

Responses to reviewers

Name of journal: World journal of clinical cases

Manuscript Number: 80329

Dear Editors and Reviewers:

Thank you for the opportunity to resubmit our revised manuscript. We also thank you for the reviewers' constructive suggestions and comments concerning our manuscript entitled **“Hyponatremic encephalopathy due to polyethylene glycol-based bowel preparation for colonoscopy: A case report”** (ID: 80329). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Our point-by-point answers to the reviewers' comments are below, with amendment in blue. We hope that the revised manuscript is now acceptable for publication.

We look forward to hearing from you.

Reviewer Comments:

Reviewer 1 (05260701):

1 Title. The title reflects the main subject of this case report.

Response: Thank you for your positive comments.

2 Abstract. The abstract summarizes and reflect the case described in the manuscript.

Response: Thank you for your positive comments.

3 Key words. The key word "neurological" should be removed.

Response: We have considered your suggestion and have removed this keyword “neurological”.

4 Background. The existing background is presented; however, more data about the prevalence of hyponatremia and PEG-based solutions should be provided.

Response: Thank you very much for your valuable comments. Hyponatremia, defined as serum sodium less than 135mmol/L, is the most common type of electrolyte abnormality in clinical practice and is associated with significant morbidity and mortality. Its clinical manifestations depend on the degree and speed of decrease in serum sodium. Hyponatremia varies in severity. In the most severe case, hyponatremia causes cerebral edema and increased intracranial pressure (Hyponatremic encephalopathy), followed by headache, nausea and vomiting, seizures, and changes in the level of consciousness. The most common condition in which hyponatremic encephalopathy occurs is in postoperative patients, with a prevalence of about 1%. At present, relevant guidelines indicate that hypertonic saline is considered to be a safe and effective treatment for acute or symptomatic hyponatremic encephalopathy. Timely and effective treatment of hyponatremia is very important for clinical diagnosis and treatment, which can shorten the treatment time and reduce the disability rate and mortality. However, inappropriate treatment may lead to irreversible brain damage. We have added more data about PEG-induced hyponatremia in the background section, which is detailed in the main text of our paper.

5 Methods. N/A since a case report

Response: N/A;

6 Results. N/A since a case report

Response: N/A;

7 Case presentation and Discussion. The authors should revise the manuscript in order to provide more clearly the differential diagnosis. Are there any previous labs?

Response: Thank you for your comments. When the patient was found unconscious, we made a series of differential diagnoses to determine whether the patient had an intracranial vascular lesion, or a cardiogenic cause, or shock, or hypoglycemia. Therefore, we monitored the patient's vital signs (including heart rate, blood pressure, respiration), electrocardiogram, head CT, blood glucose, electrolyte levels, etc. Laboratory results revealed serum sodium (114 mmol/L, reference: 136-144 mmol/L), potassium (3.4 mmol/L, reference: 3.6-5.2 mmol/L), chloride (82 mmol/L, reference: 101-111 mmol/L), bicarbonate (21 mmol/L, reference: 22-26 mmol/L), blood urea nitrogen (BUN) (32.4 mg/dl, reference: 9-20 mg/dl), creatinine (0.44 mg/dl, reference: 0.6-1.2 mg/dl), glucose (187.2 mg/dl, reference: 70-120 mg/dl). That means a total loss of 19.65g Na deficit. The level of hematocrit decreased from 32.8-29.6 vol%. A computed tomography (CT) scan was performed and revealed cerebral edema. The present patient suffered from gastrointestinal disorders with other comorbidity but did not have neurological problems. She developed coma and seizures after bowel cleansing with PEG prior to colonoscopy, and based on the associated mechanism combined with clinical practice, we have reason to suspect that it may be hyponatremic encephalopathy due to PEG-based bowel preparation. She was treated with injections of a 3% NaCl. The sodium level returned to 135 mmol/L on the following afternoon, and her neurological status also improved much.

8 Illustrations and tables. Figure is OK.

Response: Thank you for your positive comments, we have refined the pictures and tables.

9 Biostatistics. N/A since a case report

Response: N/A;

10 Units. yes

Response: Thank you for your positive comments.

11 References. Can be improved.

Response: Several updated references were added according to our revised paper.

12 Quality of manuscript organization and presentation. Both organization and presentation of the manuscript can be ameliorated. This case report does not contribute to the existing literature. The manuscript suffers in terms of English language.

Response: We are grateful for your kind comment. According to your kind suggestion, our manuscript was polished carefully once again. Besides, we have checked our references and make sure it is relevant to our text. All changes are shown with Track Changes in the manuscript. Hope it could meet with your approval.

Reviewer 2 (03544596):

Dear Editor, Thanks to the authors for this case report. Polyethylene glycol based solution is the most widely used intestinal cleansing agent and is a relatively safe option for patients. The manuscript adequately describes the background, present status and significance of the study. Also, the manuscript cites appropriately important references. Hyponatremia encephalopathy induced by PEG solutions is rare. Because of that, I think it will contribute to the literature.

Response: We are grateful for your positive comment.

Reviewer 3 (05688164):

29 September 2022 Review report on the manuscript titled ‘Hyponatremic encephalopathy due to polyethylene glycol-based bowel preparation for colonoscopy: A case report’ by Zhao Y & Dong H, submitted to World Journal of Gastroenterology Manuscript ID: 80329 Dear Authors, Zhao and Dong in the present case report entitled ‘Hyponatremic encephalopathy due to polyethylene glycol-based bowel preparation for colonoscopy: A case report’, described a case of a 63-year-old female who presented with acute hyponatremic encephalopathy and seizures after bowel cleansing with polyethylene glycol (PEG) for colonoscopy. The main strength of this manuscript is that it addresses an interesting and timely question, providing a captivating interpretation and describing how bowel preparation with PEG for colonoscopy might lead to brain edema associated with hyponatremia. In general, I think the idea of this paper is really interesting and the authors’ fascinating observations on this timely topic may be of interest to the readers of World Journal of Gastroenterology. However, some comments, as well as some crucial evidence that should be included to support the authors’ argumentation, needed to be addressed to improve the quality of the manuscript, its adequacy, and its readability prior to the publication in the present form. My overall opinion is to publish this paper after the authors have carefully considered my suggestions below, in particular reshaping parts of the ‘Introduction’ and ‘Discussion’ sections by adding more evidence. Please consider the following comments:

1. Abstract: In my opinion, the absence of a definition of ‘hyponatremia’ makes the reader unable to grasp the key aspects of this paper by just consulting the abstract. I suggest reorganizing the abstract, making sure to include an explanation of this medical condition.

Response: Thank you for your kind comments. We reorganized the abstract to ensure that readers understand the rare disease and key aspects. All changes are shown with Track Changes in the manuscript. Hope it could meet with your approval.

2. Keywords: Please list the keywords in a way that the first two sentence of the abstract use as many keywords as possible.

Response: This case describes the diagnosis and treatment of a female with hyponatremic encephalopathy after PEG-based bowel preparation. therefore, we have modified the keywords and according to the guideline for manuscript preparation and submission of the study (Please list 6 key words (including “case report”) which reflect the content): Polyethylene glycol; Intestinal preparation; Hyponatremic encephalopathy; Hyponatremia; Brain; Case report.

3. In general, I recommend authors to use more evidence to back their claims, especially in the Introduction of the manuscript, which I believe is currently lacking. Thus, I recommend the authors to attempt to deepen the subject of their manuscript, as the bibliography is too concise: nonetheless, in my opinion, less than 30 articles for a paper are insufficient. Therefore, I suggest focusing their efforts on researching more relevant literature: I believe that adding more studies and reviews will help them to provide better and more accurate background to this study.

Response: Thank you for your kind comments. According to your suggestion, we have investigated dozens of literatures and improved the main points of introduction to ensure that readers can have a better and more comprehensive understanding of the research background.

All changes are shown with Track Changes in the “Introduction” section. Hope it could meet with your approval.

4. Background: As suggested before, I strongly recommend authors to use more evidence to back their claims, especially in the Background of this manuscript, which seems inhomogeneous and dispersive. Nevertheless, I believe that more information about neurologic complications and death as a result of acute hyponatremia will provide a better and more accurate background. Thus, I suggest the authors to make such effort to provide a brief overview of the pertinent published on neurobiological signs of this disorders, because as it stands, this information is not highlighted in the text. In this regard, I would recommend citing recent studies that have focused on neurobiological mechanisms and molecular signs of neuroinflammation following chronic hyponatremia (<https://doi.org/10.3390/ijms21072431>; <https://doi.org/10.3390/ijms23136991>; <https://doi.org/10.3390/biomedicines10081897>; <https://doi.org/10.3390/cells11162607>).

Response: Thank you for your kind comments. According to your suggestion, we have cited your recommended studies, and added relevant content regarding neurobiological mechanisms and molecular signs of neuroinflammation following chronic hyponatremia. However, such articles as case report cannot be fully explained due to space and word limit. We have briefly supplemented the relevant content in the “Introduction” and “Discussion” section. All changes are shown with Track Changes in the revised paper. Hope it could meet with your approval. Hyponatremia is very frequently encountered in neurosurgical and neurocritical care settings, where it is present in up to 50% and 38% of patients, respectively. Common neurological pathologies, including subarachnoid haemorrhage, cerebrovascular

accidents, brain tumor and head trauma, result in hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or to the cerebral salt wasting syndrome (CSW), which are a consequence of the release of ADH or natriuretic peptides, respectively, from the brain as a response to an injury. The change of serum sodium concentration is closely related to the regulation of extracellular volume and homeostasis of the internal environment. The severity and the rate of decrease of serum sodium concentration can lead to different clinical symptoms. International cancer guidelines suggest that electrolyte disturbances, such as hyponatremia, may be a risk factor for chemotherapy-induced nausea and vomiting. Recent studies have shown that sodium balance plays a role in immunity, with hypertonic tissue fluids enhancing the induction of murine and human TH17 cells and upregulating inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF, tumor necrosis factor- α (TNF- α) and interleukin-2 (IL-2) are secreted, so hypertonic tissue fluid plays an important role in the immune response of lymphoid tissues. The main mechanism by which the brain ADAPTS to hyponatremia is the extrusion of intracellular electrolytes and organic osmolytes, some of which are excitatory amino acids, such as glutamate and aspartate, that can cause seizures in the absence of detectable brain edema. One of the common features of hyponatremic encephalopathy is noncardiogenic pulmonary edema, also known as Ayus-Arieff syndrome. Cerebral edema leads to increased intracranial pressure and thus pulmonary edema, which has also been reported in patients with postoperative hyponatremia and exercise related hyponatremia encephalopathy. Hypertonic saline can rapidly reverse the condition but is generally fatal if left untreated. Hyponatremic encephalopathy has no specific manifestations

on brain CT, and brain MRI often shows brain tissue edema with high signal on DWI. An overly rapid correction of chronic hyponatremia, that exceeds the brain's ability to recapture the lost osmolytes, causes an inverse osmotic gradient with a consequent dehydration of brain tissue and possible demyelination of the white matter. This dramatic consequence is known as osmotic demyelination syndrome (ODS) and occurs especially in the pons (central pontine myelinolysis), although an extrapontine myelinolysis affecting the basal ganglia, cortex, lateral geniculate body and internal capsule can also occur. Also in the pathophysiology of ODS, the cells mainly involved are the astrocytes. We cited your recommended studies in 'Background'.

5. I suggest better explaining and further describing data about the subject and provide full information on his clinical assessment (i.e., severity of disorder, pharmacotherapy duration etc.). Moreover, I suggest using more references to back their claims, especially when describing the laboratory tests used.

Response: When the patient was found unconscious, we made a series of differential diagnoses to determine whether the patient had an intracranial vascular lesion, or a cardiogenic cause, or shock, or hypoglycemia. Therefore, we monitored the patient's vital signs (including heart rate, blood pressure, respiration), electrocardiogram, head CT, blood glucose, electrolyte levels, etc.

The present patient suffered from gastrointestinal disorders with other comorbidity but did not have neurological problems. She developed coma and seizures after bowel cleansing with PEG prior to colonoscopy, and based on the associated mechanism combined with clinical practice, we have reason to suspect that it may be hyponatremic encephalopathy due to

PEG-based bowel preparation. She was treated with injections of a 3% NaCl. The sodium level returned to 135 mmol/L on the following afternoon, and her neurological status also improved much. Detailed descriptions of the patient's clinical evaluation and management are provided in revised paper. Moreover, we cited more studies to support our case diagnosis and treatment.

6. Discussion: I suggest rewriting this section more accurately. To properly present experimental findings, I think that authors should provide more details about consequences of acute hyponatremia on the brain functioning. Also, the discussion of data citation was good and captured the state of the art well, but I would have liked to see some views on a way forward: for example, I would have liked some further discussion on the requirement of non-pharmacotherapies to treat possible neurologic disorders related to hyponatremia. Notably, non-invasive brain stimulation (NIBS) techniques have been widely used to investigate brain mechanisms, for example mechanisms of defense of the brain against hypotonicity flowing hyponatremia, or to modify and enhance cognitive, behavioral, social, and emotional processes: in this regard, I believe that it could be very useful to add evidence of NIBS effect on treatment of clinical manifestations of brain adaptation capacities to a hypo-osmotic challenge, and how NIBS are often used to boost neuropsychological or psychiatric rehabilitation, through modulation of neuroplasticity (<https://doi.org/10.1016/j.neubiorev.2021.04.036>; <https://doi.org/10.1016/j.jad.2021.02.076>; <https://doi.org/10.3949/ccjm.74.5.377>).

Response: Thank you for your constructive comments. The consequences of acute hyponatremia on the brain functioning : During hyponatremic states, an osmotic gradient

develops between the circulation and the brain, resulting in water movement into the brain through aquaporin-4 channels located in astrocytes, one of the types of neuroglial cells. Astrocytes, located on the brain side of the microcirculation, help to regulate the movement of fluids and molecules across the blood brain barrier by the cells' foot processes that contact brain capillaries. This fluid movement results in cell expansion and an increase in brain volume. The resultant increase in intraparenchymal brain volume is immediately offset by the shunting of cerebrospinal fluid from the intracranial vault, which accommodates some of the volume perturbation, but this mechanism has limited capacitance. The non-invasive brain stimulation (NIBS) technique you mentioned is not carried out in our hospital at present, and we will pay more attention to it in the future.

7. In my opinion, I think the 'Conclusions' paragraph would benefit from some thoughtful as well as in-depth considerations by the authors, because as it stands, it is very descriptive but not enough theoretical as a discussion should be. The authors should make their effort to explain the theoretical implication as well as the translational application of their research.

Response: We conclude that physicians should be thoroughly familiar with a patient's medical history before prescribing PEG. And prompt identification of patients with hyponatremic encephalopathy is critical, as delayed treatment is associated with poor neurological outcomes. When early symptoms appear, treatment with 3% intravenous sodium chloride is recommended. The goal of treatment is to adequately treat cerebral edema while avoiding serum sodium correction exceeding 15 to 20 mEq/L within 48 hours of treatment, thereby preventing the development of demyelination.

8. In according to the previous comment, I would ask the authors to include a proper 'Limitations and future directions' section before the end of the manuscript, in which authors can describe in detail and report all the technical issues brought to the surface.

Response: Thank you for your comments regarding the limitations and future directions: This case report has several limitations. First, the single case itself has limitations, and high-quality evidence is needed to confirm. Second, some techniques, like non-invasive brain stimulation (NIBS) techniques, it should be more widely used in clinical practice in the future; Third, not all aspects of hyponatremia encephalopathy were discussed.

9. Overall, I suggest submitting your work to an English native speaker to help with some grammar mistakes that can be found in different sections of the manuscript. Overall, the manuscript contains 1 table, 1 figure and 11 references. I believe that this manuscript might carry important value describing how bowel preparation with PEG for colonoscopy might lead to brain edema associated with hyponatremia. I hope that, after these careful revisions, the manuscript can meet the Journal's high standards for publication. I am available for a new round of revision of this review. I declare no conflict of interest regarding this manuscript.

Response: We appreciate the careful reading of our manuscript and positive suggestions for our study. According to your kind suggestion, our manuscript's English and grammar was polished carefully once again. Besides, we have added and checked our references and make sure it is relevant to our text. All changes are shown with Track Changes in the manuscript. Hope it could meet with your approval.