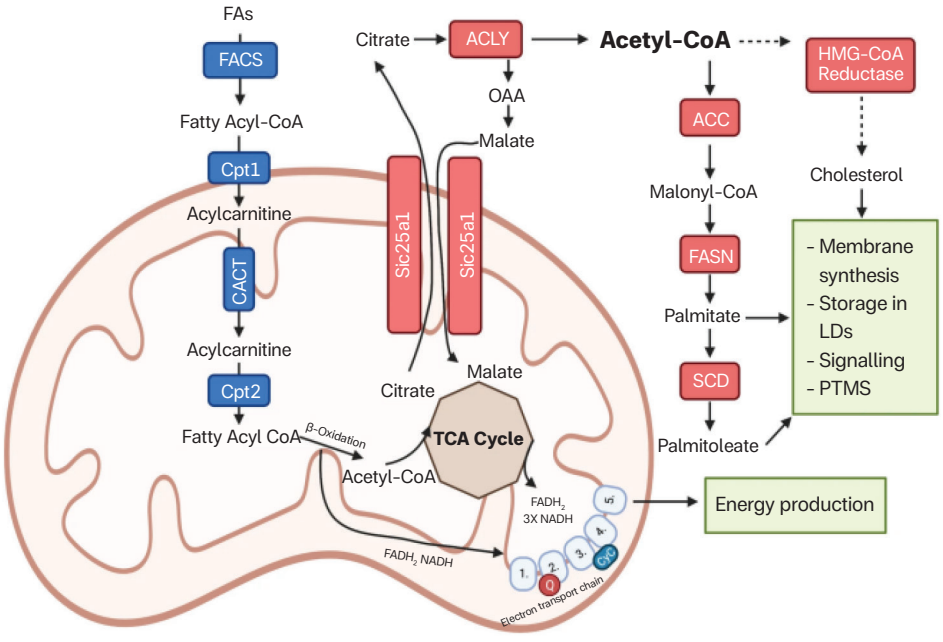

Figure 2 . Overview of lipid metabolism.[11]
Abbreviations: FAs: Fatty acids; FACS: Fatty acyl-CoA synthetase, CPT1: Carnitine palmitoyl-transferase 1; CACT: Carnitine acyl-carnitine translocase; CPT2: Carnitine palmitoyl-transferase 2; ACLY: ATP citrate lyase; OAA: Oxaloacetic acid; TCA cycle: Tricarboxylic acid cycle; $FADH_2$: Reduced flavin adenine dinucleotide; NADH: Reduced nicotinamide adenine dinucleotide; ACC: Acetyl-CoA carboxylase; FASN: Fatty acid synthase; SCD: Stearoyl-CoA desaturase; HMG-CoA: 3-Hydroxy-3-methylglutaryl-coenzyme A; LDs: Lipid droplets; PTMs: Post-translational modifications.

glycerol and free fatty acids (FFA); glycerol serves as a substrate for glucose synthesis, whereas FFA undergo mitochondrial beta-oxidation to generate acetyl-CoA, which subsequently enters the tricarboxylic acid (TCA) cycle and the electron transport chain to sustain ATP production **(Figure 2)**.[10]

FFA is changed to acyl-CoA by acyl-CoA synthetase. Propofol prevents acyl-CoA from bonding with carnitine palmitoyltransferase-I, an enzyme located outside the mitochondrial membrane. This enzyme tends to be responsible for transforming acyl-CoA into fatty acyl carnitine and entering the inner mitochondrial membrane, then binding to carnitine palmitoyltransferase-II and transforming it into carnitine. Thus, the transformation from the fatty acyl group to carnitine is hampered, and the acylcarnitine complex accumulates.[4,12]

Propofol is also known to impact the mitochondrial electron transport chain directly. Free fatty acids should undergo beta-oxidation in the mitochondria to produce acetyl-CoA for the citric acid cycle and sustain ATP production, generating free electrons as part of the biosynthetic process. Propofol disrupts oxidative phosphorylation and obstructs the flow of electrons within the electron transport chain across the inner mitochondrial membrane. There are four complex components in the transport chain. During oxidative phosphorylation, electrons from the reduced coenzymes nicotinamide adenine dinucleotide (NADH) and succinate, produced by the citric acid cycle, enter the electron transport chain (ETC) via complex I to coenzyme Q (CoQ). The second complex then converts succinate to fumarate with the assistance of CoQ. These electrons are then passed to complex III and become Cytochrome C (Cyt C), then passed to the fourth complex and become cytochrome C oxidase through CoQ. This electron transfers process drives proton translocation and accumulation in the intermembrane space of mitochondria to produce ATP energy. Propofol also acts as an uncoupling agent in the oxidative phosphorylation process.[3,4,7]

Propofol has been shown to inhibit complex I, complex IV, and cytochrome C within the mitochondrial electron transport chain and additionally acts as an uncoupling agent in oxidative phosphorylation, thereby impairing ATP production and contributing to the pathophysiological cascade underlying PRIS **(Figure 3)**.[3,4,7]

Epidemiology

Epidemiological data for PRIS still need to be determined because diagnostic criteria vary, and clinical data mostly come from case reports or case series. The reported incidence varies depending on the symptoms considered and described in each case report. An incidence of 1.1% was described by one multicenter US adult critical care investigation.[13] Another report by James et al from a level 1 trauma center in New Orleans stated that the incidence of PRIS was 4.1% with a case fatality rate of 33%.[14]

Risk Factors

The main risk factor for developing PRIS is the cumulative dose of propofol. According to evidence from case reports and studies, propofol should not be administered at a dose exceeding 4 mg/kg/hour or for more than 48 hours. Dosages beyond this have been shown to be fatal and are not recommended. Other risk factors include critical illness, elevated catecholamines, traumatic brain injury, sepsis, obesity, poor oxygen saturation, inborn errors of metabolism, usage of steroids and/or vasopressors, young age, carbohydrate depletion, and an imbalance between lipid and carbohydrate stores of the body (**Figure 4**).[3,4]

Early Detection and Prevention

Several studies have described early warning signs and markers for PRIS, but further research is still needed due to variability across cases. Although it does not appear to be an early predictor of PRIS, the current study suggests that monitoring triglycerides and/or lactic acid may be significant for the occurrence of PRIS.[15] A recent study from Memphis explores the daily measurement protocol of creatine kinase in patients receiving propofol. The study observed a significant decrease in mortality among patients on propofol when the propofol was discontinued if elevated creatine kinase was detected. Thus, any elevation of creatine kinase should prompt the cessation of propofol, but only for adults.[16]

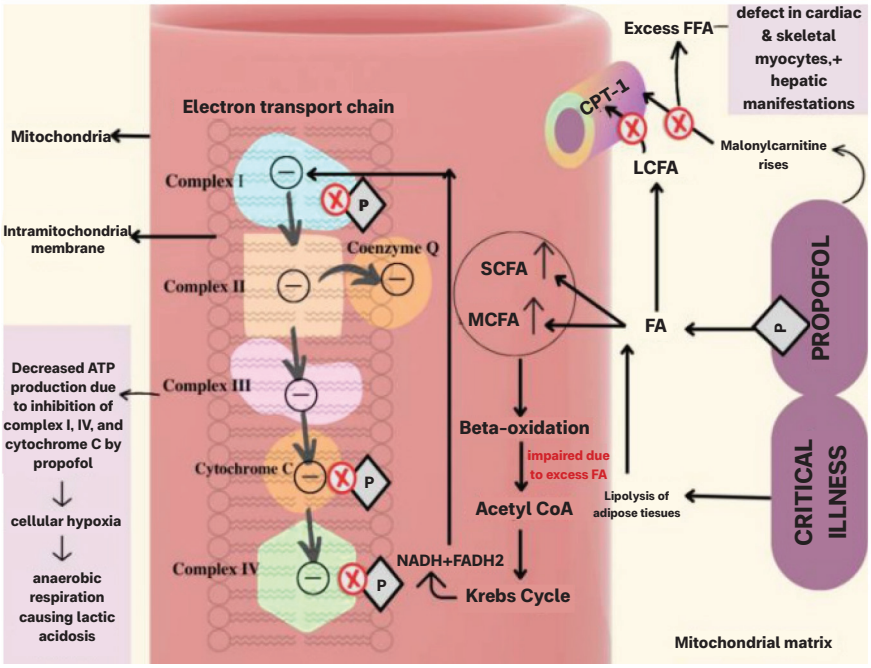

Figure 3. Pathophysiology of PRIS.[4]
Abbreviations: ATP: Adenosine triphosphate; SCFA: Short chain fatty acid; MCFA: Medium chain fatty acid; NADH: Reduced nicotinamide adenine dinucleotide; $FADH_2$: Reduced flavin adenine dinucleotide; FFA: Free fatty acid; CPT-1: Carnitine palmitoyl-transferase 1; LCFA: Long-chain fatty acid; FA: Fatty acid.

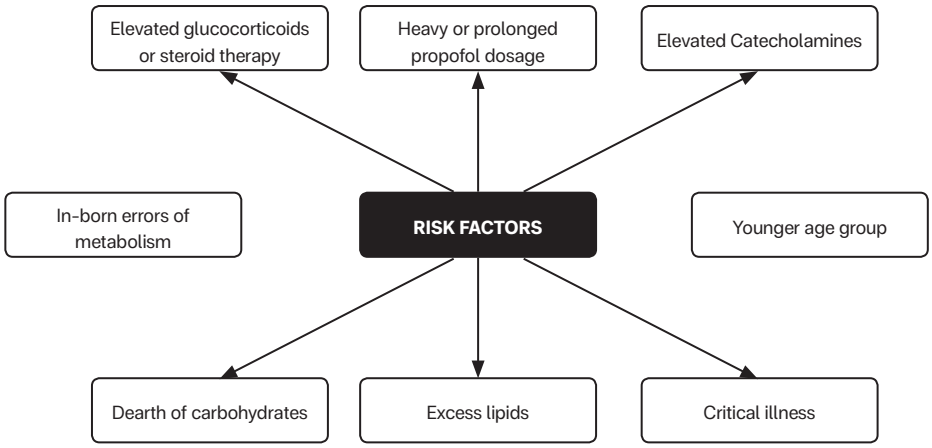

Figure 4. Risk factors of PRIS.[4]

The most effective way to prevent PRIS is to remain vigilant and maintain a high level of suspicion during prolonged propofol administration. Propofol administration should not exceed 40 hours, with a dose not higher than 4 mg/kg/hour or 67 mcg/kg/minute.[15] It is said that the risk of PRIS increases 1.93 times with every increase in the administration of propofol 1 mg/kg/hour over a dose of 5 mg/kg/hour.[17] Children tend to have a higher risk of developing PRIS because they have limited carbohydrate reserves. The use of propofol for children must be accompanied by careful consideration and strict supervision.[7,12] Carbohydrate administration is believed to help prevent or reduce the risk of PRIS, although the potential benefits of carnitine supplementation remain unclear.[3]

Clinical Presentation and Diagnosis

Propofol-related infusion syndrome manifests with a broad spectrum of symptoms affecting multiple organs (**Table 1**). The metabolic and cardiovascular systems are the most significantly impacted systems; other organs include the hepatic, skeletal, muscular, and renal systems.

Metabolic Manifestation

Metabolic manifestations include conditions such as lactic or metabolic acidosis, hypertriglyceridemia, hyperkalemia, and hyperthermia. Hyperkalemia is further worsened by metabolic acidosis due to an increase in transcellular shift. Another manifestation is HAGMA (high anion gap metabolic acidosis), which results from an increase in lactic acid levels.[3,4]

Cardiovascular Manifestation

Cardiovascular manifestations include Brugada syndrome-like patterns, ventricular tachyarrhythmias, QRS complex widening, right bundle branch block, hypotension, atrial fibrillation, cardiogenic shock, and, at worst, asystole. These conditions are impacted by elevated FFAs and depleted ATP stores, which then directly impair cardiomyocytes' functions. Propofol reduces sympathetic tone by antagonizing calcium channels and beta-adrenoreceptors, leading to bradycardia and weakened myocardial contractility; thus potentially resulting in asystole. Additionally, the ventricular arrhythmias can be attributed to the pro-arrhythmic effects of elevated serum FFAs.[3,4,6]

Hepatic Manifestation

The hepatic manifestations of PRIS include elevated liver enzymes, hepatomegaly, steatosis, and liver failure. These changes may be linked to hepatic congestion, often secondary to cardiac failure. The high levels of lipid deposition from propofol and excessively circulated FFAs contribute to hepatomegaly and other hepatic features. Other factors such as hypoxia, sepsis, hypoperfusion, vasopressor therapy, and hypermetabolic states also exacerbate hyperlipidemia and impair liver function.[3,4]

Musculoskeletal Manifestation

The musculoskeletal system undergoes an extensive lysis of myocytes due to PRIS, which can result in renal failure and myoglobinuria. The hallmarks of rhabdomyolysis in PRIS are described by the presence of histological findings: severely necrotic myocytes with disorganized sarcomeres, myofibrils,

Table 1. Clinical features of PRIS.[5]

Organ System	Clinical Presentation
Cardiovascular	Hypotension, acute systolic heart failure, pulmonary edema, RBBB, widening of the QRS, ventricular dysrhythmias (VT/VF), asystole
Renal/Urinary	Acute kidney injury, change in urine color
Musculoskeletal	Rhabdomyolysis
Metabolism/Nutrition	Hyperkalemia, lipidemia, lactemia
Hepatobiliary	Hepatomegaly, elevated transaminases, hepatic failure

Table 2. Bedside investigations for diagnosis of PRIS.[4]

BEDSIDE
ECG: Brugada-like pattern showing coved ST elevation in V1-V3 right precordial leads and widening of QRS Complex.
Arterial blood gas analysis: decreased pH, unexplained lactic acidosis, hyperkalemia.
Blood pressure: low (hypotensive)
Respiratory rate: higher than normal
Heart rate: less than 60 beats per minute (acute bradycardia that can progress to asystole)
Body temperature: higher than 38°C (febrile)

Table 3. Laboratory markers for diagnosis of PRIS.[4]

LABORATORY
Lipid profile: elevated (lipemic serum)
Liver enzymes (AST, ALT, GGT): elevated
Creatine kinase: elevated (due to rhabdomyolysis)
Serum lactate: elevated
Myoglobin in urine: elevated
Serum lipase and amylase: elevated

Abbreviations: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase.

degenerated nuclei, loss of striation, and swelling. Another primary factor suggested to cause elevated serum creatinine and rhabdomyolysis associated with PRIS is reduced oxygen supply, which leads to anaerobic metabolism.[3,4]

Renal Manifestation

Rhabdomyolysis is closely related to the renal manifestation of PRIS, which causes kidney injury and renal failure, as seen by elevated creatinine levels.[18]

Table 2 and 3 show the investigations that may be necessary to diagnose PRIS.

Treatment

There is no established guideline or specific treatment for PRIS. Treatment for PRIS begins with prompt recognition, followed by immediate discontinuation of propofol and a switch to alternative sedative agents; the remainder is supportive, as symptoms arise (**Table 4**). The antidote for PRIS has still not been found, although dextrose infusion is believed to be beneficial and generally safe for PRIS with mitochondrial origin.[18]

Management of metabolic and lactic acidosis includes administering sodium bicarbonate, although its role remains controversial. Severe hyperkalemia associated with PRIS can be treated with calcium, insulin (with or without dextrose), beta-2 agonists, sodium bicarbonate, and potassium-binding resins. Hemodialysis and hemofiltration also can be therapies of choice, particularly in cases of hyperkalemia and rhabdomyolysis, as they help to remove excess lipids and correct metabolic acidosis. The management of traumatic brain injury patients includes maintaining euvolemia while managing fluid administration.[3,4,7]

Cardiac manifestations are major concerns in PRIS management; they may be treated with vasopressors, transvenous pacing, inotropes (like norepinephrine and dobutamine), and mechanical support in refractory cases. Extracorporeal membrane oxygenation (ECMO) is recommended in severe cases, providing oxygenation and circulatory support.[3,4,7]

Table 4. Supportive management for PRIS.[5]

Awareness and suspicion of the syndrome in clinical scenarios associated with the development of PRIS
→ Consider monitoring triglyceride levels in patients receiving > 48 hours of propofol or > 4 mg/kg/hour
Immediate discontinuation of propofol
Supportive Care
→ Vasoactive and inotropic agents to support hemodynamics
→ Optimization of gas exchange
→ Cardiac pacing for bradycardia
→ Extracorporeal Membrane Oxygenation (ECMO)

CONCLUSION

Propofol-Related Infusion Syndrome is a rare and dangerous condition caused by prolonged, high-dose administration of propofol in mechanically ventilated patients with a high mortality rate. It is important to note that PRIS does not have specific signs or symptoms and may overlap significantly with other conditions that cause critical illness (such as various forms of shock or renal disease from other causes). The primary treatment for suspected PRIS is to stop the administration of propofol promptly; the rest remains limited to the management of each symptom, such as hemodialysis in acute renal failure with metabolic acidosis, rhabdomyolysis, and hyperkalemia. Prevention plays an essential role because specific therapies have not yet been found, and the mortality rate is high once the diagnosis has been confirmed. The most effective way to prevent PRIS is to remain vigilant and maintain a high level of suspicion in any prolonged administration of propofol. Therefore, clinicians should consider a broad differential diagnosis when managing a patient with a possible case of PRIS. Further research is needed for PRIS to enable more focused diagnosis and treatment, given the high mortality rate.

Acknowledgments

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Conflict of Interest

None

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