Neuroleptic Malignant Syndrome During Mitral Valve Replacement Surgery: Considerations In Diagnosis And Management

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Citation

Abstract
Neuroleptic malignant syndrome (NMS) is an unusual idiosyncratic syndrome due to central dopaminergic antagonism or deficiency. It was rarely reported after or during cardiac surgery. Here we report a 64 years old female who was on dual NMS-causing agents haloperidol for her schizophrenia and metoclopramide for her vomiting and developed NMS during her mitral valve replacement surgery. NMS and MH are two different entities but very difficult to differentiate during surgery. Other differential diagnoses include heat stroke, central nervous system infections, toxic encephalopathies, agitated delirium, status epilepticus, and more benign drug induced extrapyramidal symptoms Cardiac surgery involving cardiopulmonary bypass poses specific challenges because conditions-related to weaning off CPB such as rewarming process, metabolic acidosis, hemodynamic instabilities, dysrhythmias and hypercarnia can mimic the features of NMS. Maintaining a high index of suspicion if the patient had a history of psychiatric disorder and/or used antipsychotic medications preoperatively may facilitate early diagnosis and timely management with dantrolene and other systemic measures.

INTRODUCTION
Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic and potentially life-threatening condition in which patients exhibit hyperthermia, extrapyramidal symptoms, autonomic nervous system disturbances, and altered levels of consciousness [1]. Even though the pathogenesis of NMS is not completely clear, most studies indicated that NMS is the result of dopaminergic deficiency in the central nervous system, most commonly caused by neuroleptic medications. Excessive dopaminergic blockade occurs most commonly in psychiatric patients receiving neuroleptic medications, but some antiemetic medications used in anesthesia have also been implicated, especially droperidol, promethazine, prochlorperazine, and metoclopramide [2]. NMS has been reported in patients with a wide range of perioperative conditions [3] [4] [5]. There are also some case reports of NMS after cardiac surgery [6][7][8][9][10]. However, intraoperative NMS in cardiac surgery has rarely reported [11]. Here we report a case of NMS developed during a mitral valve replacement (MVR) surgery. The patient was dual NMS-causing agents: haloperidol for her schizophrenia and metoclopramide for her vomiting. So NMS was considered when the patient developed hyperthermia, acidosis and autonomic disturbances. Treatment with Dantrolene and other supportive measures were immediately initiated. The patient survived the surgery and the episode of intraoperative NMS. The implications for the diagnosis and management of NMS during surgery, especially during valvular cardiac surgery involving cardiopulmonary bypass and artificial rewarming processes, are discussed.

CASE REPORT
The patient is a 64-year-old African American female who presented with frequent bouts of heart failure and complaints of shortness of breath, chest pain, diaphoresis, and vomiting. She had had multiple emergency room visits and hospital admissions for the last several months for similar problems. Echocardiography showed severe mitral regurgitation with reversal flow into the pulmonary veins caused by posterior leaflet prolapse, as well as a dilated left atrium (5.5cm by 7cm), dynamic left ventricular outflow obstruction, left ventricular hypertrophy/idiopathic hypertrophic subaortic stenosis (IHSS), and normal left ventricular ejection fraction (60%) without significant wall motion abnormalities. Other cardiac structures seemed to be within normal limits. Her other medical conditions included schizophrenia, asthma, insulin-dependent diabetes, ischemic cardiomyopathy,
coronary artery disease, hypertension and chronic renal insufficiency. She did not have any history of hyperthyroidism or other metabolic disorders, nor did she have drug allergies. Physical examinations when she was admitted to the hospital revealed that her blood pressure was 139/79 mmHg, heart rate was 168 beats/minute, temperature was 37.2 °C, and her respiration rate was 36/minutes. She was a well-nourished female with a body weight of 63 Kg at a height of 162 cm. She had decreased breath sounds bilaterally with bilateral rales. She had no history of smoking, no drug or alcohol abuse. The patient’s past surgical history included cholecystectomy, bilateral cataract surgery, and pacemaker placement. Her medications included insulin, haloperidol, pancerepasipase, potassium, metoprolol, metecloploramide, albuterol, ipratropium, and magnesium sulfate. The patient’s laboratory studies showed B-type natriuretic peptide (BNP) 2600 pg/mL.

The patient was anesthetized with 16mg intravenous etomidate, 2mg midazolam, and 150µg fentanyl; and paralyzed with 60mg intravenous rocuronium. Following intubation with a #7.5 endotracheal tube, her breath sounds were bilateral and equal. After induction and intubation, transesophageal echocardiography (TEE) was placed and severe mitral regurgitation was confirmed. After sternotomy, systemic anticoagulation with heparin was achieved and the patient was placed under cardiopulmonary bypass (CPB). Patient’s mitral valve was replaced with Medtronic #27 On-X mechanic valve. After de-airing, the patient was weaned off cardiopulmonary bypass. Dobutamine (5 µg/kg/min) and milrinone (loading dose 50 mg/kg) were started. TEE showed adequate right and left cardiac contractility, two small hinge regurgitation jets and no obvious paravalvular leak. Two epicardiac pacing wires were placed and the patient was paced at 90 beats/minute. While the chest cavity was being closed, the patient’s systolic blood pressure stayed between 90-100 mmHg, and her urine output was 65 ml/hour. Volume replacement with Plasmolyte and occasional100 mcg boluses of phenylephrine were given; About 20 minutes after separation from CPB patient’s systolic blood pressure started dropping to 50-60mmHg. Arterial blood gas analysis (ABG) reported severe hyperpercarbia (PaCO₂, 55) and severe acidosis with a pH of 7.2, at a body temperature of 38.5 °C (increased from 36.7 °C). Phenylephrine 100mg was given intravenously in attempt to increase her blood pressure. Sodium bicarbonate 100 mEq intravenously and hyperventilation werealso applied to improve her acidosis. The surgeons then reopened her chest in attempt to seek surgical causes of hypotension and hyperpercarbia. Epinephrine drip started at 0.05 µg/kg/minute (it was later increased to 0.1 µg/kg/minute) to maintain blood pressure. Repeat ABG showed PaCO₂ increased to 74 even with minute ventilation at 10 liters, and pH remained at 7.2 even after intravenous sodium bicarbonate 100 mEq. Her temperature had also climbed to 39.5 °C. At this point, a diagnosis of NMS (patient was on haloperidol and metoclopramide) or malignant hyperthermia (MH) was tentatively established and treatment with dantrolene was started with loading dose of 2.5 mg/kg; the patient’s ventilator was changed, cold icepacks were applied, and cold intravenous fluid was also administered. About 25 minutes later, the patient’s vital signs started to improve, and her blood pressure was maintained at over 90/50 mmHg. Repeat ABG showed significant improvement metabolically. Prior to transferring the patient to ICU, her pH was 7.5, PaCO₂ was 41, andPaO₂ was over 500, and she remained intubated and mechanically ventilated. The patient also received four units of packed red blood cells during surgery. A summary of the medications the patient received during the surgery included etomidate 16mg, midazolam 8mg, fentanyl 150µg, rocuronium 100 mg, atracurium 10mg, aminocaproic acid 10 grams, cefozolin 2 grams, sodium bicarbonate 200 mEq, heparin 30000 units, diphenhydramine 50 mg, famotidine 20 mg, dantrolene 140 mg, furosemide 20 mg, and topically applied vancomycin 2 grams to the chest wound by the surgeons. Her recovering process was relatively uneventful and she was discharged from the hospital 8 days after surgery.

**DISCUSSION**

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening idiosyncratic reaction to neuroleptic or antipsychotic drugs [12]. Though NMS is uncommon with an incidence about 0.01-1.4% of all patients treated with antipsychotic drugs [1][13], NMS is significantly more common than MH which has an incidence of 1/50,000 anesthetics in adult patients. The risk factors for NMS can be both physiologic and environmental [14]. Dehydration, agitation or catatonia, and elevated ambient temperature all increase the risk of developing NMS; patients with prior NMS are at higher risk. Receiving high doses of neuroleptics may also be a risk factor. Other drugs potentially inducing NMS include central dopaminergic receptor-2 (D2) antagonists (haloperidol), atypical antipsychotic agents (clozapine, risperidone), anticholinergic agents, and many antiemetic medications [1]. The following antiemetics...
commonly used in anesthesia practice have been implicated in NMS: promethazine, prochlorperazine, droperidol, and metoclopramide [2]. NMS may also occur in patients who have been taking anti-Parkinsonism drugs, i.e., Levodopa if these drugs are discontinued abruptly [8]. The syndrome can develop within hours or weeks after the administration of antipsychotic medications or other medications. The likely mechanism of NMS is related to dopaminergic blockade in the basal ganglia and hypothalamus and impairment of thermoregulation [1]. Verina P et al reported that the hyperthermia seen in NMS was not brought about by the increased physical activity. The serotonin antagonist, mexiteline, attenuated the hyperthermia in the experimental studies [15]. The mortality rate can be as high as 20-30% with deaths occurring primarily due to renal failure and/or cardiac dysrhythmia.

NMS and MH are distinct conditions even though the two disorders have many similarities in clinical manifestations. NMS is characterized by dyskinesia, autonomic dysfunction, muscle rigidity, and mental status change. On the other hand, MH is caused by abnormal peripheral calcium release, which leads to muscle spasms and contractions. This may be why non-depolarizing muscle relaxants reverse the muscle rigidity seen in NMS, but not that seen in MH. Unlike MH, NMS seems not to be inherited. However, there is also opposite report that NMS has genetic predisposition [16]. Additionally, while MH patients can safely receive neuroleptics, it is not recommended to give any MH-causing agents like succinylcholine or volatile agents to patients with NMS [17], though it is still debatable whether or not patients with NMS are also prone to developing MH. It is believed that patients with NMS are not at considerably greater risk than others to develop MH during surgery or ECT [18]. Clinically it can be challenging to differentiate MH from NMS, especially during surgery; rather, muscle biopsy should be the technique of choice. Patients with NMS usually have a normal muscle biopsy. The diagnosis of NMS is usually based on history of neuroleptic drug use, autonomic nervous system dysfunction, muscular hypertonicity, high fever and negative test result of muscle biopsy for MH. If a patient develops significant hyperthermia and autonomic instabilities during or after surgery, most anesthesia providers would probably consider the diagnosis of MH and immediately start treatment with dantrolene. In our case, the patient’s clearly documented history of antipsychotic drug use offered clues to the diagnosis of NMS, though MH cannot be absolutely ruled out because patient’s refusal of muscle biopsy. A few rapid laboratory assessments are also helpful in establishing the correct diagnosis and directing appropriate treatment. Elevated CPK, myoglobin level and leukocytosis are considered to be common abnormalities in NMS [1]. Other differential diagnoses include heat stroke, central nervous system infections, toxic encephalopathies, agitated delirium, status epilepticus, and more benign drug-induced extrapyramidal symptoms [19].

NMS has been reported to occur during or after cardiac surgical procedures, AVR [10], and CABG [9][8][11]. For anesthetists, NMS poses specific challenges: There is a rewarming process when weaning off CPB, so a temperature escalating process normally exists, this may delay the diagnosis; Blood pressure fluctuations can occur frequently immediately after weaning off CPB; Cardiac dysrhythmia is not unusual in many patients just coming off CPB; Mild metabolic acidosis sometimes exists after weaning off CPB, which may mimic the metabolic status of NMS; and under general anesthesia for cardiac surgery, the muscle rigidity indicative of NMS is usually antagonized by the anesthesia’s non-depolarizing, long-acting muscle relaxant; thus, anesthesia providers must maintain a high index of suspicion if the patient has had any history of psychiatric disorder and/or used antipsychotic medications preoperatively; and if there are any metabolic and vital sign changes beyond their normal fluctuations, the possibility of NMS should immediately be investigated. To this end, ABG and electrolytes, temperature, end-tidal CO2, and cardiac functions should be monitored very closely.

Management of patients with NMS includes supportive measures like systemic and regional cooling (ice packs, cold fluids, lowering the ambient temperature) and adequate hydration; Direct-acting muscle relaxant (dantrolene) should be used as soon as possible, especially when NMS and MH cannot be differentiated, dantrolene treats both NMS and MH; Dopamine agonists, bromocriptine, and amantadine are more cause-specific treatments for NMS; Protection of vital organ functions by maintaining adequate hemodynamic and metabolic parameters is critical in the management of NMS.

References
4 of 5

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