

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Successful prolonged cardiopulmonary resuscitation after intraoperative cardiac arrest due to povidone-iodine allergy: a case report and literature review" (Manuscript NO: 69711). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval. All the amends are highlighted in red on our manuscript and the responds to the reviewer's comments are listed below:

Reviewer #1: The original finding of this manuscript is successful prolonged cardiopulmonary resuscitation after intraoperative cardiac arrest due to povidone-iodine allergy. The new hypotheses proposed that the decision for prolonged CPR requires some factors providing a favorable outcome. The new phenomenon that was found through this case report is that povidone-iodine allergy may cause cardiac arrest. Therefore, the hypothesis confirmed through this case report is that a favorable outcome of prolonged CPR is possible in patients with cardiac arrest due to povidone-iodine allergy. The conclusions appropriately summarize the data that this study provided. As pointed by the authors, The American Heart Association recommends stopping resuscitation for patients who do not respond to at least 20 minutes of advanced cardiovascular life support. However, in some conditions similar to the case presented here, prolonged CPR may be successful. The limitation of the study: 1- The decision for prolonged CPR may be difficult because the factors that favor such a decision for this treatment needs to be clearly defined. This should be emphasized in the discussion. 2- DOI and PMID numbers should be added in references. 3- The clinicopathological finding of similar recent cases should be presented as a Table to inform the readers better and compare the data with the case presented here.

Response: Thank you very much for your comments and suggestions. 1- Obviously,

your suggestions are very helpful to us in revising the manuscript, and now we have revised and added the factors that favor such a decision for prolonged CPR in the discussion section, such as the high ETCO₂ levels and good blood gas analysis results. 2- DOI and PMID numbers have been added in references. 3- The clinical features of immunoglobulin E-mediated allergy to povidone-iodine from previous case reports have been presented in Table 1.

Reviewer #2: This is a very interesting manuscript. The hypotheses that povidone iodine caused the anaphylactic shock is corroborated by your described findings in the paper. More weight should be given to the allergen in povidone iodine, and see if there are corroborating literature implicating this allergen- whether in povidone iodine or not, to anaphylactic shock. Given the multiple medications that were being given to the patient, and the possibility of neurological shock- how were these possible confounders taken into account or ruled out? It might be worth noting the ETCO₂ levels during the CPR- doing a CPR for two hours is very heroic, apart from the subjective decision to continue with the CPR, it would be interesting to know if there were any objective evidence that prompted the team to continue with the CPR. In the conclusion section, it may be worth touching on the povidone iodine anaphylaxis again- what are your recommendations based on this experience. The introduction section does not have citations. This needs to be addressed.

Response: Thank you very much for your valuable advice and recommendation. We reviewed the relevant reports on the allergen in povidone iodine and supplemented them in the discussion section of manuscript. Povidone iodine is a compound composed of iodine, povidone and surfactant. Studies have reported that iodine never participates in the allergic reaction of povidone iodine. Povidone usually causes immediate hypersensitivity reactions, while surfactant causes delayed hypersensitivity reactions. In this case, the patient suffered from anaphylactic shock due to povidone-iodine, which is considered to be an immediate allergic reaction caused by povidone.

On the one hand, by reviewing the experience of the previous surgery and anesthesia, we ruled out the possibility that this patient was allergic to the anesthetic and ancillary drug, such as sevoflurane, dexmedetomidine, propofol, remifentanyl, sufentanyl, rocuronium, crystal liquid, hydroxyethyl starch solution, succinyl gelatin solution. On the other hand, when the patient re-operated one year later, we avoided the use of povidone-iodine and the patient did not develop allergies during operation. In addition, the patient was conscious preoperatively and had no special neurological symptoms. Physical examination of the nervous system and circulatory system was normal except for slight scoliosis. So we ruled out the possibility of neurological shock and cardiogenic shock. In the section of diagnosis, we have made relevant supplement and modification.

Thank you very much for your advice. We supplemented the ETCO₂ levels during CPR in Figure 1. Obviously, the high ETCO₂ level is an important objective evidence that prompted the team to continue with the CPR. During CPR in this case, ETCO₂ was mostly maintained above 20 mmHg. In addition, the blood gas analysis is another important objective evidence. The patient did not have irreversible electrolyte disturbance, metabolic acidosis, or oxygenation disorder during CPR. We have made some necessary supplement in the discussion section.

Your suggestions are very helpful to us in revising the manuscript. We have added some recommendations based on this experience about povidone iodine anaphylaxis in the conclusion section. Also, we have addressed citations in the introduction section.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.