Metformin-associated lactic acidosis in a patient with diabetes undergoing coronary artery bypass graft surgery: a case report

Lalit Jha[a], Neeraj Kumar[a], Kunal Krishna[b]

[a]Department of Anaesthesiology, [b]Department of CTVS

Correspondence to Neeraj Kumar, Department of Anaesthesiology. Tel: +0612-2582541; Mobile: +918210104972; e-mail: neeraj.jlnmc@gmail.com

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Metformin is a commonly used first-line oral hypoglycemic agent for type 2 diabetes. Metformin associated lactic acidosis (MALA) is an extremely rare event with an estimated incidence of 0.03–0.06 per 1000 patient-years and a mortality rate of up to 50%.We report successful perioperative management of a 63-year-old man who developed MALA during his postoperative period following off-pump coronary artery bypass graft (OPCABG) surgery. MALA is a rare complication associated with metformin and is a diagnosis of exclusion. It should be considered during the perioperative period if there is suspicion of metformin accumulation. It is associated with a high mortality rate; hence, prompt recognition.

Keywords:
Metformin, lactic acidosis, diabetes mellitus, coronary artery bypass graft

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A study carried out at the All India Institute of Medical Sciences Patna, Bihar, India

Introduction

Metformin is a commonly used first-line oral hypoglycemic agent for type 2 diabetes. Metformin-associated lactic acidosis (MALA) is an extremely rare event with an estimated incidence of 0.03–0.06 per 1000 patient-years and a mortality rate of up to 50% [1]. We report successful perioperative management of a 63-year-old man who developed MALA during his postoperative period following off-pump coronary artery bypass graft (OPCABG) surgery.

Case details

A 63-year-old male with coronary artery disease presented to the Department of Cardiothoracic and Vascular Surgery for a proposed CABG. He had an episode of chest pain on exertion 9 months ago for which medical assistance was sought and coronary angiography revealed triple vessel diseases with 80% stenosis in the proximal right coronary artery, 90% stenosis in the left anterior descending (LAD) artery, and 80% stenosis in the left circumflex artery. He was also diagnosed to have diabetes as well as hypertension concomitantly. His current medications included telmisartan 40 mg, Metoprolol 50 mg, Aspirin 75 mg, Clopidogrel 75 mg, Atorvastatin 20 mg once a day and Amlodipine 5 mg, and Metformin 500 mg twice a day. His routine blood investigations were found to be within normal limits. Physical examination revealed a moderate build (76 kgs weight, 166 cm height, and body mass index of 27.6 kg/m^2) with a blood pressure of 134/82 mmHg and heart rate of 60–70 beats/min, saturation in room air 98%. 2-D echocardiography showed grade 1 diastolic dysfunction, left ventricular hypertrophy, normal valve morphology, and an ejection fraction of 55%. ECG showed a left ventricular hypertrophy pattern and normal sinus rhythm. He was advised to stop clopidogrel 5 days prior and telmisartan and metformin on the morning of surgery; the rest of the other medications were advised to be continued. He was planned for off-pump CABG. He took metformin in the morning before shifting from the ward. Well-informed written consent was taken from the patient for the publication.

On the day of surgery, the patient was shifted to the cardiac OR table, and standard ASA monitors were attached. An awake left radial arterial line was secured. Electroencephalogram (EEG) *(BIS^{TM}, Medtronic, Minneapolis, MN, USA)* electrodes were placed. After preoxygenation, general anesthesia was induced with 1 mg of midazolam, 2 μg/kg of fentanyl, 3 mg/kg of thiopentone sodium, and Vecuronium 0.1 mg/kg; and the trachea was intubated with 8.0 mm endotracheal tube fixed at 21 cm. Transesophageal echocardiography (TEE) probe was inserted and showed grade 1 diastolic dysfunction, left ventricular hypertrophy with normal valve morphology, and no regional wall motion abnormalities. Anesthesia was maintained with 2% sevoflurane and 40% oxygen. The depth of

anesthesia was monitored with a target minimum alveolar concentration (MAC) of 1 and EEG values of between 40 and 60. After median sternotomy, left internal mammary artery dissection was done following which the patient was heparinized with 2 mg/kg of heparin and post-heparin ACT was 380 s. Bypass graft from LAD to internal mammary artery, obtuse marginal and ramus artery to the ascending aorta through the saphenous vein graft was placed. The patient remained hemodynamically stable during the surgery. No new regional wall motion abnormalities were observed on TEE. Arterial blood gas (ABG) showed pH 7.41, pCO_2 37.2 mmHg, pO_2 241 mmHg, Hct 24%, glucose 142 mg/dL, and lactate 2.2 mmol/L.

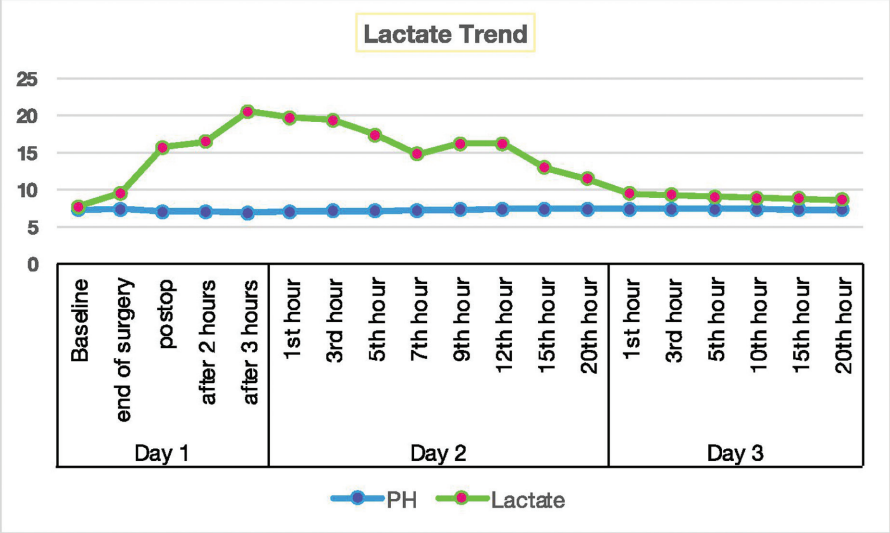
Surgery was uneventful, electively ventilated, and shifted to the cardiac intensive care unit with ionotropic support of Noradrenaline 0.05 μg/kg/min and Dobutamine 6 μg/kg/min.

After 30 min of shifting, the patient's hemodynamic gradually worsened in the form of mean arterial pressure (MAP) of 35–40 mmHg requiring the need of stepping up the inotropes, and ABG showed a pH of 7.1, pCO_2 of 41.1 mmHg, pO_2 of 351 mmHg, HCO_3 of 9 mmol/L, and lactate of 8.7 mmol/L suggestive of lactic acidosis with reduced urine output. Bolus fluids, blood products, and sodium bicarbonates were administered but the worsening persisted. The fluid status was guided by serial monitoring of systolic pressure variation, pulse pressure variation, trends of central venous pressure, and bedside transthoracic echocardiography. Central venous pressure rose from 4 to 10 and the inferior vena cava appeared distended with 2 cm diameter and reduced ejection fraction of 40%; there were no new regional motion abnormalities and grade I diastolic dysfunction on transthoracic echocardiography. Hence, the patient was planned for redo surgery for suspected graft failure and shifted back to OR. Resuscitation with fluids, vasopressors, and blood continued. Upon opening the sternum, there was adequate flow across the grafts and no areas of hemorrhage were identified. Intra-aortic balloon pump (IABP) was placed through the right femoral artery with 1:1 frequency and maximum augmentation to maintain an MAP of 60–65 mmHg. After monitoring for an hour, the chest was closed and the patient was shifted back to the ICU. Capillary blood sugar showed 519 mg/dl; ketone bodies were positive (2+) for urine dipstick test for which endocrinology opinion was taken; and metformin-associated lactic acidosis was suspected and insulin sliding scale infusion was initiated. Sustained low-efficiency dialysis (SLED) was initiated in view of hemodynamic instability. Serial arterial blood gas and blood sugars were done for continuous monitoring. On postoperative day 1, blood sugars were controlled which followed the decrease in lactate levels and correction of lactic acidosis. Augmentation in IABP was gradually reduced and frequency to 1:2 along with titrated reduction in vasopressor dosage. IABP support was weaned off on day 2 and the trachea was extubated. Vasopressors were tapered off the next day and the patient was shifted to the ward. Insulin was continued for 5 days and then changed to metformin and was discharged on the 7th day.

Discussion

Perioperative control of glycemic levels in diabetic patients undergoing cardiac surgery is paramount to reduce morbidity and mortality and improve surgical outcomes [2,3]. It is recommended that oral antidiabetics (biguanides, alpha-glucosidase inhibitors, thiazolidinediones, sulfonylureas, and glucagon-like peptide-1 agonists) and noninsulin injectables should not be taken on the day of surgery until normal food intake is resumed [2,4–6]. Metformin-associated lactic acidosis (MALA) is characterized by arterial lactate >5 mmol/L and blood pH < 7.35. The accumulation of lactate is in part due to the inhibition of the respiratory chain in the mitochondrial membrane, leading to decreased uptake of pyruvate, which acts as a precursor to lactate in gluconeogenesis. It is caused by metformin accumulation in the presence of precipitating factors, such as acute kidney injury, dehydration, hypoxemia, sepsis, and liver failure [7]. MALA is rare and a diagnosis of exclusion. In our patient, the diagnosis of MALA was suspected with its characteristics features of pH 7.1, high plasma lactate 8.7 mmol/L, and ruling out the hypovolemia, sepsis, or surgical cause of metabolic acidosis. Sepsis was considered less likely due to lack of infectious source/ fever and maintenance of scheduled antibiotic prophylaxis. Real-time TEE provides information about left and right ventricular function, regional wall motion, valve functions, and overall cardiac performance. It may facilitate the detection of worsening cardiac function as evidenced by a weakening of myocardial contraction, ventricular dilatation, or distortion of mitral and tricuspid annuli causing regurgitation during coronary occlusion. In our case, TEE showed adequate cardiac contractility with no valvular annuli distortion. Ventricles were adequately filled ruling out hypovolemia, and no new regional wall motion abnormalities were detected. The use of a stabilization system required for exposing the

Figure 1



Shows the trend of pH and Serum Lactate. SLED was initiated after 3 hours (day 1) of surgery.

posterior wall and verticalization of the heart as part of the OPCABG procedure caused intraoperative hemodynamic instability during anastomosis of grafts. Instability was assessed by TEE and managed by vasopressors and Trendelenburg position. Surgical stress and myocardial handling during anastomosis of grafts might be the precipitating factors for it. The plasma metformin level could not be measured due to the unavailability of limited resources laboratory setup. IABP was placed due to persistent refractory hypotension not responding to 3 vasopressors, viz. noradrenaline, adrenaline, and dobutamine. Sustained low-efficiency dialysis (SLED) was preferred over hemodialysis (HD) in view of refractory hypotension. SLED helped in filtering out the accumulated plasma metformin and blood urea nitrogen and improved hemodynamic post-SLED aided in establishing the diagnosis of MALA. Insulin infusion was used to maintain the glycemic level till the resumption of oral intake. In the background of metformin use, increased levels of lactate >5 mmol/L and acidic arterial pH <7.35 point toward a diagnosis of MALA. The line of management incorporates glycemic control with insulin infusion, supporting hemodynamics with inotropes and vasopressors, and hemodialysis for filtering out metformin from the plasma.

Conclusion

MALA is a rare complication associated with metformin and is a diagnosis of exclusion. It should be considered during the perioperative period if there is suspicion of metformin accumulation. It is associated with a high mortality rate; hence, prompt recognition of characteristic features helps to establish the diagnosis and formulate the management strategy timely (Fig. 1).

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Conflicts of interest

All authors have disclosed that they do not have any conflicts of interest.

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