AOB ANNALS OF BLOOD
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN HEMATOLOGY

Peer Review File

Article information: https://dx.doi.org/10.21037/aob-21-31

Reviewer A

The manuscript is a narrative review of the history of the development of cryopreserved platelets, including the rationale for their development, the findings of the major in vitro studies, and the major clinical trials and observational series. The manuscript concludes that "its (cryopreserved platelet) use in routine has been limited by the technical complications associated with its freezing and thawing and for the impact that the procedure provokes in the platelets. For these reasons currently its use is limited to some scenarios".

The manuscript is a comprehensive review of the major laboratory and clinical studies in this field. There are too many errors of English expression to list, and it would need considerable English language editing before being suitable for publication. Putting aside this concern, I have several suggestions that I believe could improve the manuscript:

1. "In order to extend the storage of platelet concentrates beyond the 7 days, the only approved alternative is to add a cryoprotectant and freeze them at temperatures of -80°C.". This is incorrect. The US FDA, for example, permits the US armed forces to store platelets at 1-6C for up to 14 days. Brief mention of cold-stored (but not frozen) platelets would be appropriate in this section.

Reply 1. We referred to the Europea Union.

Change in the text 1: Already it was mentioned in abstract, now we have added in the text page 3, line 86.

2. The limitations of the 1999 randomised controlled trial by Khuri et al. should be presented in more detail. For example, of the 73 patients randomised, only 24 were transfused cryopreserved platelets. Of the 73, there were 20 post-randomisation exclusions, including 5 for death judged 'unrelated' to platelet transfusion, 3 patients who received a prohibited medication, and 6 patients whose bleeding was judged to have a surgical cause. Post-randomisation exclusions are not generally considered a methodologically sound manner in which to conduct the primary analysis of a clinical trial. Further, this review observes "No adverse effects of the transfusion were observed", but in reality the incidence of adverse events was not reported. The manuscript states that thromboembolic complications and infections (wound infections and pneumonia) did not differ statistically between groups, but this data is not in the manuscript. This is not as reassuring as the review's statement suggests.

Reply 2: The authors state in the paper "No adverse effect of the transfusion were oberseved after the infusion of the platelets or other blood products." So we think that we can write "No adverse effects of the transfusion were observed",

Change in the text 2: We have introduced in the text that from the 73 patients randomized ,only 53 were analyzed (Page 10, lines 308-310)

3. "In 2017 a Vox Sanguinis International Forum investigated the current use of cryopreserved platelet in routine in 12 different countries (26, 27). Only in 7 of them, the product was being used in routine (Australia, Belgium, Czech Republic, the Netherlands, Poland, Spain, Switzerland)". Careful reading of this excellent paper shows that this is not what it states. For example, Australian use is limited to preparation for the military (which has not used any of the units prepared) and for clinical trials. Many of the other countries listed have also only prepared cryopreserved platelets for research use. It would be helpful to distinguish those countries which use cryopreserved platelets routinely in their civilian health services for the indications listed (e.g. highly alloimmunised patients), from those with a latent military capability, from those using cryopreserved platelets in research only.

Reply 3: The comment is correct

Changes in the text 3: We have removed ".. in routine.." Page 11, line 356

4. The one major clinical study that should be described in more detail is that of Bohonek et al., already present in the reference list. This non-randomised study compared clinical results of 25 patients transfused 81 units of cryopreserved platelets with 21 patients transfused 67 units of liquid-stored platelets, finding a lower post-transfusion platelet count in the cryopreserved group, but no other between-group differences.

Reply 4: We have described it in more detail

Changes in the text 4: Page 11, lines 336-350

5. The reason that cryopreserved platelets are not in more widespread use is, I would argue, NOT because of "technical complications associated with its freezing and thawing and for the impact that the procedure provokes in the platelets", but rather because all of the clinical studies to date have been too small to exclude the possibility of safety concerns that could reasonably be expected given what is known from preclinical data – for example, prothrombotic complications, infection, ARDS, and complications of DMSO toxicity. It would be useful for the authors to summarise the total number of patients who have been included in published randomised controlled trials when making this point.

Reply 5: We respect the opinion of the reviewer, but we do not share it.

Changes in the text 5: We have added " probably" in page 12, line 374

In conclusion, this is a comprehensive review that is of some merit. A competent English language subeditor would have little difficulty correcting its many errors. My major concern is with the lack of appreciation of the very small amount of comparative safety data available, and consequently the incorrect conclusion that the authors have reached. This must be addressed. If the authors do so, this would be a useful contribution.

Reviewer B

In the manuscript "Cryopreserved platelets: current role in transfusion therapy" the authors set out to review current methods in freezing platelets along with the impact on platelet function and structure. While very well written and structured it is not a comprehensive review of this area and is therefore limited in its scope of what the authors set out to achieve. The manuscript could have benefited from a more extensive reference list. For example over the last 10 years alone 427 papers have been published on cryopreservation of platelets with most covering many of the aspects discussed in this manuscript.

Minor issues:

• In the abstract, there is a typo line 5 "holyday" should be "holiday"

Reply :Corrected

• In section 5 "in vivo studies of CP in patients" the last sentence of the second last paragraph is confusing and suggests that 3426 is lower than 1933?? This may be mixed round but if not can the authors please clarify this section.

Reply: Mistake corrected.

Changes in the text: Modified, page 10, line 318 and 319

• In the final paragraph of section 5 looking at cardiac surgical patients. There is discussion on post op bleeding which, was suggested occurred in twice as many patients receiving standard platelet v that of CP, 55.6% v 30.4%. Wouldn't the authors expect this outcome given the CP arm received extra CP units? It would be of benefit to the reader if this section could have been summarised with the current author's conclusions on this.

Reply: None.

Changes in the text: The conclusion of the authors of the study has been added. Page 10 and 11, lines 334-337

• While the authors touch on in their review some of the limitations of CP It again would have been good for the reader to possibly discuss the advantages/disadvantages of a possible "2 tier" platelet inventory for possible emergency and standard use which has been discussed in many of the references over the years looking into this field.

Reply: Thank you, but it is out of the scope of this review.

Change in the text: none

Major issues:

• If it is the author's intention to write a short concise article in this field then they should mention this in their introduction that this is not a comprehensive review of the data in the area and why they have chosen the subsequent references only.

Reply : We did no intend to write a comprehensive review.

Changes in the text: The title has been changed to "Cryopreserved platelets: a narrative review of the current role in transfusion therapy"

• In the platelet count, section the authors use only one reference to describe what happens to the platelet count. Do other researchers find the same? On the other hand, is there support/corroboration of these findings by others? If so then authors should list.

Reply: Interestingly very few studies have looked at the impact of the freezing-thawing process in the platelet count using the "non wash" Valeri method

Changes in the text: We have added the data of Slichter et al, Transfusion2018;58:2129-38. Page 5, lines 152-155

• Throughout there is a lack of comparison and contrasting of data, primarily due to the limited reference list used. It would be helpful if the authors could remedy this and possibly compare, contrast and summarise in each of the sections they look at.

Reply: Unfortunately, the number of available references is very scarce, to do what the reviewer, suggest.

Change in the text: None

• There is a large section on the Valeri original and subsequent updated method of cryopreservation of platelets from freezing to re-suspension media on thaw. Followed by a “throw away” sentence on other re-suspension medias can be used. It would have been good to see the advantages/disadvantages of these other re-suspension medias compared to that of Valeri. Again, some comparison of data here would have been good.

Reply: Unfortunately, the number of available reference is very scarce, to do what the reviewer, suggest.

Change in the text: None

Overall, the paper is an interesting read and just touches the brief of what the authors set out to convey. However due to the selective references, the manuscript lacks a comprehensive overview of the area and would benefit from some of the changes suggested above. This is an important field of research and certainly, a review of the current area would be of benefit to many.