Abstract

A 57-year-old female patient received elective liver transplant due to nonalcoholic steatohepatitis complicated by hepatocellular carcinoma. Her preoperative Model for End-Stage Liver Disease score was 11. The total transplant ischemic time was 10 hours and 35 minutes, and the warm ischemic time was 35 minutes. Even with aggressive fluid overload and use of high concentrations of vasoactive amines, the patient developed possible primary graft dysfunction with poor response to fluids and vasopressor support, suggesting vasoplegic syndrome. On the basis of the hypothesis of vasoplegic syndrome, the patient received methylene blue intravenously (100 mg bolus for 12 h/1.5 mg/kg). The catastrophic situation was controlled. The patient’s urine output markedly improved, she was subsequently weaned from vasoactive support, and mechanical ventilation was discontinued 2 days later. The patient was discharged on the 20th postoperative day.

Key words: Circulatory shock, Graft damage, Hepatic transplant, Vasoplegic syndrome

Introduction

After graft reperfusion in liver transplant, ischemia-reperfusion syndrome is characterized by persistent hypotension with low systemic vascular resistance.

Case Report

A 57-year-old female patient received elective liver transplant due to nonalcoholic steatohepatitis complicated by hepatocellular carcinoma. The patient’s medical history included type 2 diabetes mellitus, obesity class 2 (body mass index of 35.4 kg/m²), hypertension, dyslipidemia, chronic renal disease (under renal replacement therapy), and a strong family history of cirrhosis. The patient’s preoperative Model for End-Stage Liver Disease score was 11. The total transplant ischemic time was 10 hours and 35 minutes, and the warm ischemic time was 35 minutes. Even with aggressive fluid overload and use of high concentrations of vasoactive amines, the patient developed possible primary graft dysfunction.
with poor response to fluids and vasopressor support, suggesting vasoplegic syndrome. Based on the possibility of vasoplegic syndrome, the patient was given methylene blue intravenously (100 mg bolus for 12 h/1.5 mg/kg). During the subsequent 4 to 5 hours, the patient recovered from a catastrophic situation with a good clinical response, as shown in Figure 1 and Figure 2. The patient’s urine output markedly improved, she was subsequently weaned from vasoactive support, and mechanical ventilation was discontinued 2 days later. The patient was discharged on the 20th postoperative day.

**Discussion**

A catastrophic situation was assumed for our patient, presenting as a systemic inflammatory reaction causing a vasoplegic endothelium dysfunction due to overproduction of nitric oxide closely associated with inducible nitric oxide synthase expression. The use of methylene blue was crucial to control the situation. The use of this agent for this situation is not new; however, only a few reports are available in the literature, justifying its presentation with emphasis on practical aspects.

The first use of methylene blue as an agent for the pharmacologic treatment of vasoplegic syndrome during liver transplant surgery has only been recently reported (in a 61-year-old male patient who underwent liver and kidney transplant because of hepatorenal insufficiency, secondary to autoimmune hepatitis). Shortly after methylene blue treatment was started, the patient showed significant improvement in hemodynamic function, allowing weaning and subsequent infusion of norepinephrine and vasopressin.1

Regarding the use of methylene blue to treat vasoplegic syndrome, the present case report offers the opportunity to present some useful concepts. First, methylene blue was shown to be safe at the recommended doses (the lethal dose is 40 mg/kg). Second, methylene blue did not cause endothelial dysfunction. Third, methylene blue seems to be effective in cases of nitric oxide up-regulation. Fourth, methylene blue is not a vasoconstrictor; by blocking the cGMP pathway, it releases the cAMP pathway, facilitating the epinephrine vasoconstrictor effect and acting as a possible “crosstalk” mechanism. Fifth, the most used dose of 2 mg/kg intravenously followed by the same continuous infusion was effective because the drug’s plasma concentrations sharply decreased during the first 40 minutes. Sixth, although there are no definitive multicenter studies, the use of methylene blue to treat vasoplegic syndrome after heart surgery is presently the best, safest, and most inexpensive option.2 Five years later, these concepts were revised.3

In summary, there are 2 opposing concepts regarding use of methylene blue: (1) as rescue therapy or (2) as an early adjuvant agent.4,5 Using a sepsis model in mice, Fernandes and associates demonstrated that, in a 24-hour period there are three 8-hour “window of opportunity” periods, based on different dynamic guanylate cyclase action, making possible the methylene blue activity. Vasoreactivity no longer occurs in the first 8 hours, coinciding with increased inducible nitric oxide synthase expression. During the next 8 hours, guanylate cyclase expression is absent, probably because of excessive nitric oxide production; therefore, methylene blue would not be effective during this period. Finally, during the final period, guanylate cyclase resynthesis occurs, and methylene blue would be again effective.
in inhibiting this enzyme. Therefore, there is the possibility that methylene blue does not act (second window) or acts too late (third window), when the circulatory shock is metabolically irreversible. In the present case report, the good response shown in our patient suggested methylene blue became effective during the first therapeutic window.

The use of methylene blue is not new in liver transplant. In probably the most important study, 36 patients undergoing elective liver transplant were randomized to receive an intravenous methylene blue bolus (1.5 mg/kg) before graft reperfusion or saline (placebo) treatment. Patients who received methylene blue had higher average blood pressure, increased heart rate, and less need for epinephrine. The study showed that methylene blue attenuated hemodynamic changes in transplant, acting through inhibition of guanylate cyclase. In this study, Koelzow and associates administered methylene blue before perfusion of the transplanted liver or for the prevention of ischemia-reperfusion syndrome.

In a cohort study, Fukazawa and Pretto reported on 715 orthotopic liver transplant patients, in which 105 patients received methylene blue and 610 did not. After propensity score matching, demographic and donor data were similar in the 2 groups, except for older age of recipients in the methylene blue group. No differences were seen in mean arterial pressure changes after reperfusion, and no differences were found in vasopressor requirements (bolus or infusion) or transfusion requirements. Also, there were no significant differences in incidences of primary nonfunction, retransplant within 60 days, acute rejection, or graft survival between the groups by multivariate analyses or Kaplan-Meier survival analyses. The study found that methylene blue administered at 1 to 1.5 mg/kg immediately before reperfusion did not prevent postreperfusion hypotension and did not decrease use of vasopressors or transfusion requirements after reperfusion. Also, methylene blue did not affect postoperative graft function. These findings may argue against the routine use of methylene blue during orthotopic liver transplant.

In regard to hepatopulmonary syndrome, 1 study showed a marked decrease in pulmonary shunting after administration of methylene blue, suggesting increased nitric oxide production in the lungs and proposed methylene blue treatment. Liver transplant is a viable surgical treatment option when previous medical treatments have disappointing results. Previous unsatisfactory outcomes have included use of various pharmacologic agents such as indomethacin, almitrine, octreotide, and garlic. Methylene blue should be considered and may provide a new long-term treatment approach. It is important to emphasize that our patient presented with acute hepatopulmonary syndrome, and the importance of the nitric oxide/cGMP pathway in treatment of these cases is unknown. Almeida and associates reported a 46-year-old woman with Child-Pugh class C cirrhosis and progressive dyspnea for 12 months, with clinical and laboratory results suggesting severe hepatopulmonary syndrome. Sequential inhibition of the nitric oxide/cGMP pathway using curcumin (diferuloylmethane), terlipressin, and methylene blue was associated with substantial improvements in vascular tone and hyperdynamic circulation. However, no improvement in the intrapulmonary shunt was demonstrated, suggesting the possibility of worsening of pulmonary oxygen exchange and that inhibition of the nitric oxide/cGMP pathway should be avoided.

A word of caution is needed regarding our presentation of lactate values. As shown in Figure 2, the lactate values suggested a remarkable improvement. However, this fact would not be considered as real data concerning organ perfusion, since methylene blue reacts directly with lactate, giving the false impression of immediate improvement in tissue exchange.

A multicenter study on similar patients would be difficult. The possible acceptance of this therapy will be passed on as verbal information, depending on the increase of publications and evidence-based studies. In the literature and in medical practice, there is still a certainty that the soluble guanylate cyclase blockage in distributive shock control remains underestimated. More recently, in the absence of a large trial, the literature has shown methylene blue use in isolated cases of liver transplant, sepsis complications, and even as a bridge to transplant.

References