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CASE REPORTS

Maternal respiratory distress and successful reversal with sugammadex during intrauterine transfusion with fetal paralysis

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ABSTRACT
A 70 kg, 34-year-old woman at 29 weeks-of-gestation required intrauterine transfusion for Rh (D) alloimmunization. In the ambulatory treatment clinic, 19 mg of rocuronium was administered intramuscularly in split doses into the fetal buttock. The fetus moved and inadvertent maternal neuromuscular blockade occurred, leading to respiratory distress. The patient was transferred to the operating room where she had poor muscle tone, dyspnea and dysphonia. Sugammadex 100 mg was administered intravenously and complete resolution of neuromuscular blockade was demonstrated using a Neuromuscular Transmission™ monitor. When neuromuscular blocking agents are administered in ambulatory settings, management protocols, reversal agents, and skilled assistance should be immediately available for managing potentially life-threatening complications.

Keywords: Intrauterine transfusion; Neuromuscular blockade

Introduction

Intra-uterine transfusion (IUT) is a life-saving treatment for severe fetal anemia from Rh(D) alloimmunization. Without transfusion, hemolytic anemia may cause fetal hydrops and perinatal death.[1] Intra-uterine transfusion may be performed using intraperitoneal, intravascular, intracardiac or combined approaches.[2] Intravascular fetal transfusion into the umbilical vein near the placental cord insertion site or access via the fetal liver is now preferred due to higher fetal survival rates.[2,3] The IUT complication rate is reported to be 3.1% and includes risks such as infection, rupture of the membranes, emergency cesarean delivery and perinatal death.[4,5] The most common complications of IUT are fetal bradycardia and bleeding from the maternal puncture site.[2]

Fetal paralysis during IUT may improve the safety of the procedure and has been reported to prevent 80% of procedure-related fetal heart rate changes.[1,4] A variety of neuromuscular blocking agents (NMBAs) have been used, including vecuronium, pancuronium, and atracurium.[6] The only randomized trial which compared atracurium and pancuronium for the onset and duration of fetal paralysis directly after IUT found that the onset and duration were superior with atracurium.[6] Fetuses that received atracurium showed significantly more fetal movements and accelerations, without a significant reduction in fetal heart rate variability, compared to the pancuronium group.[6] Rocuronium, a newer steroidal NMBA commonly used for general anesthesia in Canada,[7] is also used for fetal paralysis, but there is no obstetric literature available to guide dosing for IUT.

When NMBAs are used in general anesthesia, adequate reversal of neuromuscular block occurs either by spontaneous recovery or administration of reversal agents, for example an anticholinesterase such as neostigmine, or sugammadex. Confirmation of adequate recovery from neuromuscular blockade is by quantitative neuromuscular monitoring, with recovery of four twitches and a train-of-four (TOF) ratio $\geq$0.9.[8] Neostigmine, the most commonly used reversal agent, has limitations and is associated with a variable rate of reversal.[9] Factors such as depth of existing block, the dose of neostigmine administered, residual levels of inhalation anesthesia, hypothermia, acidosis, electrolyte

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disturbances, hypercarbia, and patient age may affect the efficacy and speed of reversal.[10]

Sugammadex, a novel cyclodextrin, selectively encapsulates and reverses aminosteroid NMBAs such as rocuronium. Its clinical advantages include speed of onset and possible complete reversal of rocuronium blockade, even from profound depths of neuromuscular block, within three minutes.[11]

This case highlights a previously unreported complication, namely inadvertent maternal neuromuscular blockade during IUT, causing maternal respiratory distress. This was successfully treated using sugammadex. In addition, safety recommendations for clinic-based or "out of the operating room" administration of NMBAs, particularly by non-anesthesiologists, are discussed.

Case report

A 34-year-old, 70 kg gravida 3 para 2 woman was referred to the Maternal-Fetal Medicine department for management of Rh alloimmunization. Her fetus had serial Doppler interrogations of the middle cerebral artery (MCA) to monitor fetal anemia. The patient was otherwise healthy, and had no comorbidities or allergies.

At 29 weeks-of-gestation, the MCA peak systolic velocity was greater than 1.5 multiples of the median, suggestive of fetal anemia. Trace ascites and a small pericardial effusion were noted on ultrasound. An IUT was recommended and informed consent obtained for the procedure. Packed red blood cells were cross-matched and maternal intravenous (IV) access obtained. Two Maternal-Fetal Medicine obstetricians were present for the procedure, which took place in the ambulatory fetal assessment and treatment clinic.

The patient was positioned and her abdomen prepped and draped in a sterile fashion. She was provided with 1 mg of lorazepam orally for anxiolysis. The fetus was in a breech presentation. At procedure start (time $t = 0$ min), 6 mg rocuronium (0.6 mL rocuronium, 10 mg/mL) was diluted to 1 mL with 0.4 mL normal saline and was administered into the fetal buttock intramuscularly (IM) under continuous ultrasound (US) guidance using a 22-gauge spinal needle. At $t = 15$ min, 5 mg rocuronium IM was given as the fetus remained active. In view of continued fetal movement, a third fetal IM injection of undiluted rocuronium 8 mg was administered at $t = 28$ min, making the total dose administered 19 mg of rocuronium. During the final injection the fetus moved, displacing the needle. Approximately one minute later, the patient complained of tingling in her lips and perioral numbness. At $t = 30$ min she was unable to move her arms and head. The patient vocalized her sense of dyspnea and reported respiratory distress; she was noted to be tachypneic. A 100% oxygen facemask was applied and an IV bolus of Ringer's lactate was commenced as the patient was transferred by stretcher to the birth unit. She continued to be notably dyspneic on transfer.

At $t = 35$ min the patient arrived in the birth unit operating room where anesthesiologists were available. Her initial vital signs were oxygen saturation (SpO_2) 97%, non-invasive blood pressure 130/68 mmHg, heart rate 70 beats/min and fetal heart rate 130 beats/min. She had poor muscle tone, dysphonia and was tachypneic. Anesthesia staff began immediate ventilatory assistance with 100% oxygen via bag-mask ventilation. Hemodynamic monitors were placed and a further crystalloid bolus commenced. A GE Neuromuscular Transmission (NMT module™) monitor on the adductor pollicis demonstrated an initial train-of-four (TOF) of 0/4 twitches. At $t = 40$ min sugammadex 100 mg was given IV and the TOF ratio returned to >95% within 30 s. Dyspnea improved, the need for bag-mask ventilation abated and the patient could vocalize and move all limbs spontaneously.

With stable maternal and fetal vital signs and maternal consent, the IUT was completed in the operating room. Under US guidance, 5 mg rocuronium IM was administered into the fetal buttock, with adequate subsequent paralysis. The procedure finished at $t = 137$ min and the patient was transferred to the post-anesthesia care area. After confirming a normal fetal biophysical profile (8/8) and umbilical artery and MCA Doppler interrogations, the patient was discharged home the next day, with follow-up planned for one week's time.

Discussion

Sugammadex 1.5 mg/kg provided efficient and complete reversal of rocuronium-induced muscle paralysis and respiratory distress after inadvertent maternal administration of rocuronium during IUT. We suspect that one or more of the fetal injections of rocuronium was not placed fully into the fetal buttock. While rocuronium has limited transfer through the placenta, direct intramyometrial injection of rocuronium could provide enough systemic absorption to cause maternal paralysis.[12] Intramyometrial injection is an effective method of systemic maternal drug delivery.[13] Other less likely routes for maternal systemic absorption include maternal abdominal subcutaneous or IM injection, or direct maternal intravascular injection.

When NMBAs are administered for IUT in an "out-of-operating-room" environment or by non-anesthesiologists, inadvertent maternal neuromuscular blockade may be an unrecognized complication. Skilled assistance should be immediately available with knowledge of how to manage the complication and provide pharmacological reversal. Given the known limitations of anticholinesterases, reversal with sugammadex based

on weight, and if known the degree of neuromuscular blockade, is advised. We suggest anticipating a weight-based dose of sugammadex prior to the administration of rocuronium or vecuronium for fetal paralysis. However, given the rarity of this event and the significant drug cost, it is not pragmatic to prepare the dose of sugammadex in advance.

The American College of Obstetricians and Gynecologists Committee on Patient Safety and Quality Improvement suggests that surgeons who use ambulatory facilities must be vigilant about inadequate training of personnel, inappropriate or poorly maintained equipment and instruments, and ineffective protocols or practices that may increase the likelihood of medical error and jeopardize patient safety.[14] While procedures performed in physicians' offices or freestanding surgical facilities produce cost savings and convenience for patients, they should be held to the same level of scrutiny and oversight as operating room procedures.[14]

After a quality assurance review of this case, several institutional steps were taken to help recognize and avoid this previously unanticipated adverse event. Obstetricians and Maternal Fetal Medicine staff received formal education about this complication. A policy of safety measures such as vascular access, routine measurement of maternal vital signs and ensuring the availability of a portable resuscitation cart was established. Additionally, prior to commencing IUT, a 2 mg/kg dose of sugammadex is now calculated and available in the procedure room. The Society for Maternal-Fetal Medicine suggests that if the pregnancy is viable, the procedure should be performed in close proximity to the operating room, while alerting staff of the potential need for an emergency cesarean delivery.[15] Due to the remote nature of the ambulatory clinic, the obstetric team now notify the birth unit and anesthesia staff on the morning of an IUT procedure. As an alternative, consideration should be given to completing the procedure in the operating room with an anesthesiologist in attendance.

Education and monitoring for signs and symptoms of the rare but life-threatening event of maternal neuromuscular blockade when NMBAs are used during IUT is crucial. Management protocols, resuscitative equipment, reversal agents and skilled assistance should be immediately available, to recognize and treat this potentially life-threatening complication.

Disclosure of interests

D.M. McKeen has conducted a clinical trial that was funded by Merck Canada Inc. in 2012. She has acted as a Speaker for Merck Canada Inc. in 2017. None of these directly affect the reporting of this case report and none of the other authors have any financial disclosures or conflicts of interest.

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