PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality Reduction in Septic Shock by Plasma Adsorption (ROMPA): a protocol for a randomized clinical trial.
AUTHORS	Colomina-Climent, Francisco; Giménez-Esparza, Carola; Portillo-Requena, Cristina; Allegue-Gallego, José; Galindo-Martínez, María; Mollà-Jiménez, Cristina; Antón-Pascual, José; Rodríguez-Serna, Manuel; Martín-Ruíz, José; Fernández-Arroyo, Pablo; Blasco-Císcar, Eugenia; Cánovas-Robles, José; Herrera-Murillo, Miguel; González-Hernández, Enrique; Sánchez-Morán, Fernando; Solera-Suárez, Manuel; Torres-Tortajada, Jesús; Nuñez-Martínez, José; Martín-Langerwerf, David; Herrero-Gutiérrez, Eugenio; Sebastián-Muñoz, Isabel; Palazón-Bru, Antonio; Gil-Guillen, Vicente F.

VERSION 1 - REVIEW

REVIEWER	PAOLO LENTINI, MD, phD ST BASSIANO HOSPITAL DEPARTMENT OF NEPHROLOGY AND DIALYSIS VIA DEI LOTTI, 40 BASSANO DEL GRAPPA, 36061 (VI) ITALY
REVIEW RETURNED	07-Apr-2016

GENERAL COMMENTS	ROMPA study is a multicentric randomized clinical trial protocol. the aim was is to clarify if "High dose" CPFA application can be able to reduce hospital mortality in ICU patients. The outcomes are well posed; anyway there are a problems in the protocol' setting 1) it's will be better exposed the esclusion criteria; 2) Timing to start CPFA: three days before CPFA start: sometimes in septic shock/multiorgane failure 3 days seems too many. Explain in the "methods" or in "discussion". 3) Partecipate and simple size: a 50% of the patients involved in the study have a abdominal surgical sepsis: are there any experience in Toraymixin cartridge adsorption? will they use this treatment in the control group (especially for gram negative bacteria)? 4) how about the standard care in control group? il will be better defined if they used CRRT, CVVH or others for "non renal indications" or for classical renal indications. Will they use CRRT also in intervention group (before or after CPFA?)?. Will they use other intermittent tecniques for blood purifications??? these kind of treatments can really changes parameters and clinical conditions in every two groups. Please defined well if and when they will be used. 5) Clotting : clotting problems are, of course the main big problems about CPFA: the authors will achieve a plasma dose of 0.2 l/kg/day for al least three CPFA sessions: they're developed a training program to opvercome thise hurdle; it will be very import to test this

	protocol before to start to check if really help to get delivered dose; CPFA clotting can reduce plasma depuration and really invalidate patient's care.

REVIEWER	Prof Patrick Honore ICU Dept Universitair Zikenhuis Brussel VUB University Brussels Belgium
REVIEW RETURNED	11-Apr-2016

GENERAL COMMENTS	This is an interesting study protocol over the role of CPFA in septic shock. Major Comments: 1)Speculating on a 20 % reduction of mortality in septic shock is somewhat very enthusiast…Accordingly, the number of patients to enroll is decreased down to 190 patients….I am not sure that this is the best way to go.. 2)I quoted this sentence here : “The probability of death in this population in the internal experience of the participating centers is about 50%. We have a higher mortality than what is typically reported in recent literature due to a high percentage of abdominal surgical patients.” This is very controversial and I would be very prudent about your interpretation… 3) Again I quoted this sentence “ the time between septic shock diagnosis and randomization is 12 hours maximum…” Again I think that you are very optimistic as 12 hours to complete everything including the randomization is very short and you may lose a significant number of patients… 4)Regarding this sentence , you should be more precise in my view..and I quoted “those with pathologies for which expected survival is <90 days…” 5)Regarding this other sentence, you are missing already one year of recruitment and I quoted “The recruitment period is preset between March 2015 and March 2017…” ….We are in April 2016.. 6)When I see this sentence and I quoted “ All ICUs participating in this project have extensive experience in using CRRT…” CPFA is very different from CRRT and the knowledge in CRRT is not of great help to perform CPFA.CPFA is an extremely difficult technique and needs huge experience and expertise to be perform as best as possible…. 7)I am surprised that you are not evaluating the loss of antibiotics during CPFA and also that you are not implementing some recent findings in order to adapt antibiotic dosage during CPFA…in order to avoid underdosing…

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
ROMPA study is a multicentric randomized clinical trial protocol. the aim was is to clarify if "High dose" CPFA application can be able to reduce hospital mortality in ICU patients.

The outcomes are well posed; anyway there are a problems in the protocol' setting
1) it's will be better exposed the exclusion criteria;
We have explained better our exclusion criteria in Methods (fourth paragraph of Participants and Sample Size).

2) Timing to start CPFA: three days before CPFA start: sometimes in septic shock/multiorgane failure 3 days seems too many. Explain in the "methods" or in "discussion".
We have included more information about this issue in the second paragraph of Participants and Sample Size and when we are describing the intervention group (Interventions).

3) Participating and simple size: a 50% of the patients involved in the study have a abdominal surgical sepsis: are there any experience in Toraymixin cartridge adsorption? will they use this treatment in the control group (especially for gram negative bacteria)?
We expect a mortality rate in the control group about 50% (this data is based on previous experience of the group in patients with the characteristics of those who hope to enroll). We believe that this high mortality is conditioned in part by the remarkable presence of patients with abdominal sepsis and the reason is that the participating units have among their functions to receive patients from the surgical area after being operated on for abdominal septic focus.
The trial participating hospitals belong to the public health service net and this aspect determines that use of treatments like Toraymyxyn is only feasible if it is supported by efficacy trials. If my information is correct we do not expect Euphrates clinical trial results until 2017 or 2018. At the moment it would only be possible in a compassionate use way, but in any case if the patient participates in our study non routine extracorporeal or pharmaceutical agents for sepsis during the study is prohibited to avoid confounding factors.

4) how about the standard care in control group? il will be better defined if they used CRRT, CVVH or others for "non renal indications" or for classical renal indications. Will they use CRRT also in intervention group (before or after CPFA?)?. Will they use other intermittent tecniques for blood purifications???
these kind of treatments can really changes parameters and clinical conditions in every two groups. Please defined well if and when they will be used.
We have indicated more information about the control group in Methods (Interventions, control group).

5) Clotting : clotting problems are, of course the main big problems about CPFA: the authors will achieve a plasma dose of 0.2 l/kg/day for al least three CPFA sessions: they're developed a training program to opvercome thise hurdle; it will be very import to test this protocol before to start to check if really help to get delivered dose; CPFA clotting can reduce plasma depuration and really invalidate patient's care.
We agree with your statement and hope to CPFA/circuit clotting in order to really be able to evaluate the efficacy of CPFA. Clotting was a major issue in the first COMPACT study. All investigators and staff in our study underwent a very extensive training program for use of the machine (AMPLYA and the CPFA technique). This was one of the reasons that we had a relatively slow start for enrolment, as it was mandatory for the center to become experience before starting enrolment.
As you know, clotting can be due to many factors including:
Patient related factors (especially for septic shock patients which have a higher tendency towards clotting, but also an increased risk of bleeding).
Inappropriate anticoagulation choice or lack of anti-coagulation monitoring: for our study investigators can use either heparin or citrate, but these must be used with experience in these techniques, appropriate doses and monitoring. We have suggested protocols for both heap rin and citrate as general guidelines, however the final choice is left to the physician to also allow the best personalized approach for each individual patient.
Machine alarms/problems: this can happen if there are alarms cause long downtimes or pause the

circuit and allow blood to clot. While we can not control these directly, we think that increased experience with the machine and the CPFA technique can decrease these.
We have increased awareness of all these issues. So far in our study, we have not had significant problems related to clotting.
All of this has been summarized in Why do we think we can carry out this test?

Reviewer 2:
This is an interesting study protocol over the role of CPFA in septic shock.
Major Comments:
1)Speculating on a 20 % reduction of mortality in septic shock is somewhat very enthusiast…Accordingly, the number of patients to enroll is decreased down to 190 patients….I am not sure that this is the best way to go..
Our work hypothesis is based in COMPACT I observation that in intention-to-treat analysis there was no statistical difference in hospital mortality (47.3%, controls; 45.1%, CPFA; p=0.76), but in a subgroup analysis patients who could get a dose of treated plasma superior than 0.20 l/kg/day had a lower mortality compared with controls (OR=0.36, 95% CI: 0.13-0.99). The limits of this per protocol analysis are evident (definition for the per protocol analysis was based on characteristics measured after randomization, the subgroup allocation may have been influenced by the outcome...). In consequence our objective is to test this hypothesis in a clinical trial with enough power and potency. Certainly we could choose a more conservative approach with the obvious consequence of increasing the sample size. In absolute terms I agree with your statement ("I'm not sure this is the best way to go…."), but when we were designing the trial we had to evaluate several factors including economic cost, motivated teams with previous experience in extra-renal depuration techniques, real capabilities for enrolling patients, calculation of trial duration… and in our opinion this was the most equilibrated election.
We have included a summary of this paragraph in the fifth paragraph of Participants and Sample Size.

2)I quoted this sentence here : "The probability of death in this population in the internal experience of the participating centers is about 50%. We have a higher mortality than what is typically reported in recent literature due to a high percentage of abdominal surgical patients."
This is very controversial and I would be very prudent about your interpretation…
The observation of a high mortality rate in patients with septic shock from abdominal origin is a classic finding in the scientific papers (Schoember, Weiss & Radermacher, 1998). European and North American experience of intra-abdominal sepsis is similar, with reported mortality rates for this condition ranging between 30% and 60%. Irrespective of the surgical strategies employed, laparotomy in the critically ill is associated with significant morbidity and mortality, the incidence of which increases with each re-laparotomy (Wakefield, 2001).
I agree that is a controversial point, probably not so much in fact but in the explanations. One possible explanation is that the treatment of these patients usually involves surgical attitudes and entails delays in the inevitable existence of time consumed in carrying out further tests on the other hand needed for making complex decisions.
We have included this information in the third paragraph of Participants and Sample Size.

3) Again I quoted this sentence " the time between septic shock diagnosis and randomization is 12 hours maximum…" Again I think that you are very optimistic as 12 hours to complete everything including the randomization is very short and you may lose a significant number of patients…
You're probably right and we are indeed very optimistic, but in any case it is out of sheer necessity. The relationship between time and making therapeutic measures such as administration of adequate antibiotic therapy is sufficiently demonstrated. In the work of Kumar and et al, it was established that beyond the first 12 hours despite adequate antibiotic therapy the probability of death, expressed as OR, was unacceptably high.

We assume that once the diagnosis of septic shock has been performed under the conditions described in the protocol a 12 hrs window opens to adopt measures (medical and surgical) to control septic focus, and beyond this time any additional measure results will be very poor.
Clearly establishing a wider time window would open more opportunities to recruit patients. But it would be patients with little chance of survival and that any therapeutic measure is of doomed beforehand.
In addition, we have included a phrase to clarify the choice of our timing (second paragraph of Participants and Sample Size).

4)Regarding this sentence , you should be more precise in my view..and I quoted “those with pathologies for which expected survival is <90 days…”
We analyze the mortality at 28 and 90 days. So we thought that it makes sense to exclude patients with comorbidities involving a life expectancy less than that period of time. In any case this prognosis would not be set by the ICU team but by the respective medical teams treating these pathologies.
This has been indicated in the fourth paragraph of Participants and Sample Size.

5)Regarding this other sentence, you are missing already one year of recruitment and I quoted “The recruitment period is preset between March 2015 and March 2017…” ….We are in April 2016..
Our enrollment period began on schedule and now there are 32 randomized patients.
We hope that by the end of next month all participating hospitals will be in position to access the randomization door and therefore improve our pace of enrollment (I trust not be too optimistic). We incorporated an extensive training period to make sure that the investigators and staff were experienced with the technique.
On the other hand, our protocol was approved by the relevant ethics committees and registered at ClinicalTrials.gov. Now, although we have started with the enrolment process, we have decided to publish the protocol in BMJ Open.

6)When I see this sentence and I quoted “ All ICUs participating in this project have extensive experience in using CRRT…” CPFA is very different from CRRT and the knowledge in CRRT is not of great help to perform CPFA.CPFA is an extremely difficult technique and needs huge experience and expertise to be perform as best as possible….
I absolutely agree that the two procedures are different, but at least in our acquired experience during workshops that have been organized in all participating hospitals, the different monitors that have participated have the impression that health personnel with prior experience in renal replacement therapy techniques acquire more easily the necessary skills to perform the CPFA .
This is mentioned in Why do we think we can carry out this test?

7)I am surprised that you are not evaluating the loss of antibiotics during CPFA and also that you are not implementing some recent findings in order to adapt antibiotic dosage during CPFA…in order to avoid underdosing…
Indeed the ROMPA project does not include the investigation of the effect of CPFA on the dosage of antibiotics. Part of our team is working on drafting a project to expand on that line. On the other hand, although not included in the initial draft submitted to the ethics committees, we are facilitating to the different participating hospitals agreed information about dosage of antibiotics.

VERSION 2 – REVIEW

REVIEWER	PAOLO LENTINI, MD, PhD SAN BASSIANO HOSPITAL, NEPHROLOGY BASSANO DEL GRAPPA ITALY
REVIEW RETURNED	15-May-2016

GENERAL COMMENTS	The authors provide relevant changes that significative improve the quality of the paper.

REVIEWER	Prof Patrick Honore, MD, PhD, FCCM ICU Dept Universitair Ziekenhuis Brussel VUB UNiversity 1090 Brussels Belgium
REVIEW RETURNED	24-May-2016

GENERAL COMMENTS	I am satisfy with the very comprehensive replies of the authors. The paper is now greatly improved. I have no further comments.