

Peer Review File

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Reviewer A

- General
 - o The manuscript gives a nice description of the care of two Jehovah Witness Patients (JWP) following a defined protocol.

Answer) Thank you for your review and great comments.

- o In the title, the abstract and the introduction there is discussion of use of patient blood management (PBM) to ensure an adequate blood supply and reducing transfusions. While this is certainly an important aspect of PBM, in this manuscript the focus is not on blood supply or transfusions but on those patients where blood is not an option (BNAO). A good PBM program will ensure optimal care for patients who do not accept transfusion of allogeneic blood components for religious or other reasons.

Answer) Our intension of this case reports was also not to use blood efficiently due to lack of blood supply, but to show the transfusion is not necessarily the only treatment method in patients who refuse blood transfusion, as you mentioned. Your comments improved our manuscript. Thank you again for your work.

- Title (Page 1, line 4)
 - o Suggest to change to Patient Blood Management when Blood is Not an Option – or something similar.

Answer) We changed the title as you recommended; “Patient Blood Management when Blood is Not an Option” (Page 1, Line 2), We also changed running tilte as “bloodless medical management” (Page 1, Line 4).

- Abstract
 - o Suggest to remove the first two sentences (Page 1, lines 32-35) as they are not directly relevant to the cases presented.

Answer) We deleted the first two sentences. And we added the sentences: “There are

many patients who refuse to receive blood transfusions for religious or other reasons. Bloodless medicine and surgery are no longer new concept, but patients who refuse blood transfusion are still transferred to the bloodless center, regardless of patients' intention, for treatment. Here, we discuss the need for patient blood management when blood is not an option to treat them." (Page 2, Line 7-10).

- Introduction
 - o Suggest to remove the first paragraph (Page 2, lines 11-20) as it is not directly relevant to the cases presented.

Answer) We deleted the first paragraph of introduction. Instead, we added some sentences, and took other sentences from discussion, and rearranged them: "Blood transfusion is an essential treatment, which is difficult to replace. However, there are many patients who refuse to receive transfusion for religious, such as Jehovah's Witnesses (JWs), or other reasons. According to their website (www.jw.org), there are more than 8.6 million JW in 240 countries. Some clinicians may still consider the transfusion absolutely necessary for the treatment of anemia. And refusing blood transfusion is perceived as also rejecting other treatment, forcing the patients to either receive blood transfusion or be discharged from the hospital. It is almost impossible to obtain consent for a blood transfusion from JW patients and their caregivers even in life-threatening situations. Many patients are referred to our bloodless center due to their refusal of blood transfusion. Their treatment requires consideration not only from medical perspective but also from an ethical standpoint." (Page 3, Line 8-16)

- o Consider amending the sentence to read...made through the effort of academic and professional societies...(Page 2, line 23) You may also want to consider citing:
 - The Society for the Advancement of Patient Blood Management (SABM) - <https://sabm.org/>
 - Association for the Advancement of Blood and Biotherapies (AABB) <https://www.aabb.org/>
 - Both have extensive resources on bloodless medicine.

Answer) We specifically described societies as your suggestion, and added more references: "such as the Society for the Advanced of Blood Management (SABM), Association for the Advancement for Blood and Biotherapies (AABB), and the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) (1-4)." (Page 3, Line 19-21)

- Case 1
 - o The therapy listed in the manuscript (Page 2, lines 44-47) did not appear to

match that in Table 3 (Page 8).

Answer) Although our protocol was presented, there was a variation in prescription at the discretion of attending physicians as written. To further explain this, we revised our manuscript as follows: “We have our bloodless management drug protocol of anemia (table 1), but the protocol was performed at the discretion of the attending physicians.” (Page 4, Line 3-5).

□ 20,000 IU Epokine is stated; however, the patient’s weight is needed since dosage is determined by body weight and to confirm the dose listed in the table matches that in the manuscript.

Answer) We added patients’ weight and height at the manuscript: “A JW woman in her eighties (height, 151cm; weight 62kg)” (Page 4, Line 8).

□ The manuscript states that all medication were administered every two days, however, except for rHuEpo the table states daily.

Answer) We added the sentences to explain why we prescribed our protocol of “Hb 5-7 g/dL”, despite of “Hb < 5g/dL”; “First, subcutaneous recombinant human erythropoietin (rHuEpo) (20,000 IU, Epokine®; CJ HealthCare, Seoul, Korea) and intravenous iron (200 mg, Venoferrum®; JW Pharmaceutical, Seoul, Korea) with folic acid and vitamin B₁₂ were administered every 2 days to increase the patient’s red cell mass, considering her age and condition to avoid abrupt elevation of Hb.” (Page 4, Line 18-21).

• Case 2

o It is stated “fur to a fall down” (Page 3 line 6), this does not make sense. Suggest to reword to: sustained after a fall.

Answer) There was a mistake that sentence, and considering all suggestions of you and reviewr2, we corrected that sentence: “A JW woman in her nineties (height, 140cm; weight 36kg) with CHF, CKD and hypertension was diagnosed left femur neck fracture due to a fall,” (Page 5, Line 2-3).

o The therapy listed in the manuscript (Page 3, lines 23-27) did not appear to match that in Table 3 (Page 9).

□ The dose of darbopoetin-a is listed in micrograms while Table 3 is shown in international units. The manuscript says this was administered daily, while the table states every other day. Another does of rHuEpo is listed as 10,000 IU, however, as

with Case 1 the patient's weight is needed to since dosage is determined by body weight and to confirm the dose listed in the table matches that in the manuscript.

Answer) We administered darbepoietin- α with erythropoietine for effective erythropoietin at discretion of attending doctor. And we added sentence about it: “For effective erythropoiesis, darbepoietin- α was administered with rHuEpo because darbepoietin- α has greater potency.” (Page 5, Line 22-23)

There is no mention in the text if B12 or folate was administered as required in Table 3. Please include in the text if appropriate.

Answer) We revised the sentence to add about that: “120 μ g subcutaneous darbepoietin- α (Nesp Prefilled Syringe[®], Kyowa Kirin Korea Co., Seoul, Korea) and 200 mg intravenous iron with folic acid and vitamin B₁₂ were administered daily” (Page5, Line 18-20)

- Discussion

- o It is stated that “we used our patient blood management protocol” (Page 3, lines 42,43), however, more appropriate would be to use the title of the table- bloodless management drug protocol of anemia in JW patients.

Answer) We rearranged that sentence at the first paragraph in case presentation. And we revised that sentence as you mentioned: “We have our bloodless management drug protocol of anemia (table 1), but the protocol was performed at the discretion of the attending physicians.” (Page 4, Line 3-5).

- o Change from B to read B12 (Page 3, line 48).

Answer) We revised that: “vitamin B₁₂” (Page6, Line11).

- o Suggest to change PBS to PBM (Page 4, line 18).

Answer) That was an error, and we revised that: “PBM” (Page6, Line26).

- o Remove part of the last sentence (Page 4, line 25) that states: “as well as the need to reduce the use of blood production due to limited supply,” as transfusion is not the focus of this paper.

Answer) We deleted that sentence.

- Figure 1 (Page 3, line 32)
 - o This figure of pulmonary congestion appears extraneous to the discussion of treating a severely anemic patient without blood transfusion. Suggest to remove.

Answer) We deleted figure 1, and also the sentence about figure 1.

- References
 - o Reference 4 (Page 5, lines 8-10)– This is from the Journal of Feline Medicine and Surgery and as this is a manuscript about humans, suggest to remove.

Answer) We deleted 1st paragraph in introduction as you recommended, and that reference also was deleted.

- o References 19 and 20 (Page 6, lines 6-9) are either not complete or need to be corrected for errors.

Answer) We corrected that references: “16. Jubouri M, Hedayat F, Abrar S, Mellor SL, Brown LJ, Harky A. Optimising bloodless cardiovascular surgery for Jehovah's Witnesses and beyond. *Coron Artery Dis.* 2022;31(1):52-60.
17. Chan EG, Morrell MR, Chan PG, Sanchez PG. Bilateral sequential lung transplantation in Jehovah's Witnesses. *Perfusion.* 2021;36(7):672-6.” (Page 8, Line 32-35)

- o An excellent reference to consider is: Shander, A, Goodnough, LT. Management of anemia in patients who decline blood transfusion. *Am J Hematol.* 2018; 93: 1183– 1191. <https://doi.org/10.1002/ajh.25167>

Answer) We checked that journal and inserted that as a reference in our manuscript: “12. Shander A, Goodnough LT. Management of anemia in patients who decline blood transfusion. *Am J Hematol.* 2018;93(9):1183-91.” (Page 8, Line 22-23)

Table 1 shows a protocol similar to table 3 in this manuscript on how patients who refused transfusions were treated at different hemoglobin levels using a variety of parameters.

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If the authors used any additional parameters as part of the protocol, please incorporate into the text and Table 3.

Answer) We have only protocol for hemoglobin level in patients, but other parameters are necessary because underlying diseases also should be considered in elderly patients. Therefore, we presented Hb, BUN and Cr levels at table 1(after revision, table 2). If more clinical experiences are accumulated, it will be possible to create a disease-specific protocol, and at that time, we could include other indicators in the protocol. Once again, thank you.

Reviewer B

1. Would you please find a more appropriate article which pertains to humans to replace reference 4 which pertains to cats.

Answer) Thank you for your review and great comments. We deleted that reference, according to reviewer 1's suggestion to delete first paragraph in introduction.

2. Page 2, line 41 "...for multidisciplinary access" Please change access to "planning".

Answer) We changed that sentence as your mentioned: "We set up a meeting with the Jehovah's Witness Hospital Liaison Committee and discussed with a nephrologist, cardiologist and pulmonologist for multidisciplinary **planning.**" (Page 4, Line 15)

3. Page 3, line 6 "...fur" to "..from"

Answer) There was a mistake that sentence, and considering all suggestions of you and reviewr1, we corrected that sentence:" A JW woman in her nineties (**height, 140cm; weight 36kg**) with CHF, CKD and hypertension was diagnosed left femur neck fracture **due to a fall,**" (Page 5, Line 1-2)

4. How did the pulmonologist manage the lung congestion? Did Patient #2 also refuse dialysis? Was cell salvage ever discussed?

Answer) Conservative treatment are described in the preceding paragraph:" Conservative treatment was started consisting of maintaining input/output balance with fluid restriction and diuretics, supplying oxygen" (Page 5, Line 16-17);

And She was diagnosed chronic kidney disease, but she did not undergo hemodialysis. And urine output was maintained during diuretic treatment. So we did not consider hemodialysis despite of pulmonary congestion.

And in our hospital, cell savage was not considered at bipolar hemiarthroplasty.

Page 4, line 11, "... without forcing them choose...". add "to" in between them and choose.

Answer) We revised that sentence: “without forcing them **to** choose between transfusion or discharge from hospital.” (Page 6, Line 20-21)

Page 4, line 17, What does PBS stand for ? Do you mean PBM?

Answer) That was an error, and we revised that: “**PBM**” (Page6, Line25).

Page 4, line 25, "... the use of blood products..." instead of blood production.

Answer) We deleted that sentences according to reviewer 1’s suggestion.

Page 4, line 18, in my view, blood transfusion when used appropriately can save lives but it also has complications especially if used inappropriately. Hence the sentence "Blood transfusion is still one of the best proven treatments.." need to be clarified further.

I see that your hospital has a good management protocol for patients who decline blood products. Could you further specify how your protocol is different from other bloodless hospitals?

Answer) We revised that sentences as follow: “Blood transfusion is still one of the best treatments **if used appropriately**,” (Page 6, Line 27-28);
And in terms of the protocol alone, the differences from other hospitals are not significant. But the difference in our case at this case report is that there was a rather fast correction of hemoglobin. It was described in the preceding paragraph: “Some bloodless centers attempt to increase Hb by no more than 1 g/dL per week to avoid thrombotic complications.(2) However, in our cases, aggressive treatment was needed because their advanced age and serious underlying diseases made it impossible for them to withstand very low level of Hb (lowest levels of 4.0 g/dL and 3.4 g/dL, respectively).” (Page 6, Line 13-17)