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CASE REPORT

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Successful sedation with remimazolam and alfentanil in a child susceptible to malignant hyperthermia: a case report

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Abstract

Background Malignant hyperthermia (MH) is a life-threatening autosomal-dominant disorder caused by mutations in the ryanodine receptor 1 (RYR1) gene, leading to calcium dysregulation in skeletal muscle. Patients with genetically confirmed MH susceptibility must strictly avoid volatile anesthetics and succinylcholine. Intravenous sedation presents a viable alternative, yet evidence supporting remimazolam use in pediatric MH patients remains scarce.

Case presentation We report the first case of a 1-year-old male patient with genetically confirmed MH susceptibility undergoing orchidopexy under remimazolam-alfentanil sedation combined with caudal block. The patient had no MH manifestations intraoperatively or postoperatively and recovered uneventfully.

Conclusion This case demonstrates the feasibility of remimazolam-based sedation in genetically confirmed pediatric MH patients, supporting its safety profile in this population. Further multicenter studies are needed to establish standardized protocols.

Keywords Malignant hyperthermia, Remimazolam, Pediatric anesthesia, RYR1 mutation, Sedation

Background

Malignant hyperthermia (MH) is a rare but fatal pharmacogenetic disorder primarily caused by pathogenic variants in the RYR1 gene, which disrupts calcium release from the sarcoplasmic reticulum [1]. Exposure to triggering agents (volatile anesthetics and succinylcholine) induces a hypermetabolic crisis characterized by hypercarbia, hyperthermia, muscle rigidity, and rhabdomyolysis [2]. Current guidelines recommend Total Intravenous Anesthesia(TIVA) as the standard anesthetic approach for MH-susceptible patients to avoid these triggers [3].

Remimazolam, a short-acting benzodiazepine, has emerged as a potential alternative to propofol-based TIVA in MH-susceptible individuals. Previous cellular studies demonstrated that remimazolam does not induce calcium release in RYR1-mutant cells at clinical concentrations, and limited clinical data suggest its safety in adult MH-susceptible patients [4]. However, its application in pediatric populations remains understudied due to age-related pharmacokinetic differences and the rarity of confirmed MH cases in this group.

This case report describes the successful use of remimazolam-alfentanil sedation combined with caudal block in a 1-year-old patient with genetically confirmed MH susceptibility, providing new insights into the anesthetic management of MH in pediatrics.

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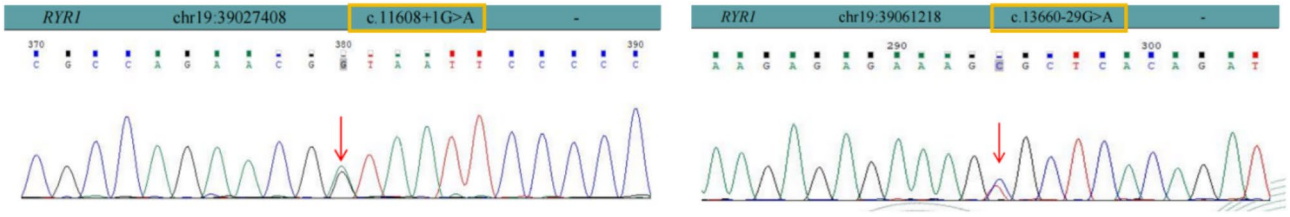

Fig. 1 The patient exhibited two heterozygous mutations in the RYR1 gene:
①c.11,608 + 1G > A: A guanine-to-adenine substitution at the + 1 nucleotide position following codon 11,608 in the coding sequence, resulting in a heterozygous mutation.
②c.13660-29G > A: A guanine-to-adenine substitution at the − 29 nucleotide position preceding codon 13,660 in the coding sequence, also classified as a heterozygous mutation.

Case presentation

A 1-year-old male infant (weight 9 kg, height 75 cm) was admitted for scheduled orchidopexy. The patient presented with right-sided cryptorchidism noted at birth, followed by progressive feeding difficulties, hypotonia, and global developmental delay observed during postnatal growth. The genetic testing revealed that the patient carried two heterozygous RYR1 mutations (c.11608 + 1G > A and c.13660-29G > A), while the father exhibited a heterozygous mutation (c.13660-29G > A) and the mother a heterozygous mutation (c.11608 + 1G > A). These mutations (c.11608 + 1G > A and c.13660-29G > A) are not listed in the ClinVar database. According to the American College of Medical Genetics and Genomics(ACMG) guidelines, these variants were classified as Variant of Uncertain Significance (VUS), but may still be considered potentially pathogenic(Fig. 1).

During the preoperative evaluation, the patient exhibited right ptosis with limited eye-opening, inability to stand or walk independently, and growth and development delay compared to age-matched peers.Preanesthetic examination and laboratory evaluation results were within the normal range. According to the European Malignant Hyperthermia Group (EMHG) guidelines [3], we prepared using an anesthesia machine previously free of volatile agents, strictly avoided volatile anesthetics and succinylcholine, and implemented remimazolam-alfentanil sedation combined with caudal block for intraoperative analgesia to minimize reliance on systemic opioids. Preoperative measures included having dantrolene readily available per Chinese drug labeling recommendations (initial dose: 1 mg/kg, with incremental doses of 1 mg/kg as needed, up to a maximum of 7 mg/kg), along with rapid cooling equipment such as ice packs, cold saline infusion, and continuous blood gas monitoring. The surgery was performed using a minimally invasive open surgical technique. After establishing intravenous access in the ward, the patient was transferred to the operating room. Upon arrival, electrocardiography, pulse oximetry, and non-invasive blood pressure monitoring were applied. No premedication was administered before anesthesia. Considering the patient's non-cooperation, remimazolam 0.2 mg/kg (actual dose: 1.8 mg) was administered first, followed by the placement of a nasal cannula with capnographic monitoring of end-tidal carbon dioxide ($EtCO_2$). Alfentanil 10 μg/kg (actual dose: 90 μg) was then administered, followed by continuous infusions of remimazolam at 1–2 mg/kg/h (total ≈ 11 mg) and alfentanil at 10–20 μg/kg/h (total ≈ 90 μg).Rectal temperature probes and radial artery catheters were placed for continuous core temperature and blood pressure monitoring. Caudal block with 0.25% ropivacaine (10 mL) provided effective intraoperative analgesia, reducing the need for additional anesthetic agents and minimizing hemodynamic fluctuations. Throughout the 40-minute procedure, the patient maintained spontaneous ventilation without the use of a laryngeal mask or endotracheal intubation. Vital signs remained stable, with $EtCO_2$ levels fluctuating between 37 and 47 mmHg and body temperature ranging from 36.5 to 37.2 °C, with no signs of MH. Sedation was maintained with preserved spontaneous ventilation, airway patency, and stable hemodynamics under remimazolam and alfentanil anesthesia combined with a regional block.The patient exhibited no purposeful response to painful stimuli during the procedure, which was more likely attributed to the excellent analgesic effect of the caudal block rather than excessive sedation. The patient spontaneously recovered 5 min after discontinuing anesthetics, and maintained stable vital signs in the postanesthesia care unit(PACU) for 30 min, followed by transfer to the general ward. On postoperative day 2, a follow-up ultrasound confirmed successful testicular fixation, with no evidence of hyperthermia, myalgia, or hematuria. The patient was discharged on postoperative day 3.

Discussion

This case report demonstrates the feasibility of remimazolam-based sedation in genetically confirmed MH-susceptible children, with no MH-related clinical manifestations observed during or after surgery. Malignant hyperthermia (MH), primarily triggered by

volatile anesthetics and succinylcholine, poses life-threatening risks in susceptible individuals. Our approach using intravenous sedation circumvents these triggers while adhering to EMHG guidelines, as evidenced by the successful management of a 1-year-old patient with heterozygous RYR1 mutations.

Remimazolam, a novel benzodiazepine acting through GABAA receptor activation [5], offers distinct advantages over traditional anesthetics. Compared to midazolam, it exhibits faster onset and shorter duration due to ester hydrolysis metabolism, minimizing postoperative recovery time and residual sedation [6]. Moreover, remimazolam demonstrates superior cardiovascular safety compared to propofol-based TIVA: lower incidence of injection site pain, less hemodynamic instability, and reversibility with flumazenil [7–8].Notably, in vitro experiments at concentrations exceeding 100 times the clinical dose demonstrated that neither remimazolam nor propofol enhanced caffeine sensitivity or RYR1-mediated calcium release in mutant RYR1-expressing cells, supporting their safety in MH-susceptible patients [9]. Although adult MH-susceptible patients have been reported to tolerate remimazolam [10, 11], this case represents the first genetically confirmed pediatric application, highlighting the paucity of data in infants (< 2 years old).

The multimodal strategy incorporating alfentanil and caudal block further optimized outcomes: alfentanil reduced opioid-related respiratory depression and hemodynamic fluctuations [12, 13], while caudal block minimized systemic anesthetic exposure, mitigating potential calcium dyshomeostasis in MH-susceptible patients.

The two RYR1 gene mutations identified in the patient (c.11608 + 1G > A and c.13660-29G > A) were classified as variants of uncertain significance (VUS) due to their absence from ClinVar and other genomic databases. Despite being annotated as potentially pathogenic based on ACMG guidelines and functional prediction algorithms (SIFT/PolyPhen-2), direct functional validation remains lacking, including calcium release assays (CICR) and in vitro contracture tests (IVCT) [14]. The diagnostic limitation was further compounded by the infant's young age (1-year-old) and parental refusal to consent to invasive procedures, precluding tissue sampling for direct assessment of calcium homeostasis via muscle biopsy.

In conclusion, this case highlights the potential of remimazolam-based sedation as a safe and effective anesthetic strategy for genetically confirmed MH-susceptible children. Despite the absence of MH manifestations, further multicenter studies are warranted to validate its broader applicability in pediatric populations.

Abbreviations

MH Malignant Hyperthermia
RYR1 Ryanodine Receptor 1
TIVA Total Intravenous Anesthesia
ACMG American College of Medical Genetics and Genomics
VUS Variant of Uncertain Significance
EMHG European Malignant Hyperthermia Group
$EtCO_2$ End-Tidal Carbon Dioxide
PACU Postanesthesia Care Unit
CICR Calcium release assays
IVCT In vitro contracture tests

Author contributions

Collection and compilation of the case and pictures: Kailai Zhu.Literature search: Shuangwei Wu, Xianglin Hao.Drafting the article and revising it critically for important intellectual content: Chuanguang Wang. All the authors reviewed and approved the final version of the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This work has been carried out by the Declaration of Helsinki (2013) of the World Medical Association. This study was approved by the Ethics Committee of Lishui Municipal Central Hospital, and all participants provided written informed consent.

Consent for publication

Written informed consent was obtained from the patient's parents for publication of clinical details, intraoperative images (Fig. 1), and genetic data. The consent form explicitly states that the patient's identifiable features have been anonymized in all published materials.

Competing interests

The authors declare no competing interests.

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