PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The premature closure of ROMPA Clinical Trial: Mortality Reduction in Septic Shock by Plasma Adsorption.
AUTHORS	Giménez-Esparza, Carola; Portillo-Requena, Cristina; Colomina-Climent, Francisco; Allegue-Gallego, José; Galindo-Martínez, María; Mollà-Jiménez, Cristina; Antón-Pascual, José; Mármol-Peis, Enrique; Dólera-Moreno, Cristina; Rodríguez-Serra, Manuel; Martín-Ruíz, José; Fernández-Arroyo, Pablo; Blasco-Císcar, Eugenia; Cánovas-Robles, José; González-Hernández, Enrique; Sánchez-Morán, Fernando; Solera-Suárez, Manuel; Torres-Tortajada, Jesús; Palazón-Bru, Antonio; Gil-Guillen, Vicente F.

VERSION 1 – REVIEW

REVIEWER	James A. Russell University of British Columbia Canada I am consultant for SIB Therapeutics who are assessing a sepsis therapy.
REVIEW RETURNED	03-Jul-2019

GENERAL COMMENTS	BMJ OPEN – GIMINEZ – ESPARZA – JULY 2, 2019 SUMMARY This is a small (n = 49) randomized controlled trial (RCT) of plasma filtration and absorption (PFA) in septic shock that was stopped prematurely because a different RCT of the same intervention showed significant harm from PFA. The ethics committee mandated cessation of the current reported RCT. As expected there was no difference in mortality or any clinical endpoints. This is a challenging intervention for a RCT and the investigators did their best to address the intervention's efficacy. There was a good training period for each center and the anti-coagulation protocol was improved for the RCT. MAJOR 1. The ARR of 20% is much too high and overly ambitious. This combined with the low sample size yields an extraordinarily low power. 2. Septic shock inclusion criteria are poorly and incompletely defined. 3. There is inconsistency in the primary outcome (intro say mortality at 28 and 90 days. Methods states mortality at 3, 28 and 90 days. There is not a singular primary outcome (?28 days ?90 days ?3 days).

	4. The sample size calculation does not state the assumed control mortality rate. The planned sample size of 190 is extraordinarily small. 5. A propensity score was used to adjust for imbalances at baseline and that is most unusual. 6. The clintrials.gov protocol does not define the primary statistical analysis (? Intent to treat) and the methods used a post hoc "actual intervention received" because 3 patients died in the first 3 days and "did not receive the intervention". 7. The primary result of the first paragraph of the discussion is an overstatement - "seemed to indicate ..CPFA group had less chance of mortality at 90 days" This is incorrect - the p value is 0.878! 8. I did not see any mention of a Data and Safety Monitoring Board or safety outcomes. MINOR 1. The information about high lactate in patients who died within 3 days is not relevant and is very well known. 2. The discussion is somewhat rambling and could be tightened up.

REVIEWER	Gaetano La Manna Alma Mater Studiorum - Università di Bologna Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale - DIMES Unità di Nefrologia, Dialisi e Trapianto Policlinico S. Orsola - Malpighi
REVIEW RETURNED	12-Jul-2019

GENERAL COMMENTS	The introduction is very clear and analyzes the limitations of COMPACT I Study and the premature closure of COMPACT II Study; at page 9 from line 21 to line 26 authors reports: "each center obtained technical proficiency with the machine and CPFA treatment before they could become "activated" for enrolment by the investigator monitoring team. This was done to avoid similar problems as those reported for the first COMPACT study". Authors should explain some of these problems. Even if authors explained methods in the previous article, it is important to underline in this review the time between septic shock diagnosis and randomization (12 hours maximum vs 6 hours maximum of the COMPACT I Study). As the authors reported, the most important limitation of this study is its premature closure and the scarce sample size; then there is the problem of randomization based on the baseline characteristics of patients (like in COMPACT II Study). At page 14, from line 24 to 35 the authors explain the role of high levels of lactate in the high risk of mortality in the first three days; they should explain the role of APACHE II Score role in the same way. At page 25, in Figure 1, there is a discordance among patients's number: among the 72 patients assessed for eligibility, authors excluded 32 patients (not explaining the reason of this exclusion for all 32 patients).

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: James A. Russell
Institution and Country: University of British Columbia, Canada
Please state any competing interests or state 'None declared': I am consultant for SIB Therapeutics who are assessing a sepsis therapy.
Please leave your comments for the authors below
BMJ OPEN – GIMINEZ – ESPARZA – JULY 2, 2019
SUMMARY
This is a small (n = 49) randomized controlled trial (RCT) of plasma filtration and absorption (PFA) in septic shock that was stopped prematurely because a different RCT of the same intervention showed significant harm from PFA. The ethics committee mandated cessation of the current reported RCT. As expected there was no difference in mortality or any clinical endpoints. This is a challenging intervention for a RCT and the investigators did their best to address the intervention's efficacy. There was a good training period for each center and the anti-coagulation protocol was improved for the RCT.
Thank you very much for your positive comments.
MAJOR
1. The ARR of 20% is much too high and overly ambitious. This combined with the low sample size yields an extraordinarily low power
We have included this statement as a limitation in the relevant place.
2. Septic shock inclusion criteria are poorly and incompletely defined.
We have explained the definition used in our research in Participants (METHODS).
3. There is inconsistency in the primary outcome (intro say mortality at 28 and 90 days. Methods states mortality at 3, 28 and 90 days. There is not a singular primary outcome (?28 days ?90 days ?3 days).
We have explained this inconsistency in Primary and Secondary Outcomes (METHODS).
4. The sample size calculation does not state the assumed control mortality rate. The planned sample size of 190 is extraordinarily small.
This has been indicated in Sample Size (METHODS), including all the information so as to calculate the sample size. With 190 patients we had a good power to contrast the difference between the groups.
5. A propensity score was used to adjust for imbalances at baseline and that is most unusual.
We agree with you, but the circumstances surrounding the way of conducting this essay are also unusual. In the document, we explained the reasons why we applied this statistical method (pages 9 and 10): "Without having the sample size calculated for the study (intermediate analysis) and having made the allocation based on a set of variables, the homogeneity of the groups was not able to be established. To minimize this problem, the propensity scores as a population overlap weight technique was applied with the objective of overcoming the problem caused by the lack of homogeneity between the two groups"
6. The clintrials.gov protocol does not define the primary statistical analysis (? Intent to treat) and the methods used a post hoc "actual intervention received" because 3 patients died in the first 3 days and "did not receive the intervention".
We have explained this inconsistency in Statistical Methods (METHODS).
7. The primary result of the first paragraph of the discussion is an overstatement - "seemed to indicate ..CPFA group had less chance of mortality at 90 days" This is incorrect - the p value is 0.878!
We have included a clarification in that statement in the last phrase of that paragraph.
8. I did not see any mention of a Data and Safety Monitoring Board or safety outcomes.
We have mentioned this point in Ethical issues (METHODS).
MINOR

1. The information about high lactate in patients who died within 3 days is not relevant and is very well known.
We have removed that paragraph in the discussion: “In our group, patients who died in the first 72 h had significantly higher initial lactate values…”
2. The discussion is somewhat rambling and could be tightened up.
With the help of a native speaker, we have made some modifications in the discussion following your guidelines.

Reviewer: 2
Reviewer Name: Gaetano La Manna
Institution and Country:
Alma Mater Studiorum - Università di Bologna
Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale - DIMES
Unità di Nefrologia, Dialisi e Trapianto, Policlinico S. Orsola - Malpighi
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
-The introduction is very clear and analyzes the limitations of COMPACT I Study and the premature closure of COMPACT II Study; at page 9 from line 21 to line 26 authors reports: “each center obtained technical proficiency with the machine and CPFA treatment before they could become “activated” for enrolment by the investigator monitoring team. This was done to avoid similar problems as those reported for the first COMPACT study”. Authors should explain some of these problems.
These problems have been indicated in parenthesis.
-Even if authors explained methods in the previous article, it is important to underline in this review the time between septic shock diagnosis and randomization (12 hours maximum vs 6 hours maximum of the COMPACT I Study).
We have added this information in Interventions (METHODS).
-As the authors reported, the most important limitation of this study is its premature closure and the scarce sample size; then there is the problem of randomization based on the baseline characteristics of patients (like in COMPACT II Study).
We believe that we have answered this question in the text under review (see pages 9 and 10):
“Without having the sample size calculated for the study (intermediate analysis) and having made the allocation based on a set of variables, the homogeneity of the groups was not able to be established. To minimize this problem, the propensity scores as a population overlap weight technique was applied with the objective of overcoming the problem caused by the lack of homogeneity between the two groups.[9] The adjustment variables were APACHE II, previous lactate levels and the presence of urinary sepsis. Finally, although it was not established in the study protocol, Kaplan-Meier survival curves were analyzed to determine differences in mortality in the analyzed groups (log-rank test) “
-At page 14, from line 24 to 35 the authors explain the role of high levels of lactate in the high risk of mortality in the first three days; they should explain the role of APACHE II Score role in the same way.

This has been removed by indication of the reviewer #1, because it is well known in the scientific literature. Consequently, we have not written a new paragraph to talk about APACHE II Score.
At page 25, in Figure 1, there is a discordance among patients's number: among the 72 patients assessed for eligibility, authors excluded 32 patients (not explaining the reason of this exclusion for all 32 patients).
We have corrected this mistake in Figure 1. Thank you very much for your feedback!