

## Peer Review File

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### Review Comments

In abstract section:

-For case description: The abstract says nothing about how MALA got into diagnosis, no mention on lactic acidosis, and brief management.

We have modified our text with the correct statement (see Page 2, lines 31-34)

In introduction:

"Metformin....it facilitates fibrinolysis, reduces lipids, prevents endothelial dysfunction and regulates blood pressure". This is a completely wrong statement.

We have modified our text with the correct statement (see Page 3, lines 53-55)

"Severe MALA is relatively rare with an incidence of 1-15 /100000 cases, and a mortality rate ranged of 10-50%". This is old statistics.

We have modified our text with the correct statement (see Page 3, lines 58-59)

Also did you mean abdominal adhesiolysis, because I dont find anything meaning adenolysis.

We have modified our text with the correct term (see Page 4, line 81)

"hemodynamic instable": Should be hemodynamically unstable.

We have fixed the grammatical error as advised (see Page 4, line 91)

"Lactic acidosis, hemodynamic instability and renal failure resolved in about thirty-six hours and the patient returned orientated" Grammar error. Could be "In about thirty-six hours, the patient was alert and oriented. Lactic acidosis, hemodynamic instability and renal failure resolved as well.

We have modified our text with the suggested sentence (see Page 5, line 94-96)

Case 1: the patient had significant elevation in amylase and lipase as well, making acute pancreatitis as a differential. Did they have any abdominal pain at all? If so, pancreatitis and AKI (pre renal leading to ATN), can explain the patient condition and this may not be a case of MALA.

We do not have this data but only the value of the GRF on admission to the emergency room and during hospitalization in intensive care.

We have modified our text (see Page 4, lines 87-88 / Page 5, line 107)

Case 2:

"Patient presented widespread abdominal pain, diarrhea, nausea, and vomiting". Should be "Patient presented with diffuse abdominal pain, diarrhea, nausea, and vomiting"

We have modified the text as advised (see Page 5, line 100)

"On physical examination confusion, polypnea, dry mouth, reduced bowel sounds, marbling and low temperature (33 °C) was observed". Grammar: Should instead be: "On physical examination, he was hypothermic, tachypneic, confused, had dry mouth, and reduced bowel sounds"

We have modified our text with the suggested sentence (see Page 5, lines 103-104)

"Arterial blood gas (ABG) analysis showed acidemia (pH 7.031), elevated anion gap, lactate >279 mg/dl (maximum detectable value)". Did you mean a lactate >27.9 instead of 279?

We have modified our text with the correct value (see Page 5, line 106)

"Norepinephrine infusion and fluid resuscitation was started. Immediately sodium bicarbonate was infused". Can be changed to: "Norepinephrine infusion and fluid resuscitation with sodium bicarbonate was started".

We have modified the text as advised (see Page 5, lines 108-109)

Case 2: Also, there is no mention at which GFR was metformin started post operatively. We do not have this data but only the value of the GRF on admission to the emergency room and during hospitalization in intensive care.

We have modified our text (see Page 4, lines 87-88 / Page 5, line 107)

Discussion:

"Metabolic acidosis with increased anion gap in MALA is caused by concomitant type B and A lactic acidosis. Type B is caused by inhibition of mitochondrial cellular respiration, type A by hypoperfusion during hemodynamic instability". Actually MALA only causes type B lactic acidosis. The type A lactic acidosis is due to other processes like hypoperfusion and shock.

We have modified the text as advised (see Page 7, lines 143-145)

"Hence, current guidelines suggest revise the dosage if the eGFR is 5 mmol L-1 and blood pH <7.35 in case of metformin recent assumption". The statement is not clear, needs to be revised.

We have modified the text as advised (see Page 7, line 151-152)

"Our patients underwent diuretic and antihypertensive therapy with ace inhibitors which worsened dehydration and electrolyte depletion, leading to pre-renal AKI.". ACEI do not cause diuresis. Please change the statement.

We have modified the text as advised (see Page 8, line 164-165)

"ACE inhibitors modify self-regulation of renal perfusion, leading to a reduction in renal filtrate. ACE inhibitors are known to contribute to the worsening of renal failure." ACE inhibitors do affect renal perfusion and in about a week cause a drop in renal function, but over the course have been shown benefits in the renal function and reduction in proteinuria, when given at a certain GFR.

We have canceled the statement

"Homeostasis can be achieved through CVVHD, although one method of hemofiltration superior to the other has not yet been identified" It is identified in recent data that hemodialysis is superior to CVVHD/CRRT for MALA.

We have canceled the statement

Both cases: Please mention what their baseline renal function was with GFR (stage of chronic kidney disease).

We have added this information (see Page 4-5, lines 87-88, 107)

Conclusion: Would you like to mention anything for when metformin should be stopped and reintroduced perioperatively per the recent guidelines?

In the discussion and conclusions section we have added some sentences to better explain some concepts concerning suspension and reintroduction of metformin into the therapy of patients undergoing surgery, as follows:

Page 9, lines 206-212

Page 9, lines 218-224

Page 10, lines 225-231

Page 10, lines 244-246