Author's response to reviewer

Reviewer 1

Q1. This paper has a good title and written structure. But the authors did not mention about how selected references, which was used or denied.

Response: Thanks to the reviewer for the suggestion made for further improvisation of the manuscript. The authors would like to mention that with a thorough literature survey, it has been stated that HBOT and chemokine have therapeutic potential in treating diabetic foot ulcers. However, setbacks are still found in bringing effective outcomes. Thus, the authors have proposed a combinatorial approach, i.e., HBOT and simultaneous administration of tissue-specific chemokine/receptor modulating factors to overcome wound healing deficits observed in diabetic conditions. However, no adequate study was done before this review emphasizes conducting various controlled trial studies with the proposed combination to explore its potentiality for developing novel strategies and better clinical practices for treating diabetic wounds.

Q2. Also they did not announce how Analysis the results too

Response: Thanks to the reviewer for the suggestion made for further improvisation of the manuscript. The authors would like to mention that they have not used any data for preparing tables or figures. Instead, the authors have carefully gone through the kinds of published research data and literature related to HBOT and chemokine-based therapeutics for treating diabetic foot ulcers and put forth a conceptual approach of combinatorial therapy as a potential alternative for the existing standard care for adequate healing of diabetic wounds.

Q3. About ethical statements, they didn't say anything

Response: Thanks to the reviewer for the valuable query. The authors would like to mention that the present manuscript discusses HBOT and chemokine-based therapeutics for treating diabetic foot ulcers, and ethical aspects are beyond the scope of

the investigation. Hence, we did not discuss the ethical aspects as part of this review manuscript.

Reviewer 2

Q1. Can you explain the technique of giving HBOT therapy specifically for diabetic foot ulcers? does he have to be given a certain amount of pressure? In addition, how long does the therapy take to achieve the expected results?

Response: Thanks to the reviewer for the valuable query. HBOT can be provided either in a monoplace or multiplace chamber for treating hypoxia-associated chronic disease conditions. However, most of the reported clinical trial studies done with HBOT for diabetic foot ulcer (DFU) have utilized a multiplace chamber in which the room is pressurized with air. At the same time, pure oxygen is delivered to the participants through a wearable mask. The duration of each HBOT session differs between 90 to 120 mins, with a compression period of 5-10 mins, a treatment period of 85-90 mins, and a decompression period of another 5-10 mins[1][2]. Also, a pressure of 2.5 to 3-atmosphere absolute (ATA) has been maintained throughout the treatment period. The likely explanation is that tissues at rest require about 60 ml of oxygen per liter of blood flow (assuming normal perfusion) to maintain normal cellular metabolism. At a pressure of 2.5 to 3 ATA (i.e.245 – 295 kPa), dissolved oxygen approaches 60 ml/l of plasma, which is almost sufficient to supply the resting total oxygen requirement for many tissues without a contribution from oxygen bound to hemoglobin. This has advantages in situations such as carbon monoxide poisoning and other chronic hypoxia conditions[3]. Thus, maintenance of stable high pressure seems to be necessary for the effective treatment of diabetic foot ulcers. The expected outcome of HBOT in diabetic foot ulcer patients differs based on the number of therapy sessions and hygiene practices. A study has shown that HBOT session for 5 days a week for a total period of 8 weeks (40 sessions) is found to have achieved complete healing in 61% of patients with diabetic foot ulcer of Wagner grade 2,3 & 4 and showed that adjunctive treatment with HBOT facilitates healing of chronic foot ulcers in selected patients with diabetes[1].

[1] Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care* 2010; 33(5): 998-1003 [PMID: 20427683 DOI: 10.2337/dc09-1754]

[2] Ma L, Li P, Shi Z, Hou T, Chen X, Du J. A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer. *Ostomy Wound Manage* 2013; 59(3): 18-24 [PMID: 23475448]

[3] Leach RM, Rees PJ, Wilmshurst P. Hyperbaric oxygen therapy. *Bmj* 1998; 317(7166): 1140-3 [PMID: 9784458 DOI: 10.1136/bmj.317.7166.1140]

Q2. In this study, it was explained that HBOT with hyperoxygenation conditions can increase the production of reactive oxygen species (ROS). It was also explained that HBOT was able to balance this situation with decreased NF-κB expression and stimulated activation of IκBα. What if in a situation, these conditions do not occur and there is an imbalance?

Response: Thanks to the reviewer for the valuable query. The authors would like to state that after a thorough literature study, no significant difference in anti-inflammatory marker profile was reported in HBOT cases. Though it has been thought that HBOT may increase radical production and the chance for oxidative stress induction is high, the meta-analysis data showed that HBOT therapy reduces inflammation and, thus, is assumed to have an indirect role in promoting the wound from a pro-inflammatory to an anti-inflammatory state through the regulation of transcriptional factors. Also, no scientific evidence is available either stating the oxidative stress induced by HBOT or the reversal effect of HBOT on preformed oxidative stress to achieve balance in the cellular environment, which needs to be thoroughly addressed for regulating the interventional procedure.

Revision reviewer

Q1: Dear editor inchief I confirm revised manuscript. Best regards

Response: Thanks for your comments.