Magnesium as Immediate Management for Suspected Intraoperative Malignant Hyperthermia Crisis: A Case Report from Indonesia

Ratna Farida Soenarto[1*], Sidharta Kusuma Manggala[1], Gabriela Montolalu[1], Tia Listyana[1], Celine Kurniawan[1]

1. *Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia*

**penulis korespondensi*

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ABSTRACT

Background: Malignant hyperthermia (MH) is a life-threatening disorder triggered by certain anesthetics and characterized by a hypermetabolic state in skeletal muscles. Magnesium sulfate is gaining recognition as a crucial adjunct in the immediate management of MH, particularly when dantrolene is not readily available. This case report presents a successful use of magnesium during an MH crisis, emphasizing its potential as a life-saving intervention in resource-limited settings. The report adds to the growing evidence supporting magnesium's role in early MH management, especially when there is a delay in dantrolene administration.

Case Illustration: A 2-year-old healthy boy underwent Achilles tendon lengthening under general anesthesia. Post-induction, the patient developed signs of increased sympathetic activity, muscle rigidity, and hypercarbia. Due to dantrolene unavailability, 400 mg of magnesium sulfate was administered, which successfully reduced muscle rigidity and stabilized hemodynamics. Dantrolene was later given, further improving the patient's condition. The patient was extubated 28 hours later and fully recovered, highlighting the critical role of magnesium in managing this crisis.

Conclusion: Early detection and management of MH are crucial for patient survival. In the absence of dantrolene, MgSO4 serves as an effective alternative for immediate intervention. This experience underlines the importance of having alternative treatment strategies in resource-limited settings and stresses the need for continued education and preparedness for MH crises.

Keywords: Anesthesia; dantrolene; inhalation; magnesium sulfate; malignant hyperthermia

Magnesium sebagai Penanganan Segera Suspek Krisis Hipertermia Maligna Intraoperatif: Laporan Kasus dari Indonesia

Ratna Farida Soenarto[1*], Sidharta Kusuma Manggala[1], Gabriela Montolalu[1], Tia Listyana[1], Celine Kurniawan[1]

1. *Departemen Anestesiologi dan Terapi Intensif, Fakultas Kedokteran, Universitas Indonesia – RSUPN Dr. Cipto Mangunkusumo, Jakarta, Indonesia*

**corresponding author*

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ABSTRAK

Pendahuluan: *Hipertermia maligna (HM) adalah gangguan yang mengancam jiwa, dipicu oleh anestesi tertentu, dan ditandai dengan keadaan hipermetabolik pada otot rangka. Magnesium sulfat semakin diakui sebagai terapi tambahan yang penting dalam penanganan segera HM, terutama ketika dantrolene tidak tersedia. Laporan kasus ini menyajikan penggunaan magnesium yang berhasil dalam krisis HM, menyoroti potensinya sebagai intervensi penyelamat jiwa di lingkungan dengan sumber daya terbatas. Laporan ini menambah bukti yang berkembang mengenai peran magnesium dalam manajemen awal HM, khususnya ketika terdapat keterlambatan dalam pemberian dantrolene.*

Deskripsi Kasus: *Seorang anak laki-laki berusia 2 tahun yang sebelumnya sehat menjalani prosedur pemanjangan tendon Achilles dengan anestesi umum. Setelah induksi, pasien mengalami tanda-tanda peningkatan aktivitas simpatik, kekakuan otot, dan hiperkapnia. Karena dantrolene tidak tersedia, diberikan magnesium sulfat sebanyak 400 mg, yang berhasil mengurangi kekakuan otot dan menstabilkan hemodinamika. Dantrolene kemudian diberikan dan semakin memperbaiki kondisi pasien. Pasien berhasil diekstubasi 28 jam kemudian dan pulih sepenuhnya, menegaskan peran penting magnesium dalam menangani krisis ini.*

Simpulan: *Deteksi dini dan manajemen cepat HM sangat penting untuk keselamatan pasien. Dalam keadaan tidak tersedianya dantrolene, $MgSO_4$ dapat berfungsi sebagai alternatif yang efektif untuk intervensi segera. Pengalaman ini menyoroti pentingnya memiliki strategi pengobatan alternatif di lingkungan dengan keterbatasan sumber daya serta menekankan perlunya edukasi dan kesiapan menghadapi krisis HM.*

Kata Kunci: *Anestesi; dantrolene; inhalasi; hipertermia maligna; magnesium sulfat*

INTRODUCTION

Malignant hyperthermia (MH) occurring perioperatively is a potentially fatal condition. Worldwide statistics indicate an incidence of MH crisis ranging from 1:10,000 to 1:150,000 for all general anesthetics.[1] Before the introduction of dantrolene in the 1970s, MH had a mortality rate of up to 70%, which has since been reduced to approximately 5%.[1] In Indonesia, however, the absence of a dedicated data registry on MH incidence limits awareness and knowledge among healthcare providers. This highlights the need for comprehensive education on MH during anesthesiology training.

We report a highly suspicious case of intra-anesthesia MH crisis, where early recognition and intervention by anesthesia residents led to a rapid improvement in the patient's condition. Notably, MgSO4 was used as an initial treatment before dantrolene became available, suggesting a potential alternative for settings without immediate access to dantrolene. This case highlights the critical importance of early detection and swift management in reducing the impact of MH and offers valuable insights for similar situations.

CASE DESCRIPTION

A 2-year-old, 15kg boy with congenital talipes equinovarus underwent elective Achilles tendon lengthening. He had a history of premature birth at 32 weeks but was otherwise healthy (ASA 1). During pre-induction, the patient was fully conscious, with a blood pressure of 121/75 mmHg, heart rate of 122 beats per minute, respiratory rate of 30 breaths per minute, room air oxygen saturation (SpO_2) of 98% and body temperature was 35.7°C. General anesthesia was administered using Laryngeal Mask Airway (LMA) and sevoflurane. After induction, blood pressure increased to 138/70 mmHg, heart rate to 160 beats per minute, SpO_2 remained the same, and end-tidal carbon dioxide ($ETCO_2$) was 48-50 mmHg. Respiratory rate setting was increased from 22 to 25 breaths per minute. Additional fentanyl was given and sevoflurane volume increased to 3%, along with 10 mL/kg crystalloid fluids.

In the first 15 minutes post-induction, the patient's blood pressure was 114/77 mmHg, heart rate 140-150 bpm, and ETCO2 48-60 mmHg, despite an additional 50 mcg of fentanyl. In the following 15 minutes, heart rate increased to 150-160 bpm, blood pressure to 135/70 mmHg, and ETCO2 to 60-70 mmHg, with SpO2 at 100% and a temperature of 37.3°C. Airway pressure rose from 18 to 33 cmH2O, and the patient developed upper extremity rigidity and jaw tightness. Sevoflurane was discontinued, and manual ventilation was initiated. Due to the unavailability of dantrolene, a 400 mg IV bolus of $MgSO_4$ was, reducing muscle rigidity, lowering blood pressure to 122/76 mmHg, heart rate to 116 bpm, and ETCO2 to 38-45 mmHg. The patient was then intubated successfully.

Upon availability, dantrolene with initial dose 37.5 mg was administered, followed by maintenance infusion. The patient's hemodynamics improved, with blood pressure at 125/77 mmHg, heart rate 105-110 beats per minute, and ETCO2 around 30mmHg. The patient was then transferred to the Pediatric Intensive Care Unit (PICU). Laboratory tests showed no hemoglobinuria or myoglobinuria, but CK was 2673 U/L, CKMB 57.1 U/L, D-dimer 890 mcg/L, and blood potassium 5.1 mEq/L. Over the next 19 hours post-crisis, body temperature ranged around 38°C without muscle rigidity, improving after IV paracetamol administration. The patient was extubated 28 hours post-crisis and returned to the ward 48 hours later.

In this case, a definitive diagnosis could not be established, as the Caffeine-Halothane Contracture Test (CHCT) is not available in Indonesia. Genetic testing for malignant hyperthermia (MH) was also not feasible due to resource limitations. Furthermore, a familial investigation was not possible because the patient is adopted, and the biological family could not be traced.

DISCUSSION

Malignant hyperthermia (MH) is a pharmacogenetic disorder affecting skeletal muscles, leading to a hypermetabolic reaction in response to triggers. The incidence of MH reactions ranges from 1:5000 to 1:50.000-100.000 anesthesia procedures. Known triggers include inhalation anesthetics (halothane, sevoflurane, desflurane), muscle relaxant

succinylcholine, and high-intensity physical activity with heat exposure.[2] The incidence in Indonesia is still unknown due to a lack of available data, leading to limited understanding and experience among anesthesiologists. At Universitas Indonesia, anesthesiology residents receive MH education early in their training, including lectures and simulations, which helps build awareness for managing suspected MH cases. In this case, the patient, a healthy child with a mild skeletal disorder, was not anticipated to experience an MH reaction during anesthesia. However, following induction, the anesthesia team observed persistently elevated sympathetic activity, raising suspicion of MH. Initial efforts focused on addressing common causes, including ensuring adequate anesthesia, analgesia, and hydration. Due to early recognition of the potential for MH, other relevant parameters were closely monitored. The factors causing doubt were related to the relatively low body temperature. However, it's important to note that late-onset temperature increases have been documented. Min et al. reported hyperpyrexia occurring 10 minutes after arrival in the post-anesthesia care unit.[3] Similarly, Turhan et al. described a MH crisis occurring postoperatively and after a second exposure to volatile anesthetics, with a one-week interval between exposures.[4] The clinical presentation of malignant hyperthermia (MH) is highly variable, with increased sympathetic activity often being a prominent feature. It is crucial to educate residents on the diverse manifestations of MH, rather than relying solely on the complete crisis picture. In this case, the initial symptom was only an increase in sympathetic tone, prompting further investigation when common causes were ruled out. Drawing on their training, the anesthesia team was encouraged to monitor for muscle rigidity, which typically appears within 15 minutes after induction. Upon detecting rigidity, the MH response management system was promptly activated. Due to the time required to procure dantrolene, intravenous $MgSO_4$ was administered as immediate symptomatic therapy, since the likelihood of complications from a malignant hyperthermia (MH) episode rises 1.6-fold with each 30-minute delay in administering dantrolene.[5]

Magnesium sulfate ($MgSO_4$) has long been used in our hospital, especially in cases of post-cardiac surgery and eclampsia. This incident marks the first experience of using $MgSO_4$ for a malignant hyperthermia (MH) crisis. In this case, the clinical symptoms changed immediately after the administration of $MgSO_4$. Our hypothesis is that Mg^{2+} not only plays a role in reducing sympathetic tone due to its antagonistic effect on Ca^{2+} but also has a specific effect on MH, as evidenced by the reduction in muscle rigidity. The cellular pathophysiological basis of MH crisis involves the excessive release of Ca^{2+} ions from the sarcoplasmic reticulum into the cytosol of skeletal muscle. This excess Ca^{2+} is responsible for hypercontraction of skeletal muscles and its consequences. Magnesium is known to have multiple roles in intracellular regulation. In simple terms, magnesium ions (Mg^{2+}) act as antagonists to calcium ions (Ca^{2+}) including at the motor-end plate.[6,7] In reality, the intracellular Ca-Mg relationship is more complex. In individuals with MH, the inhibitory site of ryanodine receptor (RyR) has reduced affinity for Mg^{2+}.[8] Under physiological conditions, a Mg2+ concentration of about 100 mcM is required for 50% inhibition of Ca^{2+} release from the sarcoplasmic reticulum.[9] In MH individuals, it can be assumed that an even higher Mg^{2+} concentration is needed.[10]

The intracellular role of Mg^{2+} is extensive, including in the regulation of Ca^{2+} besides RyR. Under normal conditions, skeletal muscle contraction is concluded with the mechanism of Ca^{2+} clearance. The majority of Ca^{2+} clearance in the cytosol involves the reuptake of Ca^{2+} bound to myofilaments, returning to the sarcoplasmic reticulum. This mechanism requires the activity of the enzyme sarcoplasmic-endoplasmic reticulum Ca-ATPase (SERCA). This enzyme requires energy for its activity obtained from the hydrolysis of ATP to ADP. In MH crisis, besides the excessive release of Ca^{2+} into the cytosol, the clearance from the cytosol is also disrupted, resulting in continuous contraction of skeletal muscles. The active pump SERCA is highly dependent on Mg^{2+}.[7,8] Choi demonstrated that ATP hydrolysis during MH crisis also increases intracellular Mg^{2+} beyond normal levels. This proves that before it can be hydrolyzed, ATP binds to Mg^{2+}.[8]Dantrolene, which remains the

only drug that stops an MH crisis, works by halting the excessive release of Ca^{2+} from the sarcoplasmic reticulum. However, it is known that dantrolene requires Mg^{2+}, and it will not be effective if intracellular Mg^{2+} levels are low. Researchers have stated that dantrolene stops the excessive release of Ca^{2+} by increasing the affinity of RyR for Mg^{2+}.[8] Given the significant role of magnesium (Mg), it is logical that this substance is crucial during an MH crisis. Previous research by Flewellen and Nelson demonstrated that intravenous $MgSO_4$ reduces MH reactions in pigs, although it does not prevent an MH crisis.[11] The optimal dosage of $MgSO_4$ during an MH crisis remains unclear, with no studies providing a definitive recommendation. In our case, $MgSO_4$ was administered in accordance with standard pediatric guidelines at a dosage of 25–50 mg/kg. While this dosage may not be optimal, it had a clinically significant impact, as the post-ICU admission temperature increase was not substantial, possibly due to a synergistic effect between dantrolene and $MgSO_4$. In Indonesia, where dantrolene is not widely available, further research is needed to establish the optimal $MgSO_4$ dosage, particularly in resource-limited settings.

CONCLUSION

The successful management of a malignant hyperthermia (MH) crisis depends on early detection and immediate intervention. In cases where dantrolene is unavailable or delayed, $MgSO_4$ is highly recommended. Magnesium mitigates MH reactions by acting on the RyR inhibitory site, inhibiting Ca^{2+} release from the sarcoplasmic reticulum, and activating SERCA to facilitate Ca^{2+} reuptake. It is also essential for healthcare providers to trace the patient's relatives for potential MH risk and educate them about it. Unfortunately, this was not possible in this case, as the patient was adopted, and no information about the biological relatives was available.

CONFLICT OF INTEREST

There are no conflicts of interest.

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