

## 이완성 자궁출혈환자에서 프로스타글란딘 E<sub>2</sub> 투여 후 발생한 고열, 관상동맥 연축 및 경련

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### High fever, coronary artery spasm and convulsion associated with prostaglandin E<sub>2</sub> in atonic uterine bleeding

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Postpartum hemorrhage is a serious condition related with maternal morbidity and mortality. Prior to surgical treatment, oxytocin and prostaglandin analogs administration are common. Pyrexia after prostaglandin E<sub>1</sub> was well known, but PG E<sub>2</sub> has been shown to have a few complication even though coronary arterial spasm was rarely reported. The 38-year old woman who delivered 3<sup>rd</sup> baby by Cesarean section was developed the atonic uterine bleeding. During the treatment with high dose sulprostone (PG E<sub>2</sub>), she complained the anterior chest pain, her body temperature was elevated to 41.2°C, and then convulsion with stuporous mentality was developed. EKG revealed inverted T wave in II, III, aVF lead, and CK-MB, troponin I was elevated. The laboratory test revealed elevated SGOT/SGPT, myoglobin, and metabolic acidosis. But CSF study, blood culture, direct/indirect Coomb's test, brain CT, and echocardiography were all negative. After supportive care, she came to be alert after 10 hours, body temperature was returned to normal after 22 hours, and the laboratory tests were eventually returned to normal within 6 days. She was discharged from the hospital without any complication. We postulate that high dose PG E<sub>2</sub> resulted in high fever, coronary artery spasm, and convulsion.

**Key Words:** Postpartum hemorrhage, Sulprostone, Coronary artery spasm, Convulsion

Postpartum hemorrhage is a leading cause of maternal morbidity and death in the world, accounts for 25% of maternal deaths.<sup>1</sup> Postpartum hemorrhage has been defined as a blood loss of 500 mL or more. Excessive blood loss, as defined by a 10% drop in hematocrit

after delivery or by need for red blood cell transfusion, occurs in approximately 4% of vaginal deliveries and 6% of Cesarean deliveries.<sup>2</sup> Atonic uterine hemorrhage is the most common cause of early postpartum hemorrhage. Prior to surgical treatment, administration of uterotonics such as oxytocin, ergometrine, or prostaglandin analog is a first step of management for preventing the hysterectomy. Sulprostone (Nalador<sup>®</sup>, Shering, Germany) is a synthetic prostaglandin analog (PG E<sub>2</sub>) used for uterine contraction

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worldwide. The most serious complication is myocardial infarction secondary to coronary arterial spasm reported rarely, and there's one report of convulsion.<sup>3</sup> To our acknowledge, there's no report about the complication of sulprostone in Korea. We report the case of a 38-year-old woman suffering high fever, coronary artery spasm and convulsion after intravenous sulprostone treatment for atonic uterine hemorrhage.

## Case report

A 38-year-old woman was admitted for postpartum hemorrhage and high fever (41.2°C). She delivered the 3<sup>rd</sup> baby by a scheduled Cesarean section at primary clinic 5 hours before referral. She didn't have any medical disease including heart disease or seizure disorder or allergy. During the antenatal care, there's nothing particular. Preoperative laboratory test were all within the normal range, and there's no specific problem in the operating room and recovery room. Two hours after Cesarean section, postpartum hemorrhage about 1,500 mL was developed despite of a continuous oxytocin infusion (Oxytocin 20 IU mixed to 5% Dextrose sodium fluid 1L, totally 20 IU for 2 hours). Under the diagnosis of atonic uterine bleeding, the patient was transfused three units of packed red cells, three units of fresh frozen plasma and received a intravenous sulprostone (1,000 µg/hr) for 2 hours. During the treatment with high dose sulprostone, she became extremely restless and complained the anterior chest pain, her body temperature was elevated to 40.8°C. Eventually she was transferred to the tertiary care center.

On arrival, she was stupor and spastic with hypertonic uterus. The uterine bleeding was ceased. The initial vital signs were systolic BP 100 mmHg, diastolic BP 50 mmHg, HR 148/min, tachypnea 32/min and 41.2°C. The infusion of sulprostone and packed blood

cells were stopped. Blood pressure of 110 mmHg systolic was maintained with intravenous dopamine 2.5 µg/kg/min. Laboratory results showed hemoglobin 9.3 g/dL, PT/ PTT 20.4/56.0 sec, fibrinogen 71.5 mg/dL, metabolic acidosis (pH 7.30, base excess -10.8 mmol/L), myoglobin 1,769 ng/mL. Direct/indirect Coomb's test, urobilinogen and serum bilirubin were normal. Electrocardiogram (EKG) revealed the ST segment elevation in I, aVL and inverted T wave in I, aVL, II, III, aVF lead. Creatine kinase (CK-MB) and troponin I were elevated to 45.7 ng/mL and 6.34 ng/mL.

Thirty minutes after admission, her body temperature was 40.9°C even though the antipyretic agent was administrated. She had a generalized tonic clonic seizure for 3 minutes which was controlled with intravenous diazepam 5 mg. Her pupils were isocoric, brain computed tomography (CT) and CSF study was performed but revealed normal. EKG showed normal sinus rhythm without ST elevation or T inversion on 3 hours later, and echocardiogram didn't show the regional wall motion abnormalities.

After supportive care with intravenous dopamine, oxytocin and transfusion of fresh frozen plasma, she came to be alert after 10 hours on admission. Hemodynamic status improved rapidly, and vital signs including body temperature were returned to normal after 22 hours on admission. She was stable without severe vaginal bleeding, and weaned off the assisted ventilation. There's no neurological deficit with clear mentality. CK-Mb and troponin I were decreased gradually and normalized on 4 days later. The liver enzyme (SGOT/SGPT) was increased gradually to 661/496 IU/L on day 4 of admission, after then decreased. Blood culture and urine culture were all negative. She was discharged from hospital without any complication on day 6, she made an uneventful recovery and returned to her usual work.

## Discussion

Postpartum bleeding remains a major cause of maternal morbidity and mortality in the world, occurring in as many as 2~3% of deliveries.<sup>4</sup> In most cases, postpartum hemorrhage is due to bleeding from the placental site, which is due to uterine atony.<sup>5</sup> As soon as excessive bleeding is observed, the obstetrician explore the uterus including genital tract and inject uterotonics such as oxytocin, ergometrine, or more recently, the uteroselective prostaglandin E<sub>1</sub> analog misoprostol<sup>6</sup> or E<sub>2</sub> analog sulprostone.<sup>7</sup> Those have been accepted as the safe drug generally, even though sulprostone might make minor complications such as uterine cramps, nausea, vomiting, sometimes. But nowadays, there were some reports about the serious complication of sulprostone as a causative factor for development of myocardial ischemia via coronary artery vasoconstriction and cardiac arrest during severe postpartum hemorrhage.<sup>8-11</sup> The effects of prostaglandin E<sub>2</sub> on coronary artery is not established. Prostaglandin E<sub>2</sub> acts through the four different rhodopsin type receptors. Sulprostone, an E-prostanoid (EP)-1 and EP-3 agonist, acts as constrictors of smooth muscle, it is believed that sulprostone could make the vasoconstriction and bronchospasm.<sup>12</sup> However, in a prospective cohort study identifying the risk factors for myocardial ischemia in patients with postpartum hemorrhage, sulprostone was not associated with myocardial ischemia.<sup>4</sup> Indeed, multivariate analysis identified low systolic and diastolic arterial blood pressure and increased heart rate as independent predictors of myocardial injury. We thought that's because of the infusion dosage. Among the five cases of acute myocardial infarction or cardiac arrest related with sulprostone, the dose and route of administration were different. In two cases,<sup>3,8</sup> it was injected directly to myometrium of uterus (250, 500 µg). In three cases,<sup>9-11</sup> it was administrated by intravenous in different

amount and infusion rate (500 µg/45 mins, 500 µg/h, 1,000 µg/3h). The manufacturer's recommended dose for this purpose is 250~1,000 µg/h, but the rate administered may be increased to 2,000 µg/h if postpartum bleeding doesn't cease or decrease markedly. So all cases were used within limiting dose. But in French guideline which was made after cardiac arrest was reported, sulprostone was given according to a strict intravenous infusion regimen. That is the initial dose is 1.7 µg/min and can be increased if necessary in steps of 1.7 µg/min every 15 min not exceeding 8.5 µg/min.<sup>7</sup> In our case, sulprostone was infused within the maximal dosage of manufacturer's guideline, but two times more than dosage of French guideline. CK-Mb and troponin I, which was believed as the standard marker for the diagnosis of acute myocardial injury, are increased as well as EKG abnormalities. But echocardiography was found nothing particular. After recovery, she didn't complain about any cardiac related symptoms, and refused the cardiac angiography. We thought the anterior chest pain and EKG change were evoked by vasoconstriction of coronary artery temporarily during sulprostone infusion.

The patients had generalized tonic clonic seizure with mental change. When it was developed, her hemodynamic status was tolerable except high fever. There's no evidence of the preeclampsia or seizure disorder. We performed the spinal tapping and brain CT to rule out the meningitis, brain hemorrhage or organic disease. But the results were normal. So we postulated it was related with sulprostone. There's a report that patient had convulsion after infusion of sulprostone.<sup>3</sup> But in that case, convulsion was developed after resuscitation of cardiac arrest without fever. In our case, she had high fever over 40°C, and we thought fever was the cause of convulsion. Prostaglandin E<sub>2</sub> is the potent hyperthermic agent to increase the core temperature.<sup>13</sup> Prostaglandin E<sub>2</sub> potentiates the IgE-mediated histamine release from

mast cell via EP3 and/or EP1 receptors.<sup>14</sup>

The malignant hyperthermia during general anesthesia, transfusion related complication, or infection such as meningitis, aspiration pneumonitis could be considered as the cause of fever. Considering the malignant hyperthermia, we could rule it out by clinical grading scale by Larach et al.<sup>15</sup> The direct/indirect Coomb's test, CSF study, blood culture and brain CT were not shown any abnormal findings either. We also reviewed the whole medication to rule out the anaphylaxis.

This case illustrates the side effects of sulprostone

administered for postpartum hemorrhage, i.e. high fever, hypertonic uterus, coronary artery spasm, stuporous mentality, convulsion. Prostaglandin E<sub>2</sub> has a short biologic half-life and the rapid recovery from high fever, convulsion, and hemodynamic instability observed in this case is also compatible with a causal relationship. These serious complications associated with PG E<sub>2</sub> were rare, but we believe that the Korean Guideline for PG E<sub>2</sub> has to be established and the sulprostone has to be used according to the strict intravenous infusion rate within maximum safe dose (such as 500 µg/h).

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**= 국문초록 =**

산후출혈은 모성 사망과 관련된 심각한 합병증으로서 수술적 치료 전에 옥시토신, 프로스타글란딘 제제 등의 자궁수축제를 사용한다. 프로스타글란딘 E<sub>1</sub>과 관련된 발열은 흔히 보고되었지만 E<sub>2</sub>제제는 비교적 안전한 것으로 알려져 왔다. 그러나 최근 에 프로스타글란딘 E<sub>2</sub> 제제와 관련된 관상동맥 연속이 보고되고 있다. 38세 여성에서 제왕절개술 시행 후 이완성 자궁출혈이 있어 sulprostone 투여한 후 흉통과 고열, 경련 및 의식소실이 발생하였다. 심전도상 T파의 역전 및 CK-Mb, troponin I의 상승이 관찰되었다. SGOT, SGPT, myoglobin의 증가 및 대사성 산증이 있었으나, 뇌척수액검사, 혈액배양검사, Coomb's test, 심초음파상의 특이 소견이 발견되지 않았다. 환자는 10시간 후 의식이 회복되었으며, 22시간 후 체온이 정상화되었고 6일 후 별다른 합병증 없이 퇴원하였다. 저자 등은 프로스타글란딘 E<sub>2</sub> 제제에 의한 고열, 관상동맥 연속, 경련이 발생한 예를 간단한 문헌고찰과 함께 보고하는 바이다.

**중심단어:** 산후출혈, 프로스타글란딘, 관상동맥 연속, 경련

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