

Misoprostol Induced Hyperpyrexia Associated with Seizures in Postpartum Parturient: Rare Side Effect and Its Management in Critical Care Settings

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ABSTRACT

Misoprostol is a synthetic prostaglandin E1 analogue and has been recommended as a safe, effective, easy to administer, cost efficient next in line drug after oxytocin, for the treatment and prevention of postpartum haemorrhage (PPH). Notwithstanding, it causes certain undesirable side effects compared to oxytocin such as nausea, vomiting, shivering, diarrhoea and transient fever. Transient pyrexia is commonly related with misoprostol administration, due to shift of hypothalamic set point. However, hyperpyrexia clubbed with seizures is a rare yet self-limiting side effect and requires prompt management strategies. There have been case reports describing fever following misoprostol administration but only few describing hyperpyrexia and even fewer describing with seizures. We report a case of hyperpyrexia associated with delayed presentation of generalised seizures after administration of rectal misoprostol and its successful management in critical care settings.

Atonic uterus is a serious complication of the third stage of labour and is the leading cause of postpartum haemorrhage (PPH) across the globe [1]. Though in most cases, it can be prevented and treated effectively [2]. Oxytocin infusion is considered as the gold standard for medical management of PPH. Misoprostol is a synthetic prostaglandin E1 analogue has been proven to be effective second line drug. It is a safe, effective, easy to administer, cost efficient and hence recommended for the treatment and prevention of PPH [2]. However, it causes undesirable effects such as nausea, vomiting, shivering, diarrhoea and transient fever. Transient pyrexia is commonly related with misoprostol administration, due to shift of hypothalamic set point [3]. However, hyperpyrexia (more than 40°C) clubbed with seizures is a rare yet self-limiting side effect and requires prompt management strategies. There have been case reports describing fever following misoprostol

administration but only few describing hyperpyrexia and even fewer describing with seizures [4-6]. We report a case of hyperpyrexia associated with delayed presentation of generalised seizures after administration of rectal misoprostol and its successful management in critical care settings.

Case Report

A 25 years female G2P2L1 at 37 weeks gestation was admitted in the obstetric unit (labour room) with lower abdominal pain. There were no associated comorbidities. She had a history of uneventful eutocic vaginal delivery at 36 weeks of gestation five years back when diagnosed with severe oligohydramnios and delivered a low birth weight baby (1.8 kg). After admission, she was immediately induced for labour in view of severe oligohydramnios and reactive non-stress

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test (NST). The eutocic vaginal delivery of a baby (2.26 Kg) was delivered followed by complete removal of placental products. Post-delivery, bleeding per-vaginum was observed with approximately 800 mls of blood loss. Suspecting PPH, all resuscitative measures were initiated as per recommendations and hospital protocol [2]. Oxytocin 20 IU infusion was immediately commenced followed by per rectal administration of misoprostol (800 mcg), in agreement with operating obstetrician. Thereafter, bleeding was successfully managed and patient was shifted to observation room under supervision of obstetrician care.

Two hours post-delivery, patient become irritable with high-grade fever (104 OF) and shivering. She also become tachypneic (respiratory rate: 40 breaths per minute) and have sinus tachycardia (pulse rate:180 bpm). Obstetrician immediately performed transabdominal ultrasonographic examination to rule out the possibility of retained products of conception. The uterine cavity was devoid of any retained products and well contracted. Subsequently, paracetamol 1 gm IV was administered to control fever. In addition, IV crystalloid infusion were started and active cooling measures were initiated. In due course, 45 minutes after the onset of fever, the patient had an episode of brief generalised tonic-clonic seizure and became unresponsive and unconscious, with Glasgow Coma Score (GCS) of 6/15. Outreach emergency anaesthesia team was called for further management of the patient. After initial assessment, patient trachea was intubated in view of low GCS and immediately shifted to the Intensive Care Unit (ICU).

In the Intensive Care Unit (ICU), patient was kept on invasive mechanical ventilatory support on synchronous intermittent mandatory ventilation (SIMV-VC) mode of ventilation, (Tidal Volume- 450 ml, Respiratory Rate-12/minute, I: E= 1:2, FIO₂- 50%, PEEP- 5cm H₂O). The patient was kept on IV infusion of morphine (0.3 mcg/kg/min), midazolam (0.015 mg/kg/hr) and dexmedetomidine (0.3mcg/kg/hr). Systemic examination of cardio-respiratory system revealed no significant findings. Her blood investigations shows hemoglobin level of 9.1g/dl, platelet count of 90,000/mm³, prothrombin index (PTI)-61% and an international normalised ratio (INR) of 1.72. Liver functions test (LFT) and renal function test (RFT) were normal. An arterial blood gas analysis (ABG) values were also within normal range. The 12 lead echocardiogram (ECG) was done which shows sinus tachycardia with ST segment depression in leads II, III and aVF. The Trop-T levels came out to be positive with levels of- 40ng/L.

Immediate resuscitative measures were initiated. Fluid boluses of 0.9% Normal Saline (20 ml/kg) were immediately infused with simultaneous monitoring of urine output. Metoprolol (2 mg) IV aliquots were given to control heart rate. Paracetamol 1 gm IV 8hrly was

charted and active cooling of the patient core temperature was continued. Antibiotic (Ampicillin 500 mg) IV 6 hourly was also started empirically. Additionally, bolus of phenytoin (800 mg) IV followed by 100 mg q 8 hourly IV were administered in view of seizure episode.

A differential diagnosis of peripartum cardiomyopathy, inferior wall myocardial infarction and acute pulmonary embolism were provisionally considered. Anticoagulation with IV unfractionated heparin 4000 IU stat followed by 800 IU/hr infusion were initiated. Cardiologist's opine for two-dimensional echocardiography, computed tomography pulmonary angiography (CTPA) and D-dimers levels to establish the cause of abovementioned clinical situation. Non contrast computed tomography (NCCT) of head and CTPA shows no abnormality. Trans-thoracic echocardiography (TTE) findings were also insignificant (Mild mitral and tricuspid regurgitation, left ventricular ejection fraction (LVEF) of 60%).

The patient continued on invasive mechanical ventilation support with supportive treatment. After 6 hours post admission in ICU, her hemodynamic parameters and mentation level improved. Fever subsided thereafter in next six hours. On second day in ICU, patient was extubated after meeting the standard extubation criteria. Patient was kept under observation for the next 24 hours post-extubation and then shifted to the ward and later discharged from hospital uneventfully.

Discussion

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE₁) is a synthetic prostaglandin E₁ (PGE₁) analogue originally comes forth for peptic ulcer management due to its mucosal protective and anti-secretory effects [7]. Now a days it is used commonly by obstetricians for varieties of conditions owing to its uterotonic and cervical priming properties [7]. Although considered a safe drug, misoprostol still has some adverse effects which can be quite distressing at times. The patient may complain of an unpleasant taste, numbness over mouth and throat when taken by sublingual route, fever with chills and rigor especially when taken in 3rd trimester or immediate post-partum period [7].

It can be administered by oral, vaginal, sublingual, buccal or rectal route [7]. The rectal route is almost always used for controlling postpartum haemorrhage rather than any other indications [7]. When administered by rectal route, it has an onset of action in nearly 100 minutes and duration of action last for 4 hours and is associated with uncertain absorption and bioavailability [7]. We observed that the onset of fever in the present patient nearly corresponds with with the onset of action of rectally administered misoprostol.

Endogenous prostaglandins, particularly prostaglandins E2 (PGE2) interaction with prostaglandin E3 (EP3) receptor is mainly responsible in pathophysiology of endogenous fever [3]. The pyrexia associated with misoprostol maybe due to the action of its active form, misoprostol acid, simulating prostaglandin E2, thereby shifting the hypothalamic set point upwards and stimulating temperature elevation [3].

Durocher et al, observed that patients who received 800 µgm of sublingual misoprostol after delivery has an increased risk for shivering and fever. Over one-third of women treated with misoprostol developed a temperature of more than 40.0°C. It was also observed that misoprostol-induced fevers followed a set pattern, and high fevers were often preceded by moderate or severe shivering within the first 20 minutes of misoprostol administration [3]. Khan et al compared 600 µgm of misoprostol through oral and rectal route respectively, and observed that the oral dose resulted in significantly higher rates of shivering and fever [8]. In our patient, the temperature rose to 104°F following 800 µgm of rectal misoprostol administration. The time lag between the peak plasma concentration and temperature may be due to the time taken for the febrile signal to be received and processed in the hypothalamus and the physiological processes to elevate the body temperature [3]. The rate of fever following misoprostol administration varies according to the period of gestation; higher temperatures were noted if given postpartum as compared to women given similar doses earlier in gestation [9].

In animal studies, it has been revealed that misoprostol decreases the threshold for convulsions, accelerate the onset of latency to convulsion and subsequently incite convulsions, when treated with convulsive or subconvulsive dose of Pentilenetetrazol (PTZ) [10]. It is surmised that alteration in levels of central catecholamines maybe the responsible for potentiation of PTZ-induced convulsions [10]. There have been case reports describing rigors, severe hyperthermia (41.5°C), tachycardia, and transient encephalopathy and ICU admission following rectal misoprostol [4-6].

The present patient had typical features of shivering, fever, tachycardia, hypertension and hyperpyrexia and seizures followed by unresponsiveness for which she requires secured airway and ventilatory support. Tachycardia and hypertension may be associated with high grade fever. All other differential diagnoses were excluded by the abovementioned investigations. It may be presumed that clinical improvement in signs and symptoms may corresponds with the metabolism of drug.

Conclusion

Although misoprostol is considered safe and universally used for management of PPH by various mentioned routes, it certainly requires intense observation and vigilance from the care givers. Rare side effects such as hyperpyrexia and associated seizures should be kept in mind while administering this drug and expeditious symptomatic measures should be initiated to reduce overall morbidity in this subset of patients.

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