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Successful management of cesarean section in a patient with Romano–Ward syndrome using landiolol, a selective and short-acting β1 receptor antagonist

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Abstract
Romano–Ward (R-W) syndrome is an autosomal dominant hereditary disorder and is characterized by a prolonged QT interval on the electrocardiogram (ECG), syncope, and sudden death. We report here a case of cesarian section in a patient with R-W syndrome whose QT prolongation was successfully managed with landiolol, a selective β1 receptor blocker. A 25-year-old woman with R-W syndrome was scheduled for cesarean section. In the operating room, the patient's ECG showed tachycardia (102 beats·min^{-1}) and marked QT prolongation (QTc = 0.56 s). After spinal anesthesia, the patient's heart rate (HR) increased to 130 beats/min accompanied by a slight decrease in arterial blood pressure to 97/57 mmHg and the QTc was prolonged to 0.57 s. Landiolol was continuously infused at a rate of 0.04 mg·kg^{-1}·min^{-1} and the HR gradually decreased to 80–90 beats·min^{-1} accompanied by the normalization of QTc to 0.48 s. We thought that the use of landiolol was more rational and was preferable to a nonselective β receptor blocker for a term-pregnant woman because blockade of the β2 receptor might cause uterine contraction. After the use of landiolol, intraoperative and postoperative courses in both the patient and the baby were uneventful.

Key words Romano–Ward syndrome · Landiolol · Uterine contraction · Cesarean section

Introduction

Romano-Ward syndrome (R-W syndrome) is an autosomal dominant hereditary disorder and is characterized clinically by a prolonged QT interval on the electrocardiogram (ECG) [1]. Patients with R-W syndrome are likely to suffer syncope or sudden death as a result of atypical polymorphic ventricular tachycardia displaying features of torsades de pointes (TdP) and ventricular fibrillation. This often, but not always, occurs during periods of high adrenergic activity, i.e., physical or emotional stress [2]. A β receptor blocker is the first choice for prevention and treatment of these tachyarrhythmias. However, as blockade of the β2 receptor may cause uterine contraction [3], a selective β1 receptor blocker is theoretically preferable for pregnant women. There have been several reports on cesarean section in patients with long QT syndrome [4,5], but there are no reports on the use of a selective β1 blocker for the management of QT interval prolongation during cesarean section. We report here a case of cesarian section in a patient with R-W syndrome who was successfully managed with landiolol, a selective and short-acting β1 receptor blocker.

Case report

A 25-year-old woman with R-W syndrome, 155 cm tall and weighing 57 kg, was scheduled for cesarean section in the 38th week of pregnancy. Her father and other relatives had also been diagnosed with R-W syndrome. The patient had a history of syncope on several occasions following hard exercise when she was about 7 years old. Apparently, the ECG at that time showed marked QT interval prolongation. After the diagnosis of R-W syndrome, she had been given a β receptor blocker. She had stopped taking the β receptor blocker when she was 13 years old at her own request, and had had no bouts of syncope since then. The preoperative ECG and laboratory values were within normal limits, including the QT interval, which was 0.44 s corrected by heart rate (QTc) according to Bazzett's formula [6] (Fig. 1a). The fetus received a diagnosis of growth delay (expected weight: 2073 g) and its heart rate showed bradycardia (110–120 beats·min^{-1}). Delivery by cesarean section was scheduled because the labor pain would

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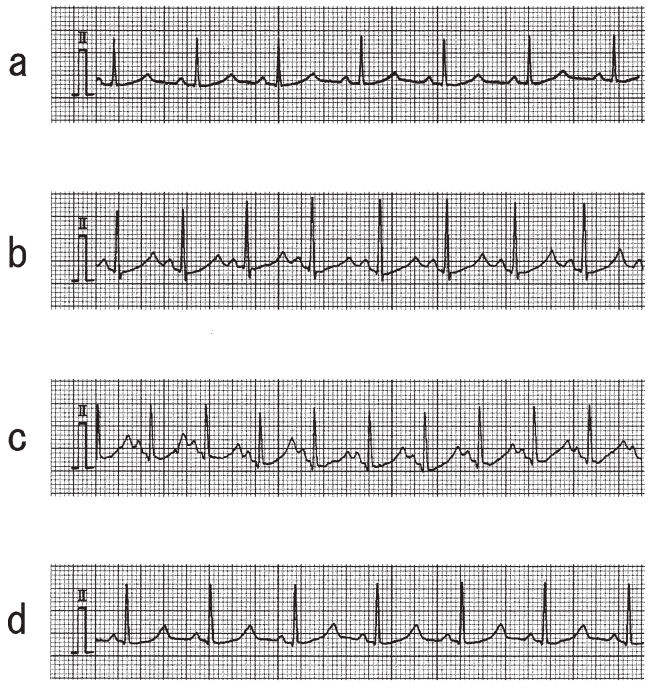

Fig. 1a–d. QT interval prolongation is diagnosed by the presence of a QTc interval longer than 0.44 s. This is obtained by Bazzett's formula. **a** Preoperative electrocardiogram (ECG) recording (QTc = 0.44), **b** ECG recording just after the patient's entry to the operating room (QTc = 0.56), **c** ECG recording after the spinal anesthesia (QTc = 0.57), and **d** ECG recording after landiolol administration (QTc = 0.48)

be likely to induce fatal arrhythmias in the mother. The patient was taken to the operating room where standard monitors were applied. The patient's ECG in the operating room showed tachycardia and marked QT interval prolongation (QTc = 0.56 s) (Fig. 1b), probably caused by anxiety. An intraarterial catheter was placed in her left radial artery and her arterial pressure was continuously monitored. She felt slight labor pain every 3 min, but her heart rate and QTc were unchanged. After placement of the epidural catheter in the L1-L2 interspace, a subarachnoid block was performed at the L3-L4 level with the patient in the right lateral position using 8 mg of 0.5% isobaric bupivacaine and 20 μg fentanyl (0.4 ml), which produced a T5 sensory level bilaterally. The patient was placed supine with a left lateral tilt. Several minutes after the subarachnoid injection, the arterial blood pressure (BP) decreased to 97/57 mmHg and the heart rate (HR) increased to 130 beats·min^{-1}. Because QTc was prolonged to 0.57 s (Fig. 1c), landiolol administration was started at a rate of 0.04 mg·kg^{-1}·min^{-1}. Ephedrine was administered to maintain systolic blood pressure above 100 mmHg. About 5 min after the continuous infusion of landiolol, QTc returned to 0.48 s (Fig. 1d) with a blood pressure of 110/65 mmHg and a heart rate of 80–90 beats·min^{-1}. The delivery proceeded uneventfully with no hemodynamic, anesthetic, or obstetric complications. The fetus weight was 2154 g and its heart rate was 130 beats·min^{-1} with normal Apgar scores. No sedatives were used even after delivery because the patient had wanted to be awake throughout the operation and, moreover, the patient appeared composed and sleepy. Landiolol administration was stopped 10 min before the patient left the operating room for the intensive care unit. The total blood-loss volume was 520 g, the urine output was 110 ml, and the total infusion volume was 1100 ml. Postoperative pain management was supplied by epidural infusion of 0.2% bupivacaine and 5.8 μg·ml^{-1} fentanyl at 2 ml·h^{-1}. The postoperative course was uneventful with the administration of propranolol.

Discussion

R-W syndrome is an autosomal dominant hereditary disorder. It is subdivided into six genotypes (LQT1 to LQT6) distinguished by mutations in at least five different ion channel genes: the sodium channel (LQT3), the rapidly activating delayed rectifier potassium channel (Ikr) (LQT2 and LQT6), and the slowly activating delayed rectifier potassium channel (Iks) (LQT1 and LQT5) [7]. QT prolongation on the ECG is induced by prolongation of the action potential duration (APD) in ventricular cells. This occurs as a result of a reduction in the net repolarization current, which both induces the generation of early-after depolarizations (EADs), leading to ectopic beats, and increases the special dispersion of ventricular repolarization creating stable conditions for reentry [8]. The control of QT interval is essential for the management of long QT syndrome. Treatment of long QT syndrome depends on the genotype [9], but when the genotype is not clearly diagnosed, a β receptor blocker, such as propranolol, is the first choice for both prevention and treatment of TdP. In this case, it was rational and preferable to use landiolol, a short-acting β1 selective blocker, for the treatment of QT prolongation because propranolol, which is not a selective β-blocker, has a potential risk of uterine contraction through β2 receptor blockade [3]. In addition, we chose landiolol but not esmolol, another selective β1 receptor blocker, because β1 receptor selectivity in landiolol is much higher than that in esmolol [10] and we thought that more delicate control of BP and HR could be performed with landiolol than with esmolol because esmolol is supposed to be given by bolus injection, whereas landiolol can be administered by continuous infusion. In fact, landiolol was effective in attenuating the prolonged QT interval without inducing any clinical symptoms relevant to uterine contraction. The safety

for the fetus when landiolol is given to the mother has not been fully established, but it was reported that landiolol, if the total amount administered is not large, caused few developmental problems in the offspring [11,12] and landiolol was safely used for a pregnant patient during cesarean section [13]. In fact, the Apgar scores of the baby were normal.

There have been several reports on both vaginal and cesarian delivery in patients with long QT syndrome using general or local anesthesia [4,5], but there is no consensus as to what type of anesthesia is preferable for cesarean section. We scheduled cesarean section but not spontaneous vaginal delivery for the patient to avoid tachycardia caused by labor, and used a combination of spinal and epidural anesthesia because many inhaled and intravenous anesthetics induce QT interval prolongation [14,15]. However, as we mentioned above, barbiturates, which induce marked QT prolongation, seem to be safe and do not cause TdP because they do not induce EADs or increase the dispersion of ventricular repolarization. Further studies will be required to clarify the effects of anesthetics on EADs and special dispersion of ventricular repolarization in association with QT prolongation.

In conclusion, we consider that it is rational and safer to use a selective β1 receptor blocker than a nonselective β receptor blocker for the treatment of QT prolongation, especially in term-pregnant women to avoid uterine contraction.

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