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Literature Review

SCREENING PROTOCOL OF PROPOFOL INFUSION SYNDROME

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ABSTRACT

Introduction: Propofol is often used as sedation for a long time in the ICU. The use is at risk of Propofol Infusion Syndrome (PRIS) which is characterized by arrhythmias or decreased heart function, metabolic acidosis, rhabdomyolysis, and acute renal failure. **Literature Review:** The pathophysiology of PRIS is due to a disturbance in cell metabolism which inhibits the transport of Free Fatty Acid (FFA) into cells and inhibits the mitochondrial respiration chain. The management of PRIS is supportive of every symptom that arises so that screening is needed as a treatment to reduce high mortality rates. Screening using creatine phosphokinase (CPK) and lactate is supporting data as an initial introduction for symptoms of PRIS. **Conclusion:** PRIS can occur if continuous administration of propofol > 4 mg / kg / hour. CPK levels> 5000 IU / L become a benchmark to stop propofol before the onset symptoms of PRIS. Implementation of screening protocol is very helpful for clinicians to reduce mortality in ICU due to the use of propofol.

Keywords: Propofol Infusion Syndrome; Screening Protocol; Intensive Care Unit

ABSTRAK

Pendahuluan: Propofol sering digunakan sebagai sedasi dalam jangka waktu lama di ICU. Penggunaan tersebut berisiko terjadinya Propofol Infusion Syndrome (PRIS) yang ditandai dengan aritmia atau penurunan fungsi jantung, asidosis metabolic, rhabdomyolisis dan gagal ginjal akut. **Review Literatur:** Patofisiologi PRIS dikarenakan gangguan metabolisme sel dimana menghambat transportasi Free Fatty Acid (FFA) ke dalam sel dan menghambat rantai respirasi mitokondria. Tatalaksana PRIS berpacu pada suportif dari setiap gejala yang timbul sehingga diperlukan skrining sebagai tatalaksana untuk menurunkan angka motralitas yang tinggi. Skrining menggunakan creatin phosphokinase (CPK) dan laktat menjadi data pendukung sebagai pengenalan awal gejala PRIS. **Kesimpulan:** PRIS dapat terjadi apabila pemberian propofol secara kontinu >4 mg/kg/jam . Kadar CPK > 5000 IU/L menjadi patokan dihentikannya penggunaan propofol sebelum munculnya gejala PRIS. Sehingga implementasi protocol skrining sangat membantu klinisi dalam menurunkan mortalitas di ICU akibat penggunaan propofol.

Kata Kunci: Propofol Infusion Syndrome; Protokol Skrining; Intensive Care Unit

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INTRODUCTION

Propofol is a drug that is often used in operating rooms and intensive care units. Introduced since 1970 and began to be modified with soybean oil and egg phospholipids as emulsification in 1986. (1) Propofol has a hypnotic sedative effect given during induction and maintenance during general anesthesia. (2) This drug is the first choice compared to other intravenous hypnotic sedation drugs due to rapid onset and short conscious recovery and minimal effects of the central nervous system. (2)

The mechanism of action from propofol by interacting allosterically at the g-aminobutyric acid (GABAA) receptor. GABA is an inhibitory neurotransmitter in the brain when inactive, hyperpolarization of the postsynaptic cell membrane occurs and inhibits the function of the postsynaptic nerve. (3) Also, propofol is capable of binding to several ion channels and receptors. Compared

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with inhalation anesthesia, propofol does not excite the spinal motor nerves. So immobility during the administration of propofol is not caused by depression of the spinal cord. (2)

Using propofol was also risky. In 1990, there were death reports from the continuous administration of propofol in children with upper respiratory infections. Some death cases as the beginning terminology of propofol infusion syndrome (PRIS). (4) PRIS is rare but has the potential to increase the rate of mortality. A study showed 153 cases reported from 1990 to 2014 found that 51 percent had died. (5)

The definition of PRIS until now still no clear boundary. Symptoms that can occur include cardiac arrhythmias, metabolic acidosis, rhabdomyolysis, and acute kidney failure. Where if there are two from four criteria after continuous administration of propofol and no other etiology causes the appearance of these symptoms. However, some researchers also discovered hepatomegaly and hyperlipidemia. (6) Initially, PRIS was not widely known by many clinicians, but since Cremer published his findings in the Lancet the clinicians began to pay attention to the incident. Cremer showed that continuous administration of propofol in patients with post-head trauma surgery. A total of 67 patients with mechanical ventilation in the ICU and propofol as the main sedation of whom 11 experienced PRIS and all reportedly died. (7) Strengthened by European policies that patients with rhabdomyolysis, metabolic acidosis, hyperkalemia, elevated levels of creatinine protein kinase (CPK), and heart failure after continuous administration of propofol it is advisable to immediately reduce or stop it. (8) Besides, the Food and Drug Administration (FDA) the United States in 2006 stated to be careful about giving propofol continuously for children as sedation for a long time. The FDA also recommends not giving propofol in doses exceeding 4 mg/kg/hour in pediatric patients. (9)

Various cases reported with a high mortality rate from PRIS make clinicians challenged to look boundaries in diagnosing PRIS. Specific therapies to restore side effects arising from propofol have not yet been found. Therapy is still limited to the management of each symptom that appears including hemodialysis in acute renal failure with metabolic acidosis, hyperkalemia, and rhabdomyolysis. However, this therapy indicates a state of delay in patients with PRIS. A PRIS prevention protocol is needed so that can decrease the number of PRIS events that have a positive impact on decreasing mortality. However, there is still little research and case reports that address the screening protocol. On this occasion, the author tries to discuss the diagnostic limits of PRIS, the latest therapies, and equally important screening of PRIS.

LITERATURE REVIEW

Propofol

Sedation drugs are widely used in the intensive care unit and operating rooms with a variety of routes intravenous administration both bolus repeatedly and continuously. In the past, benzodiazepines were the main drugs sedation in the ICU but recent studies and meta-analysis showed that nonbenzodiazepines such as propofol and dexmedetomidine had good results with fewer degrees of delirium and shorter use of ventilators. Besides, similar to benzodiazepines, propofol has no analgesic effect. (10)

Propofol is the structure of isopropyl phenol (2,6-diisopropyl phenol) which consists of 10% soybean oil, 2.25% glycerol, 1.2% egg phosphate, and 1% solvent solution. The content of soybean oil and egg lecithin is combined with long-chain triglycerides. This

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formulation is risk of bacterial growth and an increase in triglyceride levels when given continuously for a long time. Unlike thiopental, ketamine, and etomidate, propofol is a chiral compound. Mixing propofol with other drugs such as lidocaine is not recommended because the risk of pulmonary embolism. (11) People with egg allergy do not indicate that administration of propofol sedation is not permitted. In people with egg allergy, most of them are allergic to egg whites (egg albumin) not to egg lecithin derived from egg yolk.

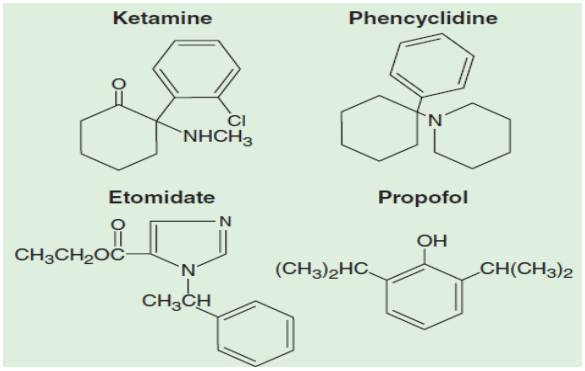

Figure 1. Structure of propofol chains compared with other groups sedative drugs (3)

G-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the brain. We know propofol works selectively at the GABAA receptor. Interactions on GABAA receptors have a sedative-hypnotic effect. When activated at the receptor there is an increase conductance of the transmembrane chloride which results in hyperpolarization of the post synapse cell membrane and the post synapse nerve. (3)

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics of propofol is quite complex compared to other sedation drugs. We know that propofol only has intravenous preparations. Propofol has a fast onset of action because it is very fat-soluble which can penetrate the blood-brain barrier quickly and distributed quickly to the peripheral tissues. Propofol oxidation in the liver which binds with glucuronic acid into propofol-1-glucuronide, quinol-1- glucuronide, and quinol-4-glucuronide which all of them can be excreted in the kidneys. (12) Only a few propofol are excreted where <1% excretion in urine and 2% in feces. All of these are inactive metabolites because speed clearance of propofol is> 1.5 L / min over the blood flow in the liver. Also, extrahepatic metabolism also occurs in the kidneys. The kidneys have an important role in propofol excretion where 30% occur in the elderly. So that becomes an explanation of why propofol has a faster clearance time. The clinician's concern is that age-related doses in which 80-year-old patients only need 50% of propofol doses compared to 20-year-old patients to achieve the same level of hypnosis because it is related to decreased volume distribution in geriatric resulting in low drug clearance. In contrast to children aged> 3 years requires a dose based on body weight because volume distribution of child larger and clearance faster. (3)

Pharmacodynamics of propofol in the respiratory system can occur apnea due to depression from the hypoxic ventilator drive and inhibition of the normal response to hypercarbia. Compared with thiopental, propofol has a better effect in suppressing upper airway reflexes during the intubation process. Besides that compared to etomidate and barbiturate, propofol has a risk of histamine release but the incidence of asthma is lower compared to etomidate and barbiturate. (1) Cardiovascular effects are also a concern for the use of propofol were a decrease in mean arterial pressure (MAP) due to vasoconstrictor inhibition of the sympathetic nerves which ends a decrease in systemic vascular resistance (SVR). Be careful in older patients or with beta-blocker treatment which further worsens decrease MAP and decreased cardiac contractility. (3)

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Propofol can reduce Cerebral Metabolic Rate for Oxygen (CMRO2), Cerebral Blood Flow (CBF), and intracranial pressure. The hypotensive effect of giving propofol causes a decrease in CBF. Besides cerebral autoregulation in response to the decline in CBF is also disrupted. The decrease in CBF velocity is also related to changes in PaCO2 related to propofol administration. (13)

Clinically, propofol used for induction and maintenance of general anesthesia. The dose that can be given when induction is 1-2.5 mg/kg and will be increasingly adjusted to age, body mass index, and volume distribution. As for maintenance doses, it ranges from 50-150 µg/kg/min both combination with opiates and nitrogen. The best step in the induction process is by titration and monitoring of propofol administration. Both opiate and midazolam can change the concentration of propofol. A combination with alfentanil can reduce elimination clearance from 2.1 L / min to 1.9 L / min while midazolam from 1.94 L / min to 1.6 L / min. (14) Another use of propofol is sedation during administration of mechanical ventilation in ICU. The speed of continuous administration and the maximum number of doses must be considered during the administration of propofol. The speed of propofol administration under regional anesthesia is half that of general anesthesia at 30 µg/kg/min. Geriatric patients should be reduced by half their speed compared to young adults. Sedation speed with propofol is a maximum 80 µg/kg / min or <5mg/kg/hour. Plus special attention when the patient is also given a vasopressor or inotropic escalation dose. (15)

Non-hypnotic effects are also present in the administration of propofol including antiemetic, anti-pruritic, anti-convulsive, and decreased bronchoconstriction. Postoperative Nausea Vomiting (PONV) can be suppressed by administering a propofol sub hypnotic dose that is around 10-15 mg IV in the Post Anesthesia Care Unit (PACU). Sub hypnotic doses can also be given to patients with chemotherapy induce nausea vomit and are equally effective when compared with ondansetron drugs. (16) Anti-pruritus effects can also be given to patients with neuraxial opioids or cholestasis. The mechanism of this effect is by the way drugs able to suppress the activity of the spinal cord. The dose that can be given is 10 mg IV. Propofol also has an anti-convulsive effect that works in GABA mediated prescription and inhibition of chloride ions in postsynaptic. Doses that can be given to suppress seizures are> 1 mg/kg. Besides, propofol also minimizes bronchoconstriction during induction and intubation in patients with a history of asthma when compared with thiopental. (17)

Propofol Infusion Syndrome

Death report after the continuous administration of propofol occurred in 1990 in Denmark where it occurred in children aged 3 years. In 1992, it was reported that 5 children also died after continuous administration of propofol. This is similar to the clinical symptoms that appeared with Danish's incident report in 1990. Terminology Propofol Infusion Syndrome (PRIS) was introduced by Bray who made observations of 18 cases of PRIS that occur in children. (18) PRIS did not only occur in pediatric patients, Cremer's case report in The Lancet where there were 18 cases of death with PRIS in post neurosurgical patients in ICU with mechanical ventilation. There are also cases of women in 30 years with acute exacerbation of bronchial asthma who have lactic acidosis and anion gap metabolic acidosis whose causes cannot be explained after receiving propofol therapy continuously for 2 hours with mechanical ventilation. (7)

PRIS definition is indeed difficult to determine because of the combination of too many case variations. So that the explanation of the collection of symptoms includes metabolic acidosis with no clear cause, rhabdomyolysis, hyperkalemia, hepatomegaly, kidney failure, hyperlipidemia, arrhythmias, and progressive heart failure. However, Bray makes it easy by dividing into 4 major components consist of:

1. Cardiac arrhythmia or heart failure
2. Metabolic acidosis
3. Rhabdomyolysis
4. Acute Kidney Failure

If there are two sets of symptoms from the 4 indicators after continuous administration of propofol by excluding the other etiology causing the symptoms mentioned above. (19)

Pathophysiology of PRIS

Normally glucose becomes the main energy in various systems in our body. However, during the process of fasting and critical illness, there is a change in the source of energy where Free Fatty Acids (FFA) are the source of energy. This change in energy source is activated by various stress hormones such as epinephrine and cortisol which are able to modulate the activity of lipase in fat tissue. Lipase activity degrades triglycerides into glycerol and FFA where glycerol is a source of glucose and FFA as a source of beta-oxidation in mitochondria. (20)

In PRIS conditions, there are 2 conditions where propofol can inhibit the formation of intracellular energy, namely by inhibiting the transport of FFA into cells and inhibition of the mitochondrial respiratory chain. Let's try to discuss this in detail. Propofol is able to inhibit FFA transportation into cells. The rule of the FFA is changed to acyl-CoA by CoA synthase. Acyl Co-A will bind to Carnitine palmitoyltransferase-I which is outside the mitochondrial membrane to acylcarnitine. acylcarnitine will enter the mitochondrial membrane by binding to carnitine palmitoyltransferase-II to carnitine. Propofol itself in this mechanism prevents acyl-coA bonding with carnitine palmitoyltransferase-I. (21)

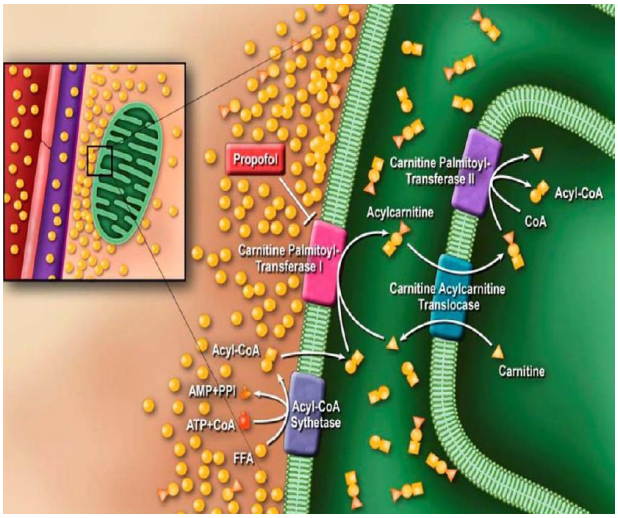

Figure 2. Pathogenesis Propofol Inhibits Transport of FFA into Cells (32)

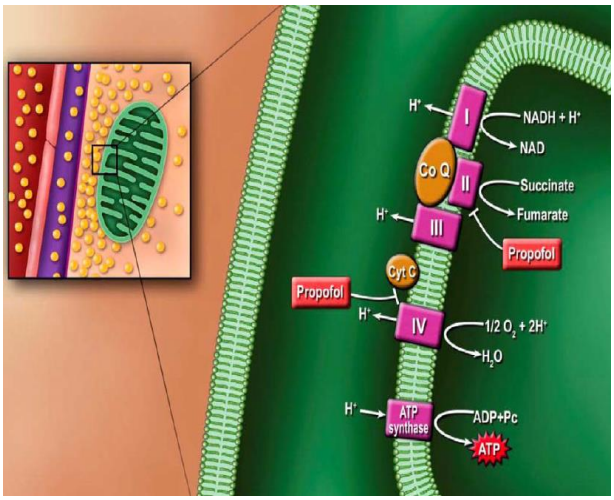

Figure 3. Pathogenesis Propofol Inhibits Mitochondrial Respiration Chain (32)

Besides that, propofol can inhibit the mitochondrial respiration chain. Normally there are 4 complex components in the respiration chain. The first complex starts from electrons passing through nicotinamide adenine dinucleotide (NADH) to coenzyme Q (CoQ). the second complex of succinate

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becomes fumarate with the help of CoQ. The third complex CoQ becomes Cytochrome c (Cyt C). the fourth complex of Cyt C becomes cytochrome c oxidase. These four processes move hydrogen ions into the intermembrane space to produce ATP energy. Propofol itself is able to inhibit processes in complexes two and four. (22)

Clinical Manifestations

Organ systems involved in PRIS include cardiovascular, liver, renal, musculoskeletal, and metabolic. In the cardiovascular system wherein the initial phase there are tachycardia and hypotension but if the condition becomes more severe it becomes bradycardia with widening QRS complexes such as Brugada like rhythm. This is due to the antagonistic response of calcium channels and beta-adrenergic receptors. If it becomes more severe, it will become ventricular fibrillation to asystole. (23) The effect of propofol also affects liver function where there is an increase in transaminases and bilirubin. On physical examination, there can be hepatomegaly. Besides, increases in serum triglycerides and cholesterol are due to kinetic lipid disorders where hepatocellular necrosis previously occurred. (24)

In PRIS often occurs Acute Kidney Injury (AKI) which is marked with greenish-red urine color. The change of urine color is due to propofol metabolism in urine and increase phenol and uric acid. Although propofol is not nephrotoxic, it is damage to the kidneys due to secondary effects of rhabdomyolysis and myoglobin toxicity. (25) Rhabdomyolysis is the most common clinical manifestation of PRIS after decreased cardiovascular function. In rhabdomyolysis there is a decrease in ATP production and an increase in cell metabolic requirements resulting in muscle cytolysis followed by degradation of muscle products such as potassium, creatinine kinase, and myoglobin. (26) Betrosian says patients who are sedated with propofol for a long time can develop muscle necrosis without either followed by hemodynamic disorders. as well as other clinical symptoms of PRIS.(27) In critically ill patients, increased lactate can occur in decreased tissue perfusion, sepsis, and liver disorders which need to be a concern in establishing the diagnosis of PRIS after excluding these other causes. However, in its development, lactate examination is an early marker of the occurrence of PRIS so that it helps clinically in establishing PRIS. (28)

Prevention

As a clinician, it is demanded to always be aware of the worst thing that can happen from every drug administration. The best measurement in the prevention of PRIS is vigilance by assuming suspicion that PRIS occurs in any propofol administration over a long period time. Based on some previous reports on the population of children treated in ICU with the administration of propofol sedation occurred PRIS. (21) Based on the pathophysiology, PRIS in children can occur because children have limited carbohydrate reserves so that they can be reduced more rapidly when in critical illness. This is certainly different when compared to adults who have more carbohydrate reserves. So it is advisable to avoid using prolonged use of propofol in children. (24)

In previous studies the risk of PRIS if propofol administration exceeds 4 mg/kg/hour or 67 mcg/kg/minute with a minimum of 48 hours of administration. This is reinforced by Cremer et al, where any increase in the administration of propofol 1 mg/kg/hour over a dose of 5 mg/kg / hour can increase the PRIS 1.93 times. (7) The provision of propofol can increase FFA levels by various mechanisms previously described. Clinicians must be vigilant when having patients with low

carbohydrate reserves and increased fat administration. Also, patients with catecholamine or steroid therapy are also of concern given the high risk of PRIS. (29)

Diagnosis

Diagnosis of PRIS is still difficult because the clinical symptoms that appear are not typical and some symptoms are similar to other diseases such as sepsis. The main point is when giving propofol more than 4 mg/kg/hour or 67 mcg/kg/minute and or in more than 48 hours. Which appears one or more symptoms of arrhythmia or decreased heart function, metabolic acidosis, rhabdomyolysis, and kidney failure. Clinicians should consider stopping the administration of propofol if heart block or arrhythmia is found. (19)

Therapy

Some of the explanations mentioned above make clinicians must be careful when finding PRIS. Prevention of PRIS is the best choice compared to providing therapy because the mortality rate is quite high. Clinicians should not exceed the dose of propofol> 4 mg/kg/hour or > 67 mcg/kg/minute. Until now there has been no specific treatment or antidote from PRIS where management is only supportive of each symptom that arises. (19)

The first therapy when a PRIS is suspected is to stop giving propofol immediately. If you still need sedation then replace it with other drugs. Hyperkalemia can be treated by the administration of calcium gluconate with insulin and dextrose. (30) Besides, the management of metabolic acidosis with hyperkalemia and rhabdomyolysis is an indication of hemodialysis. PRIS is also widely reported in cases with traumatic brain injuries that require propofol for a long time. So that adequate fluid therapy reaches euvolemia is also noteworthy. Bradyarrhythmias causing cardiogenic shock require inotropic therapy or vasopressors such as norepinephrine and dobutamine. However, we know that the pharmacology of propofol also inhibits cardiac calcium blockers and beta receptors. So that administration of drugs that are similar in performance to catecholamines is less effective. (31) If bradyarrhythmias are refractory then consider a pacemaker. No less important is the comprehensive handling of patients in the ICU such as prevent the occurrence of ventilator-associated pneumonia, deep venous thrombosis prophylaxis, stress ulcer prophylaxis and the provision of adequate nutrition, in this case, is the provision of carbohydrates. (8)

Screening Protocol

PRIS screening approach began by looking for various markers which became supporting data for the early recognition of PRIS symptoms. The daily screening protocol of PRIS uses Creatine Phosphokinase (CPK) and lactate during the continuous use of propofol. This protocol has been started since 2006 and is still being worked on until now. Propofol is stopped when CPK reaches levels> 5000 IU / L or Lactate> 4 mmol / L. Schroepel et al's study attempted to implement a screening protocol in the ICU with trauma cases. In 207 patients who received propofol continuously were divided into two phases. The first phase is patients who enter the PRIS criteria where cardiac arrhythmias occur, metabolic acidosis, rhabdomylysis, and acute kidney failure. The second phase is to impose CPK and lactate screening protocols on the continuous administration of propofol. Significant results were obtained where the PRIS group had high CPK and lactate levels. But not very significant in screening using lactate. (19) The Society of Critical Care Medicine (SCCM) recommends that for

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monitoring the occurrence of PRIS when continuous use of propofol. This was stated in the Guidelines of Pain, Agitation / Sedation, Delirium, Immobility and Sleep Disruption. (10)

The mechanism for PRIS is very complex with a mortality rate of up to 51%. Several studies have shown an extended length of stay (LOS) in the ICU and the use of ventilators in the ICU in patients with PRIS. So that it remains the best step is the prevention of PRIS by using CPK and lactate screening protocols. In addition, administration of propofol does not exceed 4 mg/kg/hour and if there is a PRIS, the treatment of each symptom must be adequate.

CONCLUSION

PRIS can occur in critically ill patients with propofol continuously exceeding 4 mg/kg/hour or 67 mcg/kg/minute. PRIS screening protocol using CPK> 5000 IU/L can be an initial marker choice to immediately stop giving propofol. The implementation of this screening protocol can be beneficial for prolonged administration of propofol sedation in the ICU.

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Conflict of Interest

There is no conflict of interest in this article writing process.

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