Le Zhang

Science Editor

Editorial Office

Baishideng Publishing Group Inc.

28 November 2019

Name of journal: World Journal of Clinical Cases

Manuscript number: 52393

Manuscript title: Multiple organ dysfunction and rhabdomyolysis associated with moonwort poisoning: Four case reports

Dear Dr Zhang,

Thank you for your recent correspondence regarding our manuscript, which we submitted to World Journal of Clinical Cases. My co-authors and I are grateful to you and the reviewer for the time you have given in the appraisal of our paper.

On behalf of all the authors, I am pleased to enclose an updated version of the manuscript, which has been revised to take into account all the comments raised in the review process. Below, I have provided point-by-point responses to each of the comments. All revisions in the manuscript are shown in red-colored font. Please note that some additional minor revisions have been made to polish the English language; these grammatical revisions have not been highlighted.

I can also confirm that the general information for our manuscript is accurate.

I look forward to hearing from you.

Yours sincerely,

Dr Chen.

**POINT-BY-POINT RESPONSES TO THE COMMENTS OF REVIEWER 00502860**

Thank you for taking the time to review our manuscript and for providing us with helpful feedback that has enabled us to enhance the quality of our paper. We hope that the revisions we have made meet with your approval.

**Comment 1:** They should provide whole blood count and blood electrolyte of hte patients before and after the treatments, as one finding of rhabdomyolysis is elevated potassium level in circulating blood.

**Response:** Thank you for this important recommendation. We have now provided clinical biochemistry and hematology data before and after treatment for all four patients in new Table 3 (the original Table 3 in the previous version of the manuscript has been renamed Table 4). As we now state in the revised manuscript, there were mild increases in white blood cell count and neutrophil count in the four patients, but electrolyte analysis did not demonstrate hyperkalemia in any of the patients. We speculate that the absence of hyperkalemia may have been due to the rapid initiation of treatment and the absence of renal injury in these four patients, which allowed the kidneys to compensate for the loss of $K^+$ from skeletal muscle. The following new text (supported by 2 new reference citations, #6 and #15) has been added to the manuscript to describe the data shown in new Table 3:

Case Presentation, lines 91–96:

However, all four patients showed marked elevations in the serum levels of cardiac troponin I and myoglobin, and three of the patients also had an increased serum level of creatine kinase

(Table 3). There were also mild increases in white blood cell count and neutrophil count (Table 3). However, electrolyte analysis did not demonstrate hyperkalemia in any of the four patients (Table 3).

Discussion, lines 161–168:

Rhabdomyolysis may be associated with hyperkalemia due to the loss of large quantities of intracellular $K^+$ from the damaged skeletal muscle and the development of acute kidney injury [15]. It is essential that hyperkalemia is rapidly corrected because it can result in potentially life-threatening arrhythmia [6]. However, it was notable that none of the four patients in our study exhibited an elevated level of plasma $K^+$ before treatment. This may have been due to the rapid initiation of treatment and the absence of renal injury in these patients, which allowed the kidneys to compensate for the loss of $K^+$ from skeletal muscle.

[6] Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care, 2016,20(1):135.

[15] Chatzizisis YS, Misirli G, Hatzitolios AI, Giannoglou GD. The syndrome of rhabdomyolysis: complications and treatment. Eur J Intern Med, 2008,19(8):568-74.

**Comment 2:** They may expand discussion section with especially rhabdomyolysis literature (for instance Rhabdomyolysis, compartment syndrome and thermal injury.Coban YK.World J Crit Care Med. 2014 Feb 4;3(1):1-7.).

**Response:** Thank you for this very helpful suggestion and for bringing the interesting paper by Coban to our attention. We have added a new paragraph to the Discussion section to expand the description of rhabdomyolysis, and we have introduced 6 new reference citations (#6 to #11), including the paper by Coban that you mentioned.

Discussion, lines 122–139:

Rhabdomyolysis is an acquired or inherited clinical syndrome characterized by the destruction of skeletal muscle and release of intracellular constituents (such as myoglobin, enzymes, and electrolytes) that lead to a variety of systemic complications [6]. The causes of acquired rhabdomyolysis are varied and include trauma, intense exertion, ischemia, thermal injury, drugs, and toxins [6, 8]. Regardless of the underlying cause, direct injury to the skeletal muscle membrane or energy depletion results in an increase in intracellular calcium that activates proteases and apoptotic pathways, leading to the generation of oxygen free radicals, mitochondrial dysfunction, and cell death [9, 10]. Rhabdomyolysis typically presents with myalgia, weakness, and/or myoglobinuria, but an accurate diagnosis is facilitated by the detection of an elevated creatine kinase level [6–10]. Acute kidney injury, the most frequent systemic complication of rhabdomyolysis, occurs with an incidence of 10–40% and is associated with a poor prognosis, especially if multiple organ failure is also present [6, 10]. Other complications include electrolyte disturbances (such as hyperkalemia), hypovolemia, compartment syndrome and disseminated intravascular coagulation [10]. The management of rhabdomyolysis includes treatment of the underlying cause, infusion of fluids to correct hypovolemia and electrolyte disturbances, alkalinization of the urine with sodium bicarbonate, and decompression of muscle compartments [10, 11].

[6] Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care, 2016,20(1):135.

[7] Zimmerman JL, Shen MC. Rhabdomyolysis. Chest, 2013,144(3):1058-1065.

[8] Coban YK. Rhabdomyolysis, compartment syndrome and thermal injury. World J Crit Care Med, 2014,3(1):1-7.

[9] Giannoglou GD, Chatzizisis YS, Misirli G. The syndrome of rhabdomyolysis: Pathophysiology and diagnosis. Eur J Intern Med, 2007,18(2):90-100.

[10] Torres PA, Helmstetter JA, Kaye AM, Kaye AD. Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner J, 2015,15(1):58-69.

[11] Cervellin G, Comelli I, Benatti M, Sanchis-Gomar F, Bassi A, Lippi G. Non-traumatic rhabdomyolysis: Background, laboratory features, and acute clinical management. Clin Biochem, 2017,50(12):656-662.

**Comment 3:** If the extract of the subject is known, what pathophysiology might be in this clinical scenario?

**Response:** Thank you for this interesting query. As we mentioned in the original version of the manuscript, a previous study found that moonwort contains flavonoids, plant proteins, cardiac glycosides, saponins and phenols, but not alkaloids and oils. Unfortunately, since no previous studies have identified which components of moonwort have the ability to induce rhabdomyolysis, it is not possible to draw any conclusions regarding the causative compound(s) in the four cases described here. We have added new text to state this.

Discussion, lines 144–146:

However, since no previous studies have identified which components of moonwort have the ability to induce rhabdomyolysis, it is not possible to draw any conclusions regarding the causative compound(s) in the four cases described here.