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Pulmonary Edema after Intramyometrial Sulprostone Administration: Two Case Reports

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Abstract

Sulprostone, a syntetic E2 analogue is given to increase uterine muscle tone and recommended for second –line treatment of atonic postpartum hemorrhage. Actually, his use in current clinical practice is increasing, specially after cesarean section; few clinical reports of side effects have been published and a recent large population-based study describe a low rates of severe side effects.

We present two cases of acute pulmonary edema in two patients after Cesarean section with sulprostone administration directly into the myometrium.

Keywords: Sulprostone; Acute pulmonary edema; Prostaglandin effects

Introduction

Sulprostone is a synthetic prostaglandin E2 analogue (PGE2), and has a dilating effect on the cervix uteri and stimulates the uterus muscles. The use of sulprostone is currently recommended, in several sets of guidelines from highresource countries, in cases of persistent blending despite oxitocin treatment, as second-line treatment for postpartum hemorrhage (PPH) aimed at avoiding non pharmacological third-line treatments, such as embolization or surgery [1-7].

Despite the potential of the drug to cause pulmonary edema and coronary artery spasm, severe cardiovascular or respiratory side effects are "uncommon" (ie, prevalence of 0.1%-1% according to the World Health Organization) in a large, prospective, population-based cohort of women with postpartum hemorrhage in France [8], and more frequently in smokers and in women above 35 years old or with cardiac diseases. Few clinical reports of side effects, like angina [9], acute myocardial infarct [10] until a cardiac arrest [11-14], pulmonary edema [15,16] have been published. Some cases were associated with a non-recommended route of administration (intravascular bolus) [12], high combined doses of sulprostone and dinoprost [13], or hemorrhagic shock [16], or women with specific class risks [14].

We describe two cases of pulmonary edema after sulprostone administration directly into uterine wall, also if intramuscular or intramyometrial administration is controindicated for a possible high plasmatic levels and induced side effects [7,17].

Case 1

A 28-year-old G2P0 Egyptian woman, weighing 68 kg and 162 cm tall (BMI 25.91 kg/m^2), was admitted at 35 weeks of gestation for premature rupture of the amniotic membranes. The patient' previous delivery six years earlier was an uncomplicated cesarean section for dynamic dystocia. Pregnancy had been uneventful and the patient denied any significant past medical history. Routine hematological investigations and electrocardiogram were normal.

A week after admission, an urgent lower segment Caesarean section was performed for fetal heart rate decelerations. Efforts to find rapidly the intrathecal space failed, so a general anesthesia was induced using a rapid-sequence induction with propofol 200 mg and succinylcholine 75 mg; tracheal intubation was easy (Cormack and Lehane grade II). An 2880 mg newborn was delivered 5 min after induction, with Apgar score 5 and 8 at 1 and 5 respectively. Anesthesia was maintained with sevoflurane 1.2-1.3% in 50% oxygen and air, fentanyl 100 mcg, rocuronium bromide 40 mg. After delivery the surgeon performed sulprostone 500 mcg directly into uterine wall. There were no cardiorespiratory events during anesthesia, and the patient remained hemodynamically stable (BP110/70 mmHg; HR 70 bpm; SpO2 98%; total diuresis 200 ml). At the end of surgery, anesthetic agent was discontinued, residual neuromuscular blockade was reversed. Estimated blood loss was 200 mL and the patient received a total of 600 mL of isotonic crystalloid. She remained in the post-anesthetic room of delivery unit with a prescribed fluid therapy at 80 ml/h with furosemide 0.8 mg/h; post-operative analgesia was set with intravenous infusion of tramadol 100 mg, ketoralac 30 mg and metoclopramide 10 mg.

In the immediate postoperative period, the patient had a cough with sputum worsening, rales at pulmonary auscultation bilaterally. Blood gas analysis, urgent blood tests were performed (Table 1). A chest-x ray showed horizontal lines reaching the lung edge, such as pulmonary edema, an enlarged cardiac silhouette, slight bulge in the left hard border, and a prominent right hilum.

The patient was rapidly treated with diuretics (furosemide 20 mg, then 40 mg after 30 min), and oxygen (FiO2 0.4) with reservoir face-mask. Symptoms improved significantly within a few hours; the patient is also subjected to echocardiography: left ventricular are normal size and wall thickness; myocardial contractility and the ejection fraction are normal (EF=0.66). The atrium and right ventricular are at the upper limit of normal; PAsP 28 mmHg. These

dysfunctions disappeared within the next day; also the chest x-ray was normal and the patient asymptomatic.

	Case 1		Case 2	
pH	7.4	7.4	7.4	7.4
PaCO2 (mmHg)	33.5	30.2	25	30.5
PaO2 (mmHg)	53.9	99	78	108
BE (mmol/L)	-1.9	-0.7	-3	-0.4
SaO2 (%)	87	98	85	98
WBC (x103/L)	8.33		17	
RBC (x106/L)	3.97		3.87	
HGB /g/dL)	10.1		12.2	
HCT (%)	32.6		35.2	
PLT (x103/L)	239		169	
INR	1.02		0.88	
Ratio	0.91		1.12	
Fibrinogeno (mg/dL)	400		459	
Ddimero (mcg/L)	575		2393	
Troponina (mcg/L)	<0.01		0.9	0.5
CK (U/L)			341	166
ASAT (U/L)			48	34
ALAT (U/L)			87	26
LDH (U/L)			396	278

Table 1: Lab data

Case 2

An Eritrean women of 30 year-old, G1P0, at 29 weeks of gestation, BMI 29.81 kg/m^2, was admitted for fetal intrauterine growth stop. She was taking a neonatal RDS prophylactic therapy with betamethasone 12 mg twice daily. The patient without notable medical history had unremarkable blood tests and normal cardiovascular parameters.

Ten days after admission, a Caesarean section was performed for fetal heart rate decelerations. She received a spinal anesthesia performed with the patient in the sitting position at L3-L4 interspace with a 27-gauge pencil-point spinal needle; after confirming free flow of cerebrospinal fluid, hyperbaric bupivacaine 10 mg was injected into the intrathecal space. An 1050 g newborn was delivered 10 minutes after induction, with Apgar score 6 and 8 at 1and 5 respectively. After successful discharge of the placenta, an oxytocin 5 U.I. bolus i.v. was given; then, despite a good uterine contractility, sulprostone 500 mcg into uterine wall was made by total diuresis was 250 ml loss was 300 mL; the patient received a total of 700 mL of isotonic crystalloid during caesarean section with a total dieresis of 250 ml. She remained in the post-anesthetic care room of delivery unit with a prescribed fluid therapy at 70 ml/h with furosemide 0.8 mg/h; post-operative analgesia was set with intravenous infusion of tramadolo 100 mg, ketoralac 30 mg and metoclopramide 10 mg.

During the two-hours stay in delivery unit, the patient reported dry cough that causes pain in the laparotomy wound. In the afternoon the cough becomes more persistent with little sputum: it is practiced aerosol with acetylcysteine and beclomethasone dipropionate. Later, the patient complained of cough that produces frothy sputum that is tinged with blood; she became hypertensive (140/90 mmHg) and tachycardic (140-150 bpm). She also complained of sudden chest pain and shortness of breath. Her peripheral oxygen saturation fell to 66% and lung crackles appeared, leading to the diagnosis of hypertensive pulmonary edema. The blood gas blood tests confirmed this diagnosis. The chest-x ray showed an upper zone vessel enlargement, bilateral increate lung markings (peri-hilar and shake like bats wings), raising of the hemidiaphragm right, enlarged cardiac silhouette. The ECG reported synus tachycardia with ventricular repolarization abnormalities.

She was rapidly treated with diuretics, intravenous nitrates and CPAP (Boussignac mask). The day after the patient had a marked improvement: decreasing dyspnea, HR (100 bpm) and blood pressure (127/80 mmHg), increasing pulse oxymetry oxygen saturation (96% with reservoir face-mask, FiO2 0.4). A middle negative fluid balance was maintained over 24 hours. Also blood tests improved; ECG and chest-x ray became normal, with only an upper zone vessel and heart enlargement.

The echocardiography showed that left ventricular are normal size and wall thickness; the ejection fraction was 0.53. The atrium and right ventricular are at the upper limit of normal; mitral and trycuspidal jet signals grade 1. Segmental kinetics abnormalities. PAsP=33 mmHg. After 48 hours the echocardiography showed only an apical interventricular septum akinesis. The pulmonary systolic pressure was normal. It was not necessary to continue with the coronary angiography. The patient was discharged home ten days later asymptomatic and with the advice to periodic cardiological control.

Discussion

Several European and American Guidelines [2-7] recommend intravenous infusion of sulprostone in cases of persistent bleeding despite oxytocin treatment. In these countries, its use in severe atonic postpartum hemorrhage might be considered as an indicator of quality of care. In fact, to optimize the use of second-line prostaglandins might help to reduce progression to severe postpartum hemorrhage and the need for invasive procedures. The Guidelines suggest a continuous intravenous infusion of sulprostone not later than 30 minutes after postpartum hemorrhage diagnosis if bleeding persists despite oxytocin administration, and a dose that should not exceed 500 mcg during the first hour and a total amount of 1.500 mcg [7].

A prospective, population-based cohort study on PPH women (4.038 cases) [8] reported only 3.5% treatment related side effects, of which 2.5% were digestive, and 0.5% (7 patients) were severe involving cardiovascular and respiratory : 1 tachycardia, 1 acute hypertension, 3 myocardial ischemia (but in hypovolemic shocks, so it is difficult to disentangle the respective roles of a possible coronary spasm attributable to sulprostone and of the hemodynamic disorders), 1 atypical chest pain and 1 acute cyanosis in a woman with asthma.

Others cases reported in the literature often occurred in presence of cardiovascular risk factors as age or tobacco use [14] or for non-recommended administration [12,13].

In effect, prostaglandin effect vascular tone; PGE2 can activate prostanoid receptor subtypes EP1, EP2, EP3, EP4. EP2 e EP4 are implicated in vascular wall remodeling and associated with vasorelaxation; the activation of EP1 and EP3 receptors cause vasoconstriction [18]. Sulprostone is a synthetic EP receptor agonist and his EP-mediated effects could be responsible of several adverse cardiovascular side effects.

In experimental models pulmonary hypertension following the administration of prostaglandins may result from stimulation of thromboxane receptors in the pulmonary artery [15] or platelet-activating factor (PAF) triggered edema, partly mediated by activation of EP3 receptors [19,20]. A PGE2-related increase of hydrostatic pressure [21] and vascular permeability [19] of the pulmonary vascular bed can lead to pulmonary edema.

Our patients had a normal cardiac function. We haven't infuse a greater volume of i.v. fluid than the amount of blood loss, so we have not thought of a pulmonary edema by overtransfusion. The cough is started after Cesarean section. We made echocardiography after only 24 hours, when symptoms were in part resolved, but in both cases pulmonary hypertension has been demonstrated, especially in the second patient where hypokinetic signs were presents in a first time, then these dysfunctions disappeared within the next days.

The rate of infusion of sulprostone and not only the total dose might be a determinant of the development for pulmonary edema. In ours cases the incorrect administration of sulprostone directly into the uterine wall resulted in a rapid increase in its ematic levels and subsequent signs and symptoms of pulmonary edema.

Incidentally, no side effect has been reported in a consecutive series of 257 women treated with sulprostone used both as second –line or as prophylactic treatment of PPH.

Conclusion

Despite the potential of sulprostone to cause pulmonary edema and coronary artery spasm, that afraid some clinicians, the use of this PGE2 analogue for atonic uterine hemorrhage is increasing and prostaglandin use in severe atonic postpartum hemorrhage can be considered as a marker of quality of care. The uncommon rates of drug-related severe cardiovascular or respiratory side effects have to reassure and encourage obstetricians to prescribe prostaglandins more often to control the uterine tone in accordance with national clinical guidelines. The cases of severe side effects reported in the literature were often described as class specific rather than drug specific.

Otherwise, it's mandatory to identify patient risk factors, to observe a proper dosage and route of administration, to survey carefully the patient in early postpartum period, to recognize and to treat quickly every side effects.

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