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The premature closure of ROMPA Clinical Trial. Presentation of the results concerning the 49 randomized patients before the study closure.

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TITLE PAGE

Title: The premature closure of ROMPA Clinical Trial. Presentation of the results concerning the 49 randomized patients before the study closure.

Short title: The closure of ROMPA Clinical Trial.

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Keywords: Shock, Septic; Coupled Plasma Filtration Adsorption; Mortality; Intensive Care Units; Clinical Trials.

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ABSTRACT

Objectives: Coupled Plasma Filtration and Adsorption (CPFA) use in septic shock remains controversial. The objective is to clarify whether the application of high dosis of CPFA in addition to the current clinical practice could reduce hospital mortality in septic shock patients in Intensive Care Units at 28 days and 90 days follow up.

Design: We designed a prospective randomized clinical trial, ROMPA (Reducción de la Mortalidad Plasma-Adsorción), to demonstrate an absolute mortality reduction of 20% [α=0.05; 1-β=0.8; n=190(95x2)].

Setting: Being aware of the pitfalls associated with previous medical device trials, we developed a training program to improve CPFA use (especially clotting problems). The protocol was approved by the ethics committees of all participating centers. Circumstances beyond our control produced a change in recruitment conditions unacceptable to ROMPA researchers and the trial was discontinued.

Participants: By closure, 5 centres from an initial 10 fulfilled the necessary trial criteria, with 49 patients included, 30 control group (CG) and 19 intervention group (IG).

Intervention: CPFA.

Main outcome measures: Hospital mortality at 28 days and 90 days follow up

Results: After 28 days, 14 patients died (46.7%) from the CG and 11 (57.9%) from the IG, not reaching statistical significance (p=0.444). At 90 days 19 patients had died (63.3%) from the CG and 11 patients (57.9%) from the IG, (p=0.878). The adjustment by propensity score or the use of the Kaplan Meier technique failed to achieve statistical difference, neither in the Intention to Treat Approach nor by the Actual Intervention Received.

Conclusion: We herewith present the results gained from the prematurely-closed trial. The results are inconclusive due to low statistical power but we consider that this data is of interest for the scientific community and potentially necessary for any ensuing debate.

Register: NCT02357433 in clinicaltrials.gov

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Randomised control clinical trial testing the efficacy of CPFA in septic shock.
- Premature closure of the trial by circumstances beyond the trial.
- Scarce sample size: underpowered trial.

INTRODUCTION

Sepsis is still a leading cause of mortality in Intensive Care Units (ICU) patients, with a 20-50% mortality rate of sepsis and septic shock [1]. There exists a feeling of frustration generated by the large series of negative randomized clinical trials (RCTs) in septic shock treatment (especially in targeting mortality) during the past 30 years [2]. Patients included in these trials have a wide variability in their probability of death translating into differences in benefits to be derived from specific therapy application, producing a handicap to sample size calculation. This can lead to the trial having less power than initially planned increasing risk of a type 2 error and undoubtedly this is the origin of unexpected results.[3] It questions the use of subgroups in an attempt to extract some kind of useful information in negative RCTs.[4]

The COMPACT 1, a multicentre RCT study, failed to show benefit by using Coupled Plasma Filtration and Adsorption (CPFA) therapy in a population with septic shock. In a per protocol analysis, patients treated with CPFA at treated plasma volume superior to 0.20 l/kg/day showed a reduction in mortality rate [5]. Although an interesting finding, our group considered it was necessary to carry out a RCT to confirm this hypothesis.

The response to this question was the ROMPA (Reducción de la Mortalidad Mediante Plasma-Adsorción en Shock séptico), a multicenter RCT carried out in ICUs of southeastern Spain. The ROMPA Study (NCT02357433 in clinicaltrials.gov) tried to clarify whether the application of high doses CPFA in addition to the current clinical practice was able to reduce hospital mortality in septic shock patients in ICUs. The protocol of ROMPA has been published in a free access support and the details of the protocol could be consulted without restrictions.[6]

In October 2017, COMPACT 2 (NCT01639664 in clinical trials.gov) trial investigators, a similar study to ROMPA conducted in Italian ICUs,[7] reported the premature closure of the study for having detected an increase in early mortality (3 first days) in the intervention branch, 6/42 (12.5%) vs 19/58 (32.8%) p=0.020, not having reached the sample size prefixed in the protocol (350 patients). The adjusted odds ratio (OR) of the treatment yielded by logistic regression is 2.1 (95% CI: 0.7-6.6, p=0.19) and the adjusted hazard ratio (HR) yielded by the Cox model is 2.5 (95% CI: 1.4- 4.4, p=0.002). This information was immediately reported to our Ethical Committee and these results were published on the research group website in Italian.[8] Subsequent events, including a provisional warning by the product supplier, motivated us to take the final decision of closing ROMPA. At that time, of the 10 initial hospitals only 5 had exceeded the technical capacity requirements and availability of resources required to access the randomization portal. In this paper and as a result of events of such severity, our group shows the data collected to date and the results from the 49 enrolled patients (30 control and 19 intervention groups).

METHODS

Protocol

The full study protocol was previously published.[6] A synthesis of it is made in this section (Methods) .

Setting and participants

The study was performed in 5 ICUs, in the southeast of Spain, that follow the same protocol in the treatment of septic shock, based on the recommendations of the Surviving Sepsis

Campaign with the participation of the following centers: Vega Baja Hospital of Orihuela, General University Santa Lucía Hospital of Cartagena, University Hospital of San Juan de Alicante, Lluís Alcanyís Hospital of Xàtiva and Francesc de Borja Hospital of Gandía.

The ROMPA study is a multi-centric, randomized, prospective, open clinical trial with 28- and 90-day follow-up and allocation ratio 1:1, assessing the mortality reduction by CPFA in patients with septic shock. Furthermore, we analyzed 3-day mortality to compare our results with the Italian group.

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,[4] and also because CPFA is not routinely done in Spain and a new machine with improved anticoagulation support was subsequently developed and used for this trial.

Participants

Patients ≥18 years old admitted to the ICU of the participant hospitals, with a diagnosis of septic shock can be included in the study. The inclusion and exclusion criteria are detailed in the published protocol.

Interventions

The patient is considered registered once the informed consent form has been obtained by the patient or legal representative. The recruitment process ends with the patient randomization. Patients were divided randomly into two arms (control and intervention). ROMPA has a stratified randomization based on gender, age (≤ 65 or >65 years) and SAPS III score (<50 or ≥51). On the one hand, in the control group we followed the suggestions provided by the

recent surviving sepsis guidelines, as well as standard care guidelines typically followed in Spain. On the other hand, in the CPFA group, we applied the same protocol plus high doses of CPFA in the first 3 days after randomization.

Variables and measurements

Primary and Secondary Outcomes

The primary outcome variable is all-cause of mortality assessed at 3, 28 and 90 days from the recruitment of the patient. Moreover, at the descriptive level and in order to check homogeneity of both groups, the following variables will be collected at the time of recruitment: birth year, gender, height, dry weight, body temperature, heart rate, blood pressure, blood cell count, coagulation values, glucose level, plasma creatinine, bilirubinemia, plasma C reactive protein, procalcitonin level, blood gas analysis, lactate, urinary output (ml/kg/h), Pa O_2/FiO_2 ratio, APACHE II, SOFA and SAPSIII scores.

Sample Size

Originally, a sample size of 190 patients was calculated to determine differences in mortality rates in both groups with a power-of-contrast of 80%. A partial analysis with the first 49 patients has been carried out as described in this paper. Using the data from the initial sample size calculation, these patients represent an approximate power-of-contrast of 30%.

Statistical analysis

Initially, the calculation of the indicators of clinical relevance (relative risk, RR, absolute risk reduction, ARR, relative risk reduction, RRR, number needed to treat, NNT, by intent to treat, ITT) was planned. 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). Since a significant number of patients died in the first three days and were unable to receive the technique (n = 3) we decided to perform the analysis by actual intervention received (AIR).

Ethical issues

The study was originally approved by all Ethics Committees of the different Hospitals participating in the study. There was a general agreement that the trial closure was the best option, since the decision adopted by the Italian group to close its trial had been made public through its website and the supplier consequently marked their product used for the test with a warning.

RESULTS

A total of 49 patients were included in the final analysis (30 in the control group and 19 in the intervention group) (Figure 1). The randomization tables are displayed in Table 1. Parametric statistics did not allow us to establish significant differences between the analyzed factors due to the small sample size. However, we can see a mean difference between the two groups of 1.9 on an APACHE II score, 0.6 mmol/l of lactate levels and 10.9% in the prevalence of urinary sepsis. All these factors have been used in the propensity score test.

With regard to mortality (without adjusting by propensity score), 7 patients (23.3%) died in the first three days from the control group and 8 patients (40.6%) died from the intervention group (p=0.146). After 28 days, 14 patients died (46.7%) from the control group and 11 patients died (57.9%) from the intervention group, not reaching statistical significance (p=0.444). At 90 days 19 patients had died (63.3%) from the control group and 11 patients had died (57.9%) from the intervention group, which is to say no patient died from the intervention group between 28 and 90 days (p=0.878). Adjusting by propensity score and using the Kaplan-Meier technique (Figure 2), statistical significant difference was not reached, neither in the ITT (Table 2) approach nor by the AIR approach (Table 3).

In patients who died in the first three days, we found that the base-line levels of lactate were higher compared with the rest (in mmol/L): 7.96±4.79 vs 4.43±2.41, p=0.015. This situation was similar in the APACHE score: 29.7±5.1 vs 27.5±5.5, p=0.194, although this variable was not significant.

DISCUSSION

Summary

Our results seem to indicate that the patient who received CPFA had less chance of mortality in the long term (90 days), whether by ITT analysis or AIR analysis. However, in the short and medium term during ITT analysis, CPFA had a detrimental effect and when using AIR analysis the effect was protected. In any case, the statistical power to obtain conclusions from these results was low.

Limitations of the study

This RCT was designed to determine medium and long-term differences between the CPFA and the standard care. For this purpose, a sample size of 190 patients was pre-determined. In these partial results, the sample size of 190 was not reached and therefore the statistical power of the comparison contrast is very low (~ 30%). In addition, as the randomization process was done based on the baseline characteristics of the patient, this can produce differences between the groups. Moreover, we can observe that the sample sizes of the two groups are not similar (the control group has approximately 50% more patients). All this has led to the use of propensity score adjustment in order to obtain results similar to an RCT (totally homogeneous groups, except in the intervention received). [9] However, even if we apply this technique we still have a low power of contrast. Despite this limitation, we want to communicate our partial results following the premature closure of the RCT COMPACT 2.

Comparison with the existing literature

We agreed with the Ethics Committee to review the incidence of early mortality in our trial on account of the findings communicated to us by the COMPACT 2 team. It should be emphasised that the ROMPA investigators were not given any impression of these COMPACT 2 findings during their own clinical practice. In any case, the analysis of what happened in the ROMPA sample collected up to that moment was carried out having a statistical power of only 30%, as expressed previously. Therefore, from a methodological point of view, it cannot have more value than the purely descriptive one. The results reported by the group of researchers of COMPACT 2 here deserve a special mention [8]. In these results, as occurred in our group, a preliminary analysis was developed that is far from the sample size initially calculated and therefore with low statistical power of contrast (not indicated by them in their report). In addition, as in our study, the COMPACT 2 group used a randomization system based on prognostic scores, [6] which means that the groups will not

be similar until the end of recruitment (which is reason to introduce the propensity score in our results).

In this situation, subgroup analysis has the problem of introducing analytic challenges and can lead to overstated and misleading results, [10] and as such we have to consider the remarkably low mortality of the control group, together with a remarkably high mortality of the intervention group. These results seem to be far removed from those that are obtained in usual clinical practice. This situation was not observed in the first COMPACT trial [5] and we have not heard of a retrospective analysis to explain these results.

In our group, patients who died in the first 72 h had significantly higher initial lactate values than the rest of the patients included in the trial (7.96±4.79 vs 4.43±2.41, p=0.015). Increased blood lactate in sepsis or trauma reflects anaerobic glycolysis due to hypoperfusion, and / or increased aerobic glycolysis.[11] In septic shock it mainly reflects hypoperfusion. At the present time, there is solid evidence about the predictive role of high lactate levels with respect to mortality in septic shock patients and our results are reflecting this.[12-18]

Lastly, we would like to comment on the margin of time chosen by the Italian group to carry out its partial results. We think it is important to assess the patient's mortality, but this mortality should be assessed with a global calculation. In other words, for a technique to be effective, it must decrease the patient's mortality in a reasonable period of time in order to allow the healing of sepsis and its possible subsequent consequences. For this reason, the period of 28 and 90 days was fixed by our protocol. Consequently, for the sake of conducting an effective clinical trial, it is not of relevance that the patient unfortunately dies early, but whether the patient dies in a period of time where he has a high mortality risk due to sepsis. In addition, in the calculation of the sample size of the Italian group, this was not

contemplated and could be a result of random error or heterogeneous groups in the treatment allocation. At this point, it must be stated that the ROMPA investigators are not at any moment criticising the COMPACT 2 decision to halt their trial. ROMPA's researchers remain aware of the complexity of such a decision and that it involves multiple factors, the most important being the security of the patients.

Implications to research

Our study was halted prematurely for the reasons we have previously explained when only 49 patients had been randomized (out of a target 190 patients). In the intervention arm, 19 patients were randomized and 30 patients randomized in the control arm. In both approaches (ITT and real intervention), we have not found evidence of either benefit or harmful effect in the tested treatment and, of course, this comes as no surprise due to the premature termination.

At this level of recruitment and with a power of 30% our sample is absolutely exposed to the random effect, resulting in a lack of homogeneity in the levels of basal risk. This lack of homogeneity pre-determines that the technique can be presented as either beneficial or harmful. In fact the technique appears less beneficial in the subgroup (not predefined) of patients who died in 72 hours and that, logically, were patients with an elevated basal risk, primarily expressed through lactate levels and APACHE 2 score .

We would like to comment on a controversial issue. Three patients who had been randomized to the intervention group died in the first 72 hrs and did not receive the CPFA treatment. The rapid hemodynamic deterioration of the patients did not allow the connection to the extracorporeal circuit. It is obvious that in the ITT analysis these patients are considered to all effects as belonging to the intervention group, assuming the great negative impact they will

have on the efficacy analysis. It should always be borne in mind that these 3 patients, representing 20% of total intervention group who died early, did not actually receive treatment. Undoubtedly, adequate sample size management would minimize the problem. But if what we are considering is the possible harmful effect of the technique in a non pre-specified subgroup of an underpowered sample we cannot ignore this situation. It seems reasonable to think that if we talk about the possible harmful action of a device, the technique in question should have actually been applied.

CONCLUSIONS

In this paper we have presented the results of the 49 patients randomized in our trial up until the moment of closure. As a consequence of the procedure being underpowered, it was not possible to do an analysis of contrast of hypothesis and under this inconvenience, we present the results obtained for the interest of all concerned in knowing what has happened in our trial. When all is taken into consideration, we have not found a difference in mortality between the two groups.

AUTHORS' CONTRIBUTIONS

CG drafted the paper of the protocol, CP helped draft the paper, and the rest of the authors critically reviewed the paper before sending it to *BMJ Open*.

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COMPETING INTERESTS STATEMENT

The authors declare no conflict of interest.

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FIGURE LEGENDS:

Figure 1: Flow chart of the clinical trial (partial results).

Figure 2: Survival analysis using the Kaplan-Meier estimator comparing both groups.

Red, intervention; Blue, control.

A, intention to treat; B, real intervention.

TABLES:

Table 1: Comparison between the intervention and the control group.

Variable	Control group n=30 n(%)/x±s	CPFA n=19 n(%)/x±s	p-value
Gender male	18(60.0)	11(57.9)	0.884
Abdominal sepsis	12(40.0)	8(42.1)	0.884
Cancer	11(36.7)	7(36.8)	0.990
Community-acquired pneumonia	5(16.7)	3(15.8)	>0.999
Nosocomial pneumonia	3(10.0)	3(15.8)	0.665
Diabetes	9(30.0)	5(26.3)	0.781
Urinary sepsis	8(26.7)	3(15.8)	0.492
APACHE II	28.9±5.6	27.0±5.1	0.244
SOFA	12.8±3.3	12.2±4.4	0.541
SAPS II	74.5±20.9	70.7±21.0	0.587
Lactate (mmol/l)	5.3±3.4	5.9±4.1	0.580
Age (years)	70.0±13.6	71.0±14.5	0.812

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; CPFA, Coupled Plasma Filtration Adsorption; n(%), absolute frequency (relative frequency); SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; x±s, mean ± standard deviation.

Table 2: Clinical relevance of the intervention (intention-to-treat) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT/NNH*	p-value
3-day mortality	1.67(0.51-5.46)	-0.67(-4.46 to 0.49)	-0.17(-0.54 to 0.20)	6 (H)	0.667
28-day mortality	1.28(0.57-2.87)	-0.28(-1.87 to 0.43)	-0.13(-0.53 to 0.28)	8 (H)	0.537
90-day mortality	0.92(0.48-1.76)	0.08(-0.76 to 0.52)	0.05(-0.35 to 0.45)	19 (T)	>0.999

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; H, Harm; NNH, Number Needed to Harm; NNH, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction; T, Treat.

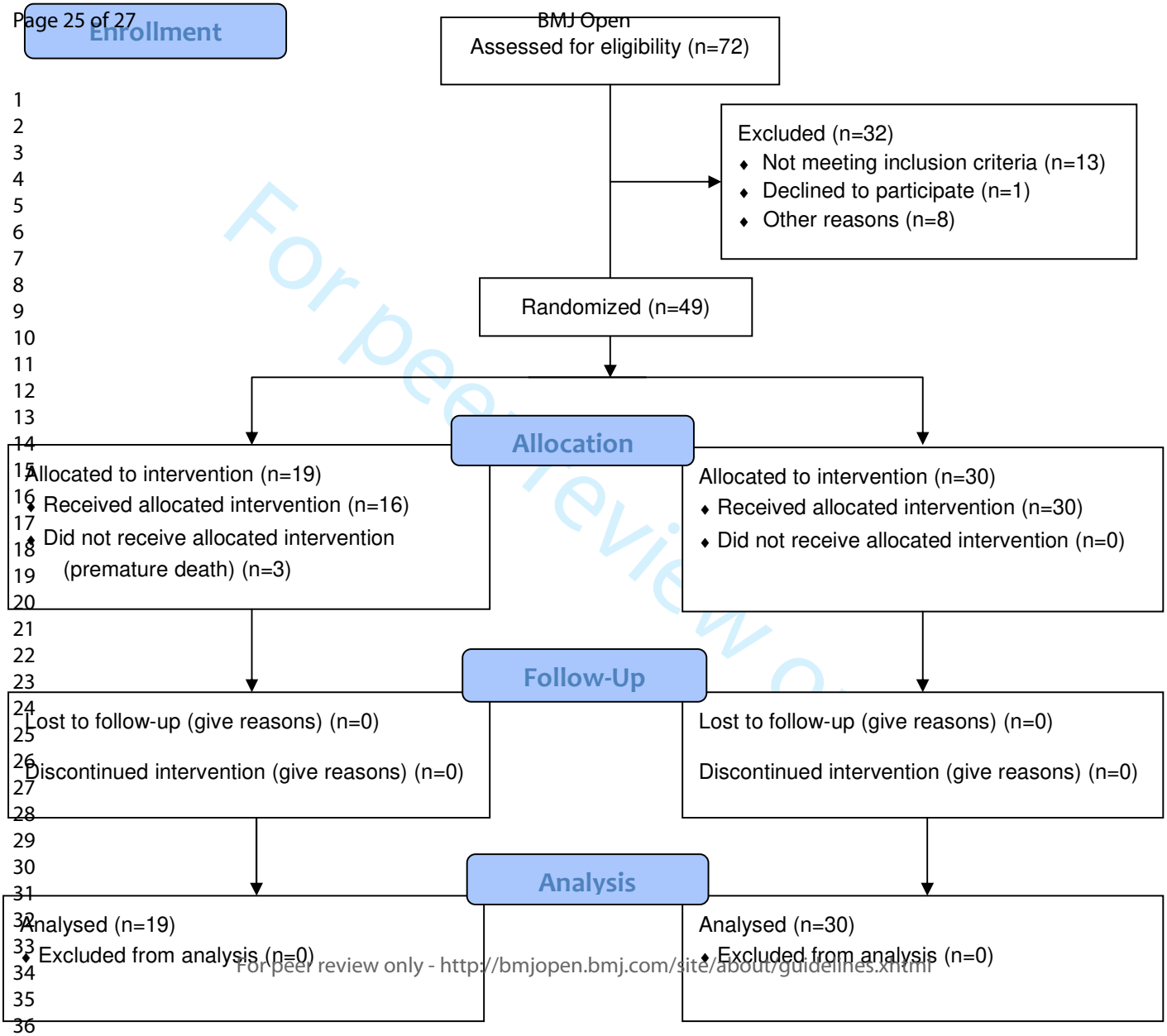
*, not possible to compute the confidence interval (division by zero).

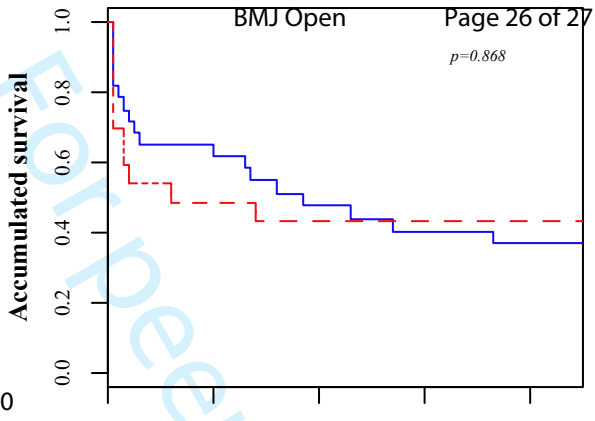
Table 3: Clinical relevance of the intervention (real group) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT *	p-value
3-day mortality	0.84(0.26-2.73)	0.16(-1.73 to 0.74)	0.06(-0.32 to 0.44)	18	>0.999
28-day mortality	0.93(0.42-2.06)	0.07(-1.06 to 0.58)	0.04(-0.37 to 0.45)	26	>0.999
90-day mortality	0.72(0.35-1.48)	0.28(-0.48 to 0.65)	0.19(-0.21 to 0.59)	6	0.417

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; NNT, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction.

*, not possible to compute the confidence interval (division by zero).





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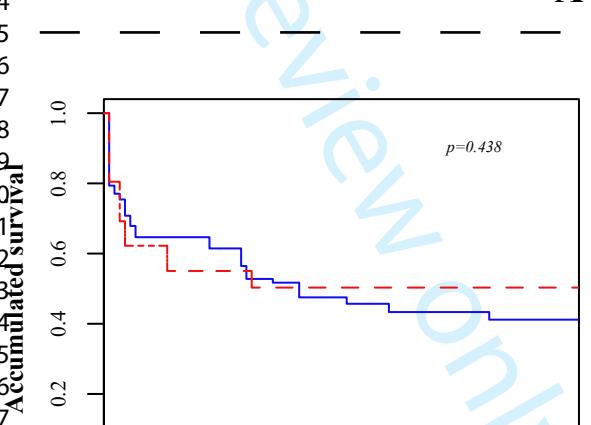

B

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7-10
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7-8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Protocol

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9-10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	6-7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	21
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-15
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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TITLE PAGE

Title: The premature closure of ROMPA Clinical Trial. Presentation of the results concerning the 49 randomized patients before the study closure.

Short title: The closure of ROMPA Clinical Trial.

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ABSTRACT

Objectives: Coupled Plasma Filtration and Adsorption (CPFA) use in septic shock remains controversial. The objective is to clarify whether the application of high dosis of CPFA in addition to the current clinical practice could reduce hospital mortality in septic shock patients in Intensive Care Units at 28 days and 90 days follow up.

Design: We designed a prospective randomized clinical trial, ROMPA (Reducción de la Mortalidad Plasma-Adsorción), to demonstrate an absolute mortality reduction of 20% [α=0.05; 1-β=0.8; n=190(95x2)].

Setting: Being aware of the pitfalls associated with previous medical device trials, we developed a training program to improve CPFA use (especially clotting problems). The protocol was approved by the ethics committees of all participating centers. Circumstances beyond our control produced a change in recruitment conditions unacceptable to ROMPA researchers and the trial was discontinued.

Participants: By closure, 5 centres from an initial 10 fulfilled the necessary trial criteria, with 49 patients included, 30 control group (CG) and 19 intervention group (IG).

Intervention: CPFA.

Main outcome measures: Hospital mortality at 28 days and 90 days follow up

Results: After 28 days, 14 patients died (46.7%) from the CG and 11 (57.9%) from the IG, not reaching statistical significance (p=0.444). At 90 days 19 patients had died (63.3%) from the CG and 11 patients (57.9%) from the IG, (p=0.878). The adjustment by propensity score or the use of the Kaplan Meier technique failed to achieve statistical difference, neither in the Intention to Treat Approach nor by the Actual Intervention Received.

Conclusion: We herewith present the results gained from the prematurely-closed trial. The results are inconclusive due to low statistical power but we consider that this data is of interest for the scientific community and potentially necessary for any ensuing debate.

Register: NCT02357433 in clinicaltrials.gov

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Randomised control clinical trial testing the efficacy of CPFA in septic shock.
- Premature closure of the trial by circumstances beyond the trial.
- Scarce sample size: underpowered trial.

INTRODUCTION

Sepsis is still a leading cause of mortality in Intensive Care Units (ICU) patients, with a 20-50% mortality rate of sepsis and septic shock [1]. There exists a feeling of frustration generated by the large series of negative randomized clinical trials (RCTs) in septic shock treatment (especially in targeting mortality) during the past 30 years [2]. Patients included in these trials have a wide variability in their probability of death translating into differences in benefits to be derived from specific therapy application, producing a handicap to sample size calculation. This can lead to the trial having less power than initially planned increasing risk of a type 2 error and undoubtedly this is the origin of unexpected results.[3] It questions the use of subgroups in an attempt to extract some kind of useful information in negative RCTs.[4]

The COMPACT 1, a multicentre RCT study, failed to show benefit by using Coupled Plasma Filtration and Adsorption (CPFA) therapy in a population with septic shock. In a per protocol analysis, patients treated with CPFA at treated plasma volume superior to 0.20 l/kg/day showed a reduction in mortality rate [5]. Although an interesting finding, our group considered it was necessary to carry out a RCT to confirm this hypothesis.

The response to this question was the ROMPA (Reducción de la Mortalidad Mediante Plasma-Adsorción en Shock séptico), a multicenter RCT carried out in ICUs of southeastern Spain. The ROMPA Study (NCT02357433 in clinicaltrials.gov) tried to clarify whether the application of high doses CPFA in addition to the current clinical practice was able to reduce hospital mortality in septic shock patients in ICUs. The protocol of ROMPA has been published in a free access support and the details of the protocol could be consulted without restrictions.[6]

In October 2017, COMPACT 2 (NCT01639664 in clinical trials.gov) trial investigators, a similar study to ROMPA conducted in Italian ICUs,[7] reported the premature closure of the study for having detected an increase in early mortality (3 first days) in the intervention branch, 6/42 (12.5%) vs 19/58 (32.8%) p=0.020, not having reached the sample size prefixed in the protocol (350 patients). The adjusted odds ratio (OR) of the treatment yielded by logistic regression is 2.1 (95% CI: 0.7-6.6, p=0.19) and the adjusted hazard ratio (HR) yielded by the Cox model is 2.5 (95% CI: 1.4- 4.4, p=0.002). This information was immediately reported to our Ethical Committee and these results were published on the research group website in Italian.[8] Subsequent events, including a provisional warning by the product supplier, motivated us to take the final decision of closing ROMPA. At that time, of the 10 initial hospitals only 5 had exceeded the technical capacity requirements and availability of resources required to access the randomization portal. In this paper and as a result of events of such severity, our group shows the data collected to date and the results from the 49 enrolled patients (30 control and 19 intervention groups).

METHODS

Protocol

The full study protocol was previously published.[6] A synthesis of it is made in this section (Methods) .

Setting and participants

The study was performed in 5 ICUs, in the southeast of Spain, that follow the same protocol in the treatment of septic shock, based on the recommendations of the Surviving Sepsis

Campaign with the participation of the following centers: Vega Baja Hospital of Orihuela, General University Santa Lucía Hospital of Cartagena, University Hospital of San Juan de Alicante, Lluís Alcanyís Hospital of Xàtiva and Francesc de Borja Hospital of Gandía.

The ROMPA study is a multi-centric, randomized, prospective, open clinical trial with 28- and 90-day follow-up and allocation ratio 1:1, assessing the mortality reduction by CPFA in patients with septic shock. Furthermore, we analyzed 3-day mortality to compare our results with the Italian group.

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 (coagulation of the extracorporeal circuit, technical problems intimately linked to the management of a complex extracorporeal circuit, problems related to necessary logistic that require an extracorporeal technique such as CPFA as necessary and problems related to the need for specialized personnel),[4] and also because CPFA is not routinely done in Spain and a new machine with improved anticoagulation support was subsequently developed and used for this trial.

Participants

Patients ≥18 years old admitted to the ICU of the participant hospitals, with a diagnosis of septic shock can be included in the study. This was defined as documented or suspected infection with systemic manifestations of infection accompanied by signs of organ failure, or tissue hypoperfusion with persistent hypotension despite administration of adequate fluid resuscitation (at least 30ml/kg crystaloides) and in the absence of other causes of hypotension. The inclusion and exclusion criteria are detailed in the published protocol.[6]

Interventions

The patient is considered registered once the informed consent form has been obtained by the patient or legal representative. The recruitment process ends with the patient randomization. The time between septic shock diagnosis and randomization was established in 12 hours, because this window adjusts much more to the reality of the clinical scenario, at least that of the hospitals that participated in the ROMPA study. The researchers of the COMPACT 2 study reached the same conclusion.[7]

Patients were divided randomly into two arms (control and intervention). ROMPA has a stratified randomization based on gender, age (≤ 65 or >65 years) and SAPS III score (<50 or ≥51). On the one hand, in the control group we followed the suggestions provided by the recent surviving sepsis guidelines, as well as standard care guidelines typically followed in Spain. On the other hand, in the CPFA group, we applied the same protocol plus high doses of CPFA in the first 3 days after randomization.

Variables and measurements

Primary and Secondary Outcomes

The primary outcome variable is all-cause of mortality assessed at 3, 28 and 90 days from the recruitment of the patient. The analysis of 3-day mortality, although it was not initially pre-specified in the protocol, it was a recommendation of our Ethical Committee after knowing the data of the Italian group.[8]

Moreover, at the descriptive level and in order to check homogeneity of both groups, the following variables will be collected at the time of recruitment: birth year, gender, height, dry weight, body temperature, heart rate, blood pressure, blood cell count, coagulation values, glucose level, plasma creatinine, bilirubinemia, plasma C reactive protein, procalcitonin

level, blood gas analysis, lactate, urinary output (ml/kg/h), Pa O_2/FiO_2 ratio, APACHE II, SOFA and SAPSIII scores.

Sample Size

Originally, a sample size of 190 patients was calculated to determine differences in mortality rates in both groups with a power-of-contrast of 80%. The assumed control mortality rate was 50% and we tried to demonstrate a reduction in mortality of 20% with the intervention (similar to the COMPACT I results).[4] A partial analysis with the first 49 patients has been carried out as described in this paper. Using the data from the initial sample size calculation, these patients represent an approximate power-of-contrast of 30%.

Statistical analysis

Initially, the calculation of the indicators of clinical relevance (relative risk, RR, absolute risk reduction, ARR, relative risk reduction, RRR, number needed to treat, NNT, by intent to treat, ITT) was planned. 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). Since a significant number of patients died in the first three days and were unable to receive the technique (n = 3, 15.8%) we decided to perform the analysis by actual intervention received (AIR). Although initially we did not plan this analysis

(clinicaltrials.gov), the fact that one out of six patients did not receive the intervention could produce results completely different from its real effect.

Ethical issues

The study was originally approved by all Ethics Committees of the different Hospitals participating in the study. There was a general agreement that the trial closure was the best option, since the decision adopted by the Italian group to close its trial had been made public through its website and the supplier consequently marked their product used for the test with a warning. A Data and Safety Monitoring Board periodically review and evaluate the study data for the safety of the patients. It was formed by the Principal Investigator, the Senior Investigator and the Biostatistician of the project.

Patient and Public Involvement

Patients were not involved.

RESULTS

A total of 49 patients were included in the final analysis (30 in the control group and 19 in the intervention group) (Figure 1). The randomization tables are displayed in Table 1. Parametric statistics did not allow us to establish significant differences between the analyzed factors due to the small sample size. However, we can see a mean difference between the two groups of 1.9 on an APACHE II score, 0.6 mmol/l of lactate levels and 10.9% in the prevalence of urinary sepsis. All these factors have been used in the propensity score test.

With regard to mortality (without adjusting by propensity score), 7 patients (23.3%) died in the first three days from the control group and 8 patients (40.6%) died from the intervention group (p=0.146). After 28 days, 14 patients died (46.7%) from the control group and 11 patients died (57.9%) from the intervention group, not reaching statistical significance (p=0.444). At 90 days 19 patients had died (63.3%) from the control group and 11 patients had died (57.9%) from the intervention group, which is to say no patient died from the intervention group between 28 and 90 days (p=0.878). Adjusting by propensity score and using the Kaplan-Meier technique (Figure 2), statistical significant difference was not reached, neither in the ITT (Table 2) approach nor by the AIR approach (Table 3).

In patients who died in the first three days, we found that the base-line levels of lactate were higher compared with the rest (in mmol/L): 7.96±4.79 vs 4.43±2.41, p=0.015. This situation was similar in the APACHE score: 29.7±5.1 vs 27.5±5.5, p=0.194, although this variable was not significant.

DISCUSSION

Summary

Our results seem to indicate that the patient who received CPFA had less chance of mortality in the long term (90 days), whether by ITT analysis or AIR analysis. However, in the short and medium term during ITT analysis, CPFA had a detrimental effect and when using AIR analysis the effect was protected. In any case, the statistical power to obtain conclusions from these results was low and these were non-significant, consequently we are only describing the estimation of the analyzed parameters (HR and proportions).

Limitations of the study

This RCT was designed to determine medium and long-term differences between the CPFA and the standard care. For this purpose, a sample size of 190 patients was pre-determined. In these partial results, the sample size of 190 was not reached due to the cessation of the trial and therefore the statistical power of the comparison contrast is very low (~ 30%). As a consequence, the ARR of 20% is much too high and overly ambitious. This combined with the low sample size yields an extraordinarily low power. In addition, as the randomization process was done based on the baseline characteristics of the patient, this can produce differences between the groups. Moreover, we can observe that the sample sizes of the two groups are not similar (the control group has approximately 50% more patients). All this has led to the use of propensity score adjustment in order to obtain results similar to an RCT (totally homogeneous groups, except in the intervention received). [9] However, even if we apply this technique we still have a low power of contrast. Despite this limitation, we are obliged to communicate our partial results following the premature closure of the RCT COMPACT 2.

Comparison with the existing literature

We agreed with the Ethics Committee to review the incidence of early mortality in our trial on account of the findings communicated to us by the COMPACT 2 team. It should be emphasised that the ROMPA investigators were not given any impression of these COMPACT 2 findings during the ROMPA clinical trial. The results reported by the group of researchers of COMPACT 2 here deserve a special mention [8]. In these results, as occurred in our group, a preliminary analysis was developed that is far from the sample size initially calculated and therefore with low statistical power of contrast (not indicated by them in their report). In addition, as in our study, the COMPACT 2 group used a randomization system

based on prognostic scores, [6] which means that the groups will not be similar until the end of recruitment (which is reason to introduce the propensity score in our results).

In this situation, subgroup analysis has the problem of introducing analytic challenges and can lead to overstated and misleading results, [10] and as such we have to consider the remarkably low mortality of the control group, together with a remarkably high mortality of the intervention group. These results seem to be far removed from those that are obtained in usual clinical practice. This situation was not observed in the first COMPACT trial [5] and we have not heard of a retrospective analysis to explain these results.

Lastly, we would like to comment on the margin of time chosen by the Italian group to carry out its partial results. We think it is important to assess the patient's mortality, but this mortality should be assessed with a global calculation. For a technique to be effective, it must decrease the patient's mortality in a reasonable period of time in order to allow the healing of sepsis and its possible subsequent consequences. For this reason, the period of 28 and 90 days was fixed by our protocol. Consequently, for the sake of conducting an effective clinical trial, it is not of relevance that the patient unfortunately dies early, but whether the patient dies in a period of time where he has a high mortality risk due to sepsis. In addition, in the calculation of the sample size of the Italian group, this was not contemplated and could be a result of random error or heterogeneous groups in the treatment allocation. At this point, it must be stated that the ROMPA investigators are not at any moment criticising the COMPACT 2 decision to halt their trial. ROMPA's researchers remain aware of the complexity of such a decision and that it involves multiple factors, the most important being the security of the patients.

Implications to research

Our study was halted prematurely for the reasons we have previously explained when only 49 patients had been randomized (out of a target 190 patients). In the intervention arm, 19 patients were randomized and 30 patients randomized in the control arm. In both approaches (ITT and real intervention), we have not found evidence of either benefit or harmful effect in the tested treatment and, of course, this comes as no surprise due to the premature termination.

At this level of recruitment and with a power of 30% our sample is absolutely exposed to the random effect, resulting in a lack of homogeneity in the levels of basal risk. This lack of homogeneity pre-determines that the technique can be presented as either beneficial or harmful. In fact the technique appears less beneficial in the subgroup (not predefined) of patients who died in 72 hours and that, logically, were patients with an elevated basal risk, primarily expressed through lactate levels and APACHE 2 score.

We would like to comment on a controversial issue. Three patients who had been randomized to the intervention group (20%) died in the first 72 hrs and did not receive the CPFA treatment. The rapid hemodynamic deterioration of the patients did not allow the connection to the extracorporeal circuit. Undoubtedly adequate sample size management minimized this problem, but if what we are considering is the possible harmful of the technique in a non-pre-specified subgroup of an underpowered sample we cannot ignore this situation of the technique not being applied.

CONCLUSIONS

In this paper we have presented the results of the 49 patients randomized in our trial up until the moment of closure. As a consequence of the procedure being underpowered, it was not

possible to do an analysis of contrast of hypothesis and under this inconvenience, we present the results obtained for the interest of all concerned in knowing what has happened in our trial. When all is taken into consideration, we have not found a difference in mortality between the two groups.

AUTHORS' CONTRIBUTIONS

CG designed the study and drafted the paper of the protocol; CP participated in the study design and helped draft the paper; FC, JMA, MG, CM, José LAP, EM, CD, MR, JLM, PJA, EMB, JC, EG, FS, MS, JT and VFG participated in the study design and reviewed critically the manuscript; AP participated in the study design, performed the statistical analysis and reviewed critically the manuscript. All the authors approved the final version of the text to be submitted for publication.

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COMPETING INTERESTS STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Francisco Colomina-Climent, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of all the Ethics Committee which approved the study.

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FIGURE LEGENDS:

Figure 1: Flow chart of the clinical trial (partial results).

Figure 2: Survival analysis using the Kaplan-Meier estimator comparing both groups.

Red, intervention; Blue, control.

A, intention to treat; B, real intervention.

TABLES:

Table 1: Comparison between the intervention and the control group.

Variable	Control group n=30 n(%)/x±s	CPFA n=19 n(%)/x±s	p-value
Gender male	18(60.0)	11(57.9)	0.884
Abdominal sepsis	12(40.0)	8(42.1)	0.884
Cancer	11(36.7)	7(36.8)	0.990
Community-acquired pneumonia	5(16.7)	3(15.8)	>0.999
Nosocomial pneumonia	3(10.0)	3(15.8)	0.665
Diabetes	9(30.0)	5(26.3)	0.781
Urinary sepsis	8(26.7)	3(15.8)	0.492
APACHE II	28.9±5.6	27.0±5.1	0.244
SOFA	12.8±3.3	12.2±4.4	0.541
SAPS II	74.5±20.9	70.7±21.0	0.587
Lactate (mmol/l)	5.3±3.4	5.9±4.1	0.580
Age (years)	70.0±13.6	71.0±14.5	0.812

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; CPFA, Coupled Plasma Filtration Adsorption; n(%), absolute frequency (relative frequency); SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; x±s, mean ± standard deviation.

Table 2: Clinical relevance of the intervention (intention-to-treat) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT/NNH*	p-value
3-day mortality	1.67(0.51-5.46)	-0.67(-4.46 to 0.49)	-0.17(-0.54 to 0.20)	6 (H)	0.667
28-day mortality	1.28(0.57-2.87)	-0.28(-1.87 to 0.43)	-0.13(-0.53 to 0.28)	8 (H)	0.537
90-day mortality	0.92(0.48-1.76)	0.08(-0.76 to 0.52)	0.05(-0.35 to 0.45)	19 (T)	>0.999

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; H, Harm; NNH, Number Needed to Harm; NNH, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction; T, Treat.

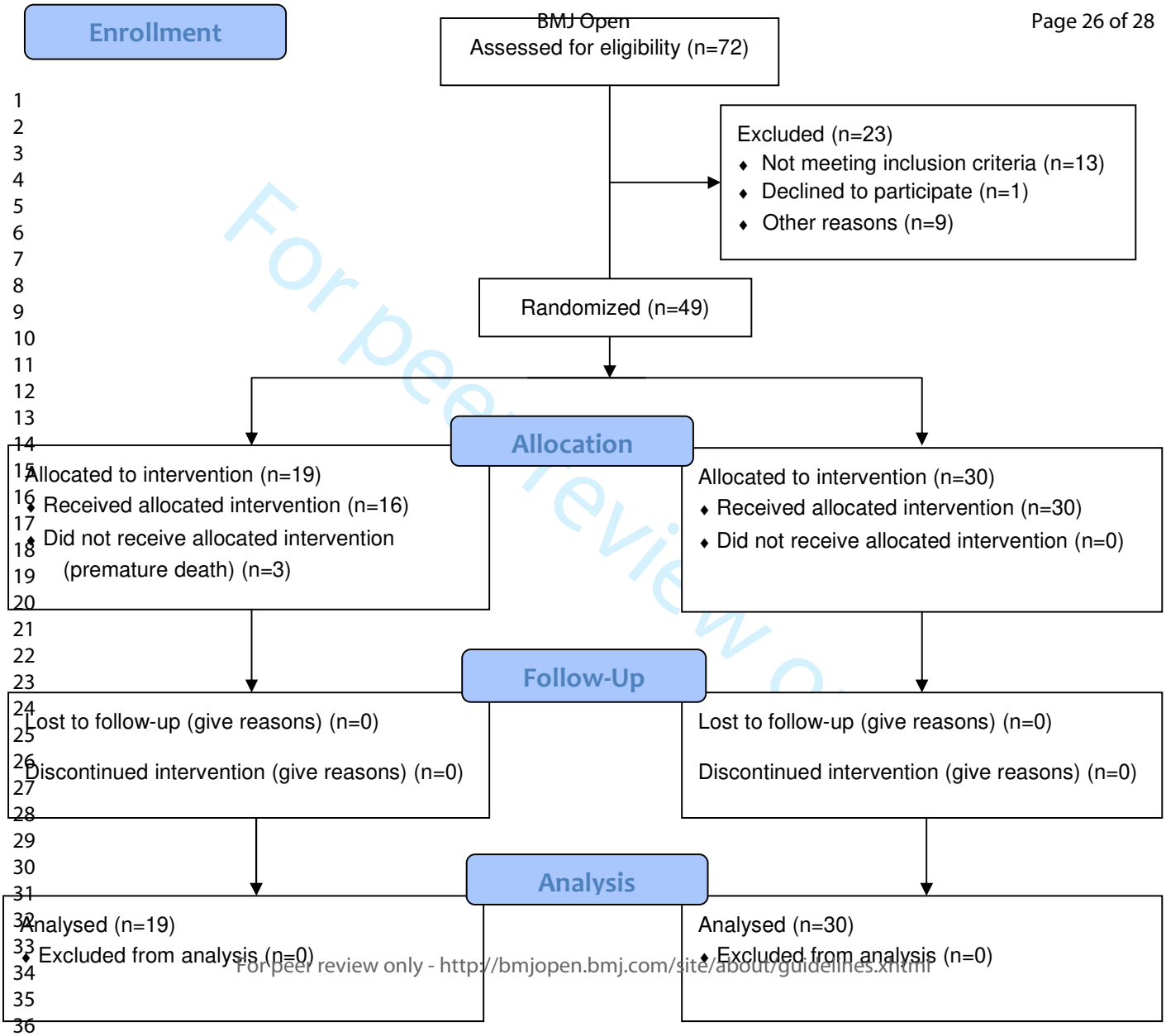
*, not possible to compute the confidence interval (division by zero).

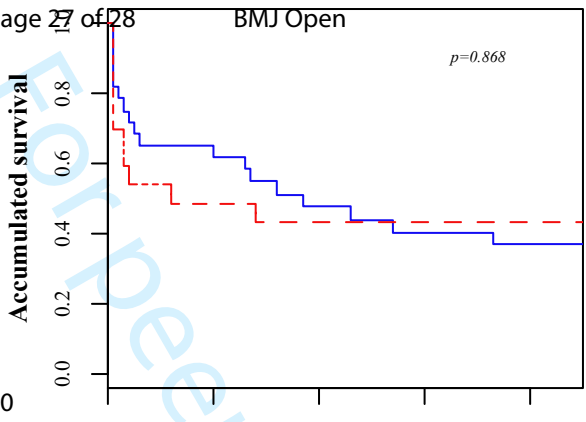
Table 3: Clinical relevance of the intervention (real group) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT *	p-value
3-day mortality	0.84(0.26-2.73)	0.16(-1.73 to 0.74)	0.06(-0.32 to 0.44)	18	>0.999
28-day mortality	0.93(0.42-2.06)	0.07(-1.06 to 0.58)	0.04(-0.37 to 0.45)	26	>0.999
90-day mortality	0.72(0.35-1.48)	0.28(-0.48 to 0.65)	0.19(-0.21 to 0.59)	6	0.417

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; NNT, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction.

*, not possible to compute the confidence interval (division by zero).





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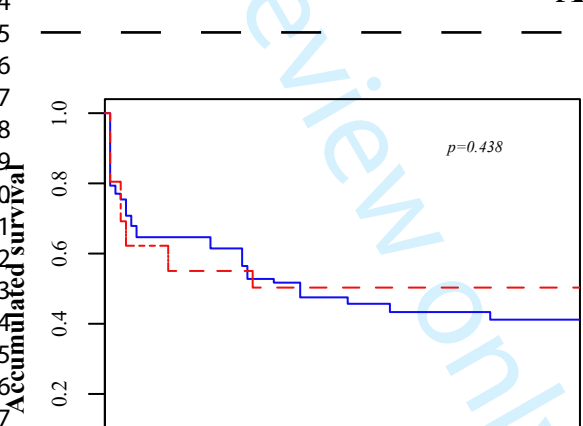

B

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7-10
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7-8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9-10
Sample size	7a	How sample size was determined	9-10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Protocol

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	6-7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	21
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-16
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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The premature closure of ROMPA Clinical Trial: Mortality Reduction in Septic Shock by Plasma Adsorption.

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Secondary Subject Heading:	Intensive care, Infectious diseases
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TITLE PAGE

Title: The premature closure of ROMPA Clinical Trial: Mortality Reduction in Septic Shock by Plasma Adsorption.

Short title: The closure of ROMPA Clinical Trial.

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ABSTRACT

Objectives: Coupled Plasma Filtration and Adsorption (CPFA) use in septic shock remains controversial. The objective is to clarify whether the application of high doses of CPFA in addition to the current clinical practice could reduce hospital mortality in septic shock patients in Intensive Care Units at 28 days and at 90 days follow-up.

Design: We designed a prospective randomized clinical trial, ROMPA (Reducción de la Mortalidad Plasma-Adsorción), to demonstrate an absolute mortality reduction of 20% [α=0.05; 1-β=0.8; n=190(95x2)].

Setting: Being aware of the pitfalls associated with previous medical device trials, we developed a training program to improve CPFA use (especially clotting problems). The protocol was approved by the ethics committees of all participating centers. Circumstances beyond our control produced a change in recruitment conditions unacceptable to ROMPA researchers and the trial was discontinued.

Participants: By closure, 5 centers from an initial 10 fulfilled the necessary trial criteria, with 49 patients included, 30 in the control group (CG) and 19 in the intervention group (IG).

Intervention: CPFA.

Main outcome measures: Hospital mortality at 28 days and 90 days follow-up.

Results: After 28 days, 14 patients died (46.7%) from the CG and 11 (57.9%) from the IG, not reaching statistical significance (p=0.444). At 90 days, 19 patients had died (63.3%) from the CG and 11 patients (57.9%) from the IG, (p=0.878). The adjustment by propensity score or the use of the Kaplan Meier technique failed to achieve statistical difference, neither by Intention to Treat nor by the Actual Intervention Received.

Conclusion: We herewith present the results gained from the prematurely closed trial. The results are inconclusive due to low statistical power but we consider that this data is of interest for the scientific community and potentially necessary for any ensuing debate.

Register: NCT02357433 in clinicaltrials.gov

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Randomized control clinical trial testing the efficacy of CPFA in septic shock.
- Premature closure due to circumstances beyond the control of the trial.
- Scarce sample size: underpowered trial.

INTRODUCTION

Sepsis is still a leading cause of mortality in Intensive Care Unit (ICU) patients, with a 20-50% mortality rate from sepsis and septic shock [1]. There has been a feeling of frustration generated by the large amount of negative randomized clinical trials (RCTs) in septic shock treatment (especially in those targeting mortality) over the past 30 years [2]. Patients included in these trials vary widely in their probability of death. This translates into differences in the benefits derived from specific therapy application, which in turn handicaps sample size calculation. This can lead to the trial having less statistical power than initially planned, increasing the risk of a type 2 error and this is the origin of unexpected results. [3] It questions the use of subgroups in an attempt to extract some kind of useful information in negative RCTs. [4]

The COMPACT 1, a multicenter RCT study, failed to show any benefits when using Coupled Plasma Filtration and Adsorption (CPFA) therapy in a population with septic shock. In a per-protocol analysis, patients treated with CPFA using a volume of treated plasma superior to 0.20 l/kg/day demonstrated a reduction in mortality rate [5]. Although an interesting result, our group considered it was necessary to carry out a RCT to confirm this hypothesis.

The response to this question was ROMPA (Reducción de la Mortalidad Mediante Plasma-Adsorción en Shock séptico), a multicenter RCT carried out in ICUs of southeastern Spain. The ROMPA Study (NCT02357433 in clinicaltrials.gov) tried to clarify whether the application of high doses of CPFA in addition to the current clinical practice was able to reduce hospital mortality in septic shock patients in ICUs. The protocol of ROMPA has been published in a free access journal and the details of the protocol can be consulted without restrictions. [6]

In October 2017, the trial investigators of COMPACT 2 (NCT01639664 in clinicaltrials.gov), a similar study to ROMPA conducted in Italian ICUs [7], reported the premature closure of the study for having detected an increase in early mortality (3 first days) in the intervention branch (6/42 (12.5%) vs 19/58 (32.8%) p=0.020, not reaching the 350 patient sample size prefixed in the protocol). The adjusted odds ratio (OR) of the treatment yielded by logistic regression is 2.1 (95% CI: 0.7-6.6, p=0.19) and the adjusted hazard ratio (HR) yielded by the Cox model is 2.5 (95% CI: 1.4- 4.4, p=0.002). This information was immediately reported to our Ethical Committee and these results were published on the research group website in Italian [8]. Subsequent events, including a provisional warning by the product supplier, led us to close ROMPA. At that time, of the 10 initial hospitals, only 5 had exceeded the technical capacity requirements and availability of resources required to access the randomization portal. Due to the severity of the events, our group wishes to show the data collected so far and the results from the 49 enrolled patients (30 control and 19 intervention groups).

METHODS

Protocol

The full study protocol has been published previously. [6] In this section, a synthesis of the protocol is given (Methods).

Setting and participants

The study was performed in 5 ICUs in the southeast of Spain, all following the same protocol in the treatment of septic shock, which is based on the recommendations of the Surviving Sepsis Campaign. The following centers participated: Vega Baja Hospital of Orihuela,

General University Santa Lucía Hospital of Cartagena, University Hospital of San Juan de Alicante, Lluís Alcanyís Hospital of Xàtiva and Francesc de Borja Hospital of Gandía.

The ROMPA study is a multi-center, randomized, prospective, open clinical trial with 28- and 90-day follow-up and allocation ratio 1:1, assessing the mortality reduction by CPFA in patients with septic shock. Furthermore, we analyzed 3-day mortality to compare our results with the Italian group.

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, firstly, in order to avoid similar problems as those reported in the first COMPACT study (coagulation of the extracorporeal circuit; technical problems intimately linked to the management of a complex extracorporeal circuit; logistical problems which required an extracorporeal technique such as CPFA; problems related to the need for specialized personnel). [4] Secondly, as CPFA is not routinely administered in Spain, a new machine with improved anticoagulation support was developed and used for this trial.

Participants

Patients ≥18 years-old with a diagnosis of septic shock and admitted to the ICU of the participant hospitals are eligible to be included in the study. Diagnosis of septic shock was defined as documented or suspected infection with systemic manifestations of infection accompanied by signs of organ failure, or tissue hypoperfusion with persistent hypotension despite administration of adequate fluid resuscitation (at least 30ml/kg crystaloides) and in the absence of other causes of hypotension. The inclusion and exclusion criteria are detailed in the published protocol. [6]

Interventions

The patient is registered once the informed consent form has been obtained by the patient or legal representative. The recruitment process ends with the patient randomization. The time between septic shock diagnosis and randomization was established in 12 hours, because this window adjusts much more to the reality of the clinical situation, at least that of the hospitals that participated in the ROMPA study. The researchers of the COMPACT 2 study reached the same conclusion. [7]

Patients were divided randomly into two arms (control and intervention). ROMPA has a stratified randomization based on gender, age (≤ 65 or >65 years) and SAPS III score (<50 or ≥51). On the one hand, in the control group we followed the suggestions provided by the recent surviving sepsis guidelines, as well as standard care guidelines typically followed in Spain. On the other hand, in the CPFA group, we applied the same protocol plus high doses of CPFA in the first 3 days after randomization.

Variables and measurements

Primary and Secondary Outcomes

The primary outcome variable is all-cause mortality assessed at 28 and 90 days after the recruitment of the patient. The analysis of 3-day mortality, although not initially specified in the protocol, was an added recommendation by our Ethical Committee once the data of the Italian group had become known. [8]

Moreover, at the descriptive level and in order to check homogeneity of both groups, the following variables will be collected at the time of recruitment: birth year, gender, height, dry weight, body temperature, heart rate, blood pressure, blood cell count, coagulation values, glucose level, plasma creatinine, bilirubinemia, plasma C reactive protein, procalcitonin

level, blood gas analysis, lactate, urinary output (ml/kg/h), Pa O_2/FiO_2 ratio, APACHE II, SOFA and SAPSIII scores.

Sample Size

Originally, a sample size of 190 patients was calculated to determine differences in mortality rates in both groups with a power-of-contrast of 80%. The assumed control group mortality rate was 50% and we tried to demonstrate a reduction in mortality of 20% in the intervention group (similar to the COMPACT I results). [4] A partial analysis with the first 49 patients has been carried out as described in this paper. Using the data from the initial sample size calculation, these patients represent an approximate power-of-contrast of 30%.

Statistical analysis

Initially, the calculation of the indicators of clinical relevance (relative risk, RR, absolute risk reduction, ARR, relative risk reduction, RRR, number needed to treat, NNT, by intent to treat, ITT) was planned. 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 could not be established. 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 not established in the study protocol, Kaplan-Meier survival curves were analyzed to determine differences in mortality in the analyzed groups (log-rank test). Since a significant number of patients died in the first three days and were unable to receive the technique (n = 3, 15.8%) we decided to perform the analysis by actual intervention received (AIR). Although **this**

analysis was not initially planned (clinicaltrials.gov), the fact that one out of six patients did not receive the intervention necessitated it.

Ethical issues

The study was originally approved by all Ethics Committees of the Hospitals participating in the study. There was a general agreement that the trial closure was the best option, since the decision adopted by the Italian group to close its trial had been made public through its website resulting in the device supplier marking their product used for the test with a warning. A Data and Safety Monitoring Board was set up to periodically review and evaluate the study data for the safety of the patients. It was formed by the Principal Investigator, the Senior Investigator and the Biostatistician of the project.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

A total of 49 patients were included in the final analysis (30 in the control group and 19 in the intervention group) (Figure 1). The randomization tables are displayed in Table 1. Parametric statistics did not allow us to establish significant differences between the analyzed factors due to the small sample size. However, we can see a mean difference between the two groups based on three variables: 1.9 on an APACHE II score, 0.6 mmol/l of lactate levels and 10.9%

in the prevalence of urinary sepsis. All these factors have been used in the propensity score test.

With regard to mortality (without adjusting by propensity score), 7 patients (23.3%) had died in the first three days from the control group and 8 patients (40.6%) had died from the intervention group (p=0.146). After 28 days, 14 patients had died (46.7%) from the control group and 11 patients had died (57.9%) from the intervention group, not reaching statistical significance (p=0.444). At 90 days 19 patients had died (63.3%) from the control group and 11 patients had died (57.9%) from the intervention group, which is to say no patient died from the intervention group between 28 and 90 days (p=0.878). Adjusting by propensity score and using the Kaplan-Meier technique (Figure 2), statistical significant difference was not reached, neither by ITT (Table 2) nor by the AIR. (Table 3).

In patients who died in the first three days, we found that the base-line levels of lactate were higher compared with the rest of the patients (in mmol/L): 7.96±4.79 vs 4.43±2.41, p=0.015. A similar situation was revealed in the APACHE score: 29.7±5.1 vs 27.5±5.5, p=0.194, although this variable was not significant.

DISCUSSION

Summary

Our results seem to indicate that the patients who received CPFA had less chance of mortality in the long term (90 days), whether by ITT analysis or AIR analysis. However, in the short and medium term during ITT analysis, CPFA had a detrimental effect and when using AIR analysis the effect was protective. In any case, the statistical power to obtain conclusions from these results was low and therefore non-significant. As a consequence, we are only describing the estimation of the analyzed parameters (HR and proportions).

Limitations of the study

This RCT was designed to determine medium and long-term differences between CPFA and standard care. For this purpose, a sample size of 190 patients was pre-determined. In these partial results, the sample size of 190 was not reached due to the cessation of the trial and therefore the statistical power of the comparison contrast is very low (~ 30%). As a consequence, the ARR of 20% is much too high and unrealistic. Combined with the low sample size, this yields a very low statistical power. In addition, as the randomization process was undertaken based on the baseline characteristics of the patient, this can produce differences between the groups. Moreover, we can observe that the sample sizes of the two groups are not similar (the control group has approximately 50% more patients). All this has led to the use of propensity score adjustment in order to obtain results similar to an RCT (homogeneous groups, except in the intervention received). [9] However, even if we apply this technique we still have a low power of contrast. Despite this limitation, we are obliged to communicate our partial results following the premature closure of the RCT COMPACT 2.

Comparison with the existing literature

We agreed with the Ethics Committee to review the incidence of early mortality in our trial after the findings communicated to us by the COMPACT 2 team. It should be emphasized that the ROMPA investigators were not given any impression of these COMPACT 2 findings during the ROMPA clinical trial. The results reported by the group of researchers of COMPACT 2 here deserve a special mention [8]. In these results, as occurred in our group, a preliminary analysis was developed that is far from the sample size initially calculated and therefore with low statistical power of contrast (not indicated by them in their report). In addition, as in our study, the COMPACT 2 group used a randomization system based on

prognostic scores, [6] which means that the groups will not be similar until the end of recruitment (which is reason to introduce the propensity score in our results).

In this situation, subgroup analysis has the problem of introducing analytic challenges and can lead to overstated and misleading results, [10] and**,** as such**,** we have to consider the remarkably low mortality of the control group, together with a remarkably high mortality of the intervention group. These results seem to be far removed from those that are obtained in usual clinical practice. This situation was not observed in the first COMPACT trial [5] and we have not heard of a retrospective analysis to explain these results.

Lastly, we would like to comment on the margin of time chosen by the Italian group to carry out its partial results. We think it is important to assess the patient's mortality, but this mortality should be assessed with a global calculation. For a technique to be effective, it must decrease the patient's mortality in a reasonable period of time in order to allow the healing of sepsis and its possible consequences. For this reason, the periods of 28 days and 90 days were fixed by our protocol. Consequently, for the sake of conducting an effective clinical trial, it is not of relevance that the patient dies early, but whether the patient dies in a period of time where he has a high mortality risk due to sepsis. Additionally, in the calculation of the sample size of the Italian group, mortality at three days was not contemplated and could be a result of either random error or heterogeneous groups in the treatment allocation. At this point, it must be stated that the ROMPA investigators are not at any moment criticizing the COMPACT 2 decision to halt their trial. ROMPA's researchers remain aware of the complexity of such a decision and that it involves multiple factors, the most important being the security of the patients.

Implications to research

Our study was halted prematurely for the reasons we have previously explained when only 49 patients had been randomized (out of a target 190 patients). In the intervention arm, 19 patients were randomized and 30 patients in the control arm. In both approaches (ITT and real intervention), we have not found evidence of either benefit or harmful effect in the tested treatment and, of course, this comes as no surprise due to the premature termination.

At this level of recruitment and with a statistical power of 30%, our sample is exposed to the random effect, resulting in a lack of homogeneity in the levels of basal risk. This lack of homogeneity pre-determines that the technique can be presented as either beneficial or harmful. In fact the technique appears less beneficial in the subgroup (not predefined) of patients who died in 72 hours and these were patients with an elevated basal risk, primarily expressed through lactate levels and APACHE 2 score.

We would like to comment on a controversial issue. Three patients who had been randomized to the intervention group (20%) died in the first 72 hours and did not receive the CPFA treatment. The rapid hemodynamic deterioration of the patients did not allow the connection to the extracorporeal circuit. Undoubtedly, adequate sample size management minimized this problem, but if what we are considering is the potential harmfulness of the technique in a non-pre-specified subgroup of an underpowered sample size, we cannot ignore the fact that the technique was not applied.

CONCLUSIONS

In this paper we have presented the results of the 49 patients randomized in our trial up until the moment of closure. As a consequence of the procedure being underpowered, it was not possible to do an analysis of contrast of hypothesis and under this inconvenience, we present

the results obtained for the interest of all who are concerned about what happened in our trial. When all is taken into consideration, we have not found a difference in mortality between the two groups.

AUTHORS' CONTRIBUTIONS

CG designed the study and drafted the paper of the protocol; CP participated in the study design and helped draft the paper; FC, JMA, MG, CM, José LAP, EM, CD, MR, JLM, PJA, EMB, JC, EG, FS, MS, JT and VFG participated in the study design and reviewed critically the manuscript; AP participated in the study design, performed the statistical analysis and reviewed critically the manuscript. All the authors approved the final version of the text to be submitted for publication.

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This work was supported by Bellco, who provided all the devices and materials related to the use of CPFA for the treatment group. This entity did not play any role in study design; collection, management, analysis, and interpretation of data; writing of this report; the decision to submit this report for publication.

COMPETING INTERESTS STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The complete data that supports the findings of this study is available from Francisco Colomina-Climent. Upon reasonable request and with the permission of all the Ethics Committees who approved the study, this data may be freely accessed by the authors.

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FIGURE LEGENDS:

Figure 1: Flow chart of the clinical trial (partial results).

Figure 2: Survival analysis using the Kaplan-Meier estimator comparing both groups.

Red, intervention; Blue, control.

A, intention to treat; B, real intervention.

TABLES:

Table 1: Comparison between the intervention and the control group.

Variable	Control group n=30 n(%)/x±s	CPFA n=19 n(%)/x±s	p-value
Gender male	18(60.0)	11(57.9)	0.884
Abdominal sepsis	12(40.0)	8(42.1)	0.884
Cancer	11(36.7)	7(36.8)	0.990
Community-acquired pneumonia	5(16.7)	3(15.8)	>0.999
Nosocomial pneumonia	3(10.0)	3(15.8)	0.665
Diabetes	9(30.0)	5(26.3)	0.781
Urinary sepsis	8(26.7)	3(15.8)	0.492
APACHE II	28.9±5.6	27.0±5.1	0.244
SOFA	12.8±3.3	12.2±4.4	0.541
SAPS II	74.5±20.9	70.7±21.0	0.587
Lactate (mmol/l)	5.3±3.4	5.9±4.1	0.580
Age (years)	70.0±13.6	71.0±14.5	0.812

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; CPFA, Coupled Plasma Filtration Adsorption; n(%), absolute frequency (relative frequency); SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; x±s, mean ± standard deviation.

Table 2: Clinical relevance of the intervention (intention-to-treat) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT/NNH*	p-value
3-day mortality	1.67(0.51-5.46)	-0.67(-4.46 to 0.49)	-0.17(-0.54 to 0.20)	6 (H)	0.667
28-day mortality	1.28(0.57-2.87)	-0.28(-1.87 to 0.43)	-0.13(-0.53 to 0.28)	8 (H)	0.537
90-day mortality	0.92(0.48-1.76)	0.08(-0.76 to 0.52)	0.05(-0.35 to 0.45)	19 (T)	>0.999

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; H, Harm; NNH, Number Needed to Harm; NNH, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction; T, Treat.

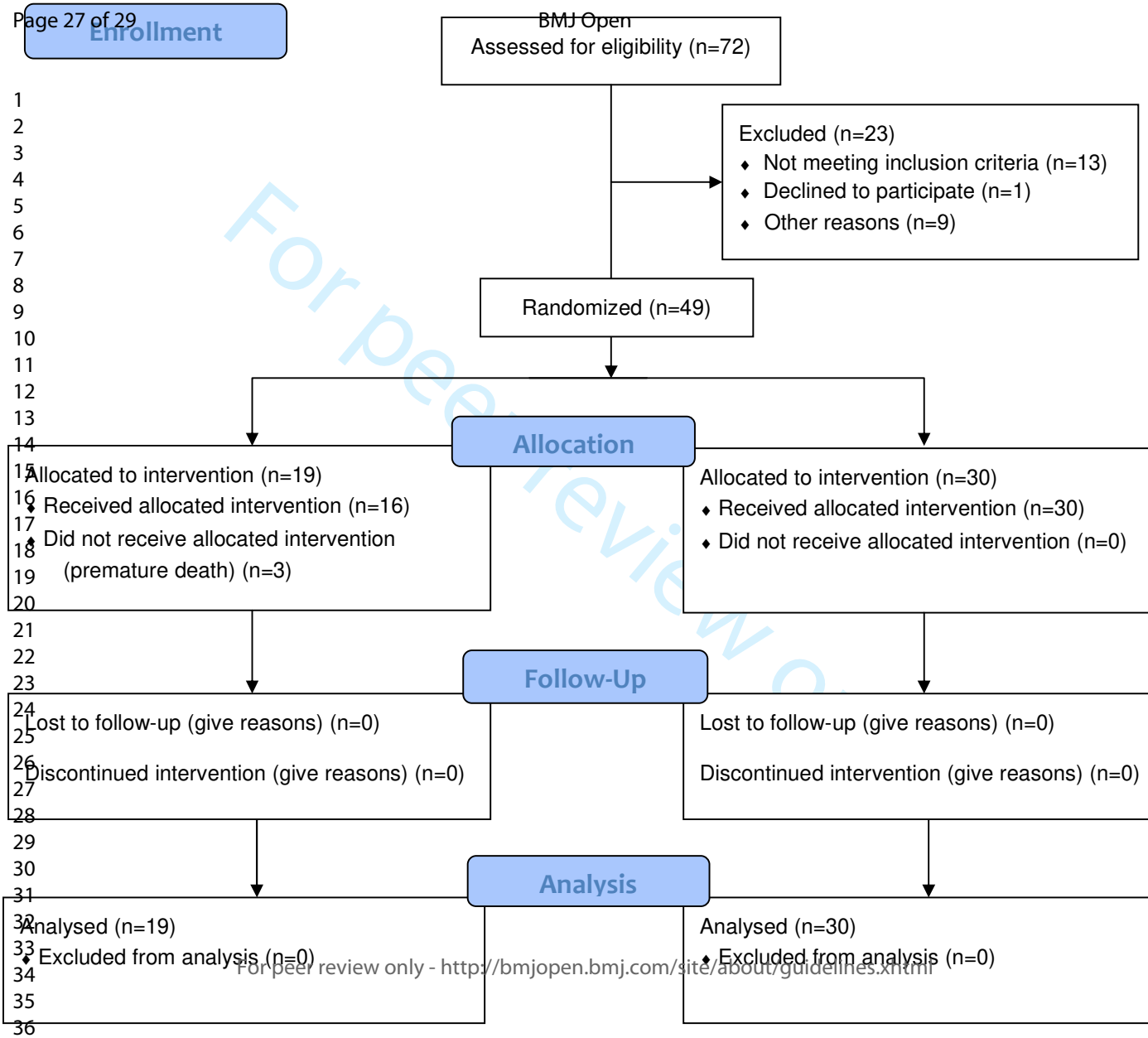
*, not possible to compute the confidence interval (division by zero).

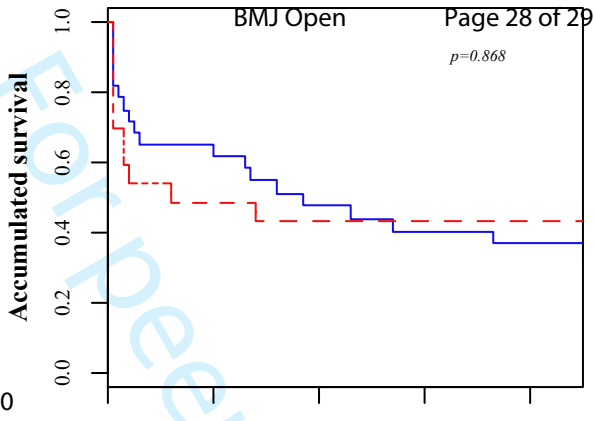
Table 3: Clinical relevance of the intervention (real group) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT *	p-value
3-day mortality	0.84(0.26-2.73)	0.16(-1.73 to 0.74)	0.06(-0.32 to 0.44)	18	>0.999
28-day mortality	0.93(0.42-2.06)	0.07(-1.06 to 0.58)	0.04(-0.37 to 0.45)	26	>0.999
90-day mortality	0.72(0.35-1.48)	0.28(-0.48 to 0.65)	0.19(-0.21 to 0.59)	6	0.417

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; NNT, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction.

*, not possible to compute the confidence interval (division by zero).





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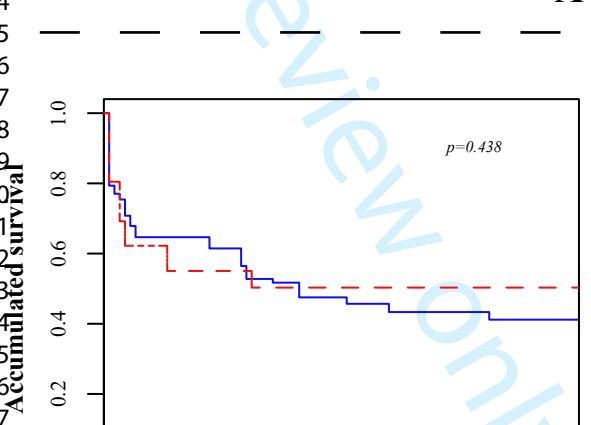

B

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7-10
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7-8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9-10
Sample size	7a	How sample size was determined	9-10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Protocol

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	6-7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	21
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-16
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.