Title: Feasibility of conservative fluid administration and deresuscitation compared with usual care in critical illness: the Role of Active Deresuscitation After Resuscitation-2 (RADAR-2) randomised clinical trial.

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Take-home message: In this randomised clinical trial which included 180 mechanically ventilated adult patients, a strategy of conservative fluid administration and deresuscitation was feasible and reduced fluid balance compared with usual care.

Tweet: RADAR-2 trial: conservative fluid management and deresuscitation trial feasible and reduces fluid balance. Larger trials needed!

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Abstract

Purpose. Fluid overload is common in critical illness and is associated with mortality. This study investigated the feasibility of a randomised trial comparing conservative fluid administration and

deresuscitation (active removal of accumulated fluid using diuretics or ultrafiltration) with usual care in critical illness.

Methods. Open-label, parallel-group, allocation-concealed randomised clinical feasibility trial. Mechanically ventilated adult patients expected to require critical care beyond the next calendar day were enrolled between 24 and 48 hours following ICU admission. Patients were randomised to either a 2-stage fluid strategy comprising conservative fluid administration and, if fluid overload was present, active deresuscitation; or usual care. The primary endpoint was fluid balance in the 24 hours up to the start of study day 3. Secondary endpoints included cumulative fluid balance; mortality; and duration of mechanical ventilation.

Results. 180 patients were randomised. After withdrawal of 1 patient, 89 patients assigned to the intervention were compared with 90 patients assigned to the usual care group. The mean (SD) 24-hour fluid balance up to study day 3 was lower in the intervention group (-840 ± 1746 mL) than the usual care group (+130 ± 1401 ml; p<0.01). Cumulative fluid balance was lower in the intervention group at days 3 and 5. Overall, clinical outcomes did not differ significantly between the two groups, although the point estimate for 30-day mortality favoured the usual care group (intervention arm: 19 of 90 (21.6%) versus usual care: 14 of 89 (15.6%), P=0.32). Baseline imbalances between groups and lack of statistical power limit interpretation of clinical outcomes.

Conclusions. A strategy of conservative fluid administration and active deresuscitation is feasible, reduces fluid balance compared with usual care, and may cause benefit or harm. In view of wide variations in contemporary clincal practice, large, adequately powered trials investigating the clinical effectiveness of conservative fluid strategies in critically ill patients are warranted.

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Declarations

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Introduction

Intravenous fluid therapy is a a ubiquitous element of critical care practice. Intravenous fluids are often given in large volumes for resuscitation of a critically ill patient, with the aim of improving cardiac output and ameliorating shock [1]. In addition, intravenous fluids are also used in the care of these patients to maintain hydration, correct electrolyte abnormalities, and as a solvent for intravenous medications. In the setting of reduced fluid excretion due to renal and endocrine factors [2-5], accumulation of a positive fluid balance is typical.

Observational studies consistently demonstrate a dose-dependent relationship between a positive fluid balance and adverse outcomes, including mortality and increased duration of mechanical ventilation[6-9]. No safe threshold for fluid accumulation has ever been identified. The term 'fluid overload', although poorly defined, is often taken to imply clinically apparent peripheral or pulmonary oedema, typically in the setting of documented positive cumulative fluid balance.

Two main strategies have evolved to address the issue of fluid overload. A restrictive approach to fluid resuscitation has been investigated in pilot trials, which have demonstrated the safety of this strategy and suggest an association with improved clinical outcomes [10, 11]. Even if shown to be effective in adequately powered clinical trials, however, it is unlikely that such approaches will be sufficient to prevent the occurrence of fluid overload, given the much greater contribution of other sources of fluid intake such as drug diluents and nutrition [9, 12, 13].

Deresuscitation refers to the active removal of accumulated fluid using diuretics or ultrafiltration. Although the strategy is commonly used, indications, approaches, and end-points have yet to be identified or widely accepted [14]. In a systematic review and meta-analysis, conservative fluid or deresuscitative strategies resulted in shorter duration of mechanical ventilation and ICU stay compared with liberal fluid administration or usual care in patients who were beyond the early resuscitation phase of critical illness [15]. However, interpretation was limited by clinical heterogeneity. Furthermore, in a post-hoc analysis of a small subset of patients from the landmark Fluids and Catheter Treatment Trial [16], conservative fluid management strategy was associated with cognitive dysfunction at 12 months [17]. Overall, therefore, the benefits and harms of conservative fluid administration and deresuscitation are uncertain.

The objectives of this pilot randomised clinical trial were to investigate the feasibility, safety, and clinical outcomes of a strategy of conservative fluid administration and targeted deresuscitation compared with usual care in critically ill adult patients.

Methods

Trial design

The Role of Active Deresuscitation After Resuscitation-2 (RADAR-2) trial was an open-label, parallel-group, allocation-concealed randomised pilot trial comparing a strategy of conservative fluid administration and active deresuscitation with usual care in critically ill adults. Study allocation was unblinded due to the nature of the intervention. The study protocol and statistical analysis plan were published prior to data analysis [18] and the study was prospectively registered (ClinicalTrials.gov, NCT03512392). Ethical approval for the study was provided by the Office of Research Ethics Committees Northern Ireland, and written approval for enrolment was obtained from patient representatives. The study was overseen by a Data Monitoring and Ethics Committee (DMEC). The study was conducted in accordance with Good Clinical Practice guidelines, local regulations, and the ethical principles described in the Declaration of Helsinki.

Patients

Patients were eligible for enrolment if they were receiving invasive mechanical ventilation, were between 24 and 48 hours from ICU admission, and were deemed likely to require treatment in an ICU beyond the next calendar day.

Exclusion criteria included active treatment for diabetic ketoacidosis, hyperosmolar hyperglycaemic state, non-traumatic subarachnoid haemorrhage, acute cardiac failure, cardiogenic shock, end-stage renal failure, or diabetes insipidus. The full list of reasons for exclusion are detailed in the trial protocol (appendix 1).

Patients were randomly assigned in a 1:1 ratio in random permuted blocks of 4 or 6 and stratified by site, using an online randomisation tool (www.sealedenvelope.com). Clinicians and study personnel were aware of group assignment from randomisation.

Fluid management in intervention group

Patients allocated to the intervention group received a 2-stage fluid strategy (Figure E1). From randomisation until study day 5, maintenance intravenous fluids were discontinued, and clinical teams were requested not to administer intravenous fluids unless required for suspected blood or other overt fluid loss. Intravenous fluid for cardiovascular instability where alternative therapies had failed or were contraindicated, or for electrolyte abnormalities, was permitted. Medications were reviewed and administered in the minimum volumes permitted according to local guidelines. Nutrition was administered according to clinician direction and unit guidelines.

The second stage of the intervention consisted of a daily review of eligibility for deresuscitation between study days 2 and 5. Patients were eligible for deresuscitation if they had acquired a cumulative fluid balance greater than 2000 mL from ICU admission; or had clinical evidence of oedema in at least 2 areas (lung, flanks, upper or lower limbs), and had no contraindications. Contraindications to deresuscitation were: (a) norepinephrine or epinephrine at a dose greater than 0.2 mcg/kg/min, (b) more than 1 vasopressor agent in use, (c) serum lactate > 3.5 mmol/L, (d) uncorrected serum potassium <3.0 mmol/L, or (e) serum sodium <130 mmol/L or > 150 mmol/L.

On each study day that patients met eligibility criteria for deresuscitation, combination diuretic therapy was prescribed, consisting of intravenous Furosemide with adjunctive Indapamide 5mg enterally and Spironolactone 100mg enterally. Furosemide was administered as a 0.5mg/kg bolus dose (maximum 40mg) followed by infusion at 2.5-20 mg/hour and titrated with the aim of achieving a negative daily fluid balance of between 1000 and 3000 mL/day (Figure E1). For patients receiving renal replacement therapy (RRT), diuretics were not given, and ultrafiltration was adjusted to achieve the same fluid balance target. If the fluid balance target was not achieved despite the maximum protocol-specified dose of diuretics, advice was given to commence RRT, however this decision was at the discretion of the treating clinician.

The intervention was discontinued on study day 5 or on discharge from critical care, death or discontinuation of active treatment, or withdrawal of consent.

Fluid management in comparator group

Patients randomised to usual care received fluids, diuretics and ultrafiltration at the discretion of the treating clinical team according to usual practices.

Data collection

Patients were followed daily by the study team until day 5, and at 28 and 180 days following randomisation. Demographic, physiological, and clinical data were obtained from patient records.

Process outcomes

The primary outcome was the feasibility of achieving a separation between groups in fluid balance for the 24-hour period from the beginning of study day 2 to the beginning of study day 3. Secondary process outcomes included separation in cumulative fluid balance from ICU admission until the beginning of study days 3 and day 5, recruitment rates, and incidence of protocol deviations.

Safety outcomes
Safety outcomes included the incidence of serious and non-serious adverse events.

Clinical outcomes
Clinical outcomes included mortality at 28 and 180 days, duration of mechanical ventilation and ICU stay; and incidence of new acute kidney injury. Acute kidney injury was defined in two ways: KDIGO Stage 3 by creatinine criteria (uncorrected), and KDIGO stage 3 by creatinine criteria after correction for fluid balance, using a standard formula [19] (corrected).

Patients were contacted by telephone at or as close as possible to 180 days and asked to complete a series of questionnaires evaluating cognitive function (Montreal Cognitive Assessment-BLIND) [20], quality of life (ED-5Q-5L) [21], symptoms of anxiety and depression (Hospital Anxiety and Depression scale) [22], and post-traumatic stress disorder (Impact of Events Scale-Revised) [23]. The interviewer was blinded to group assignment.

Exploratory outcomes
Near-infra red spectroscopy was used to measure cerebral and quadriceps muscle oximetry for up to 72 hours in a subset of participants in two study centres. Other exploratory outcomes listed in the protocol (appendix 1) will be reported in a separate manuscript.

Statistical analysis
Based on an expected fluid balance in the usual care group of 494 +/- 1512 mL, a sample size of 174 patients (87 in each group) was calculated to have 90% power at a two-tailed significance level of 0.05 to detect a difference in fluid balance of 750 mL over 24 hours. The sample size was increased to 180 patients (90 per group) to allow for a drop-out rate of 3%.

For continuous variables including the primary outcome, between-group comparisons were made using independent samples t-tests or non-parametric alternatives. Categorical variables were compared using Chi-squared tests or Fisher's exact tests. Overall survival was evaluated using both Cox PH models and residual mean survival time methods. The Aalen-Johansen method was used to analyse competing risks data on ICU discharge and MV liberation. Equality of hazards was tested using log-rank tests and a Cox proportional hazard model. Repeated measures ANOVA was used to analyse serial measures over time for continuous variables.

The primary analyses were carried out on an intention-to-treat basis, with a P value of 0.05 considered to indicate significance. A single analysis was carried out at the end of the trial with no interim analyses, using 'R' software (version 3.6.2, R foundation for statistical computing, Vienna, Austria).

Additional analyses
Two pre-planned per-protocol analyses were performed, the first excluding patients in the intervention group who did not receive the intravenous infusion of Furosemide on at least 50% of the days on which they were eligible and in the second, including only patients in the intervention group who met the target of 1000 to 3000 mL negative fluid balance, and excluding patients in the usual care group who received diuretics. Multiple regression analyses were undertaken for clinical

outcomes of 28-day mortality, duration of mechanical ventilation in survivors, and duration of ICU stay in survivors, with group assignment as the main exposure and covariates selected on the basis of clinical plausibility.

Pre-planned analyses were performed for clinical subgroups: patients with acute respiratory distress syndrome (ARDS) and sepsis. Planned subgroup analysis for patients with traumatic brain injury was omitted due to the small number of such patients enrolled. Subgroup analyses according to inflammatory phenotype were also omitted due to the low number of patients with a hyperinflammatory phenotype.

All analyses were performed by the study statistician according to the predefined statistical analysis plan (appendix 2).

Results

Patients

From April 2018 to January 2020, 1068 patients were screened in 8 participating centres. The main reasons for exclusion were cardiac failure, expectation of poor outcome, lack of clinician equipoise, and refusal of consent. Consent was declined in 90 of 272 patients approached (33.1%). Of 180 patients randomised, 90 were assigned to conservative fluid and deresuscitation, and 90 were assigned to usual care (Figure 1). One patient was withdrawn from the study at the request of their legal representative prior to receiving the intervention, leaving 179 patients for the primary analysis.

Baseline characteristics of the cohort are shown in Table 1. There were baseline differences between groups: patients in the intervention group were more likely to have ARDS and were more likely to be receiving vasopressors and RRT.

Fluid balance outcomes

For the primary outcome of fluid balance for the 24-hour period from the beginning of study day 2 to the beginning of study day 3, patients in the intervention group had a significantly lower fluid balance than those in the usual care group (mean -840 mL (SD 1756mL) versus +130 mL (SD 1401 mL), P<0.001).

Cumulative fluid balance was significantly lower in the intervention group than the usual care group on days 3 and 5 (Table 2 and Table E1-E2). Daily fluid balance and cumulative fluid balance over time are shown in Figure 2. Patients in the intervention group received less bolus and maintenance intravenous fluid, and had higher mean daily urine and RRT output (Figure 3, Tables E3-E4). In a post-hoc analysis of patients on RRT, fluid balances were higher in both arms, although the magnitude of separation was greater than those not on RRT (Table E5).

Process outcomes

Patients in the intervention group met criteria for deresuscitation in 183 of 260 possible study days (oedema in more than one body site, N=156; or cumulative fluid balance >2000mL, N=130). RRT was commenced at the discretion of the clinical team and in no patients was RRT advised per protocol for diuretic unresponsiveness. In 24 patients the intervention was not administered by the treating clinical team on one or more days and in a further 5 patients the intervention was administered incorrectly (Table E6). Furthermore, 30 of 90 patients (33.3%) in the usual care group received diuretics during the study period.

Safety outcomes

Rates of serious adverse events did not differ between groups (6 of 89 patients (6.7%) in the intervention arm compared with 5 of 90 patients (5.6%) receiving usual care, P=0.78, Table 2). Non-

serious adverse events were reported in 31 patients (34.4%) in the intervention group and 17 patients (18.9%) in the usual care group (P=0.03) (Tables 2 and E7). Metabolic alkalosis, defined as serum bicarbonate >35 mmol/L and serum pH>7.5, was more common in the intervention group (9 of 89 versus 0 of 90 patients, P<0.01). The two most frequent adverse events, metabolic alkalosis and hypernatraemia, were not reported in patients receiving RRT.

Clinical outcomes

For the overall cohort, there were no significant differences in mortality at 28 or 180 days, length of ICU stay, or duration of mechanical ventilation between intervention and usual care groups (Tables 2, E8 and E9, Figures E2-E4). Neither trajectories in overall SOFA scores nor individual organ components of the SOFA score from baseline to day 3 or 5 were different between intervention and usual care groups (Table 2). Incidence of new acute kidney injury requiring RRT did not differ between groups. In the 40 patients who underwent telephone follow-up, there was no difference in the incidence of cognitive dysfunction between intervention and usual care groups at 180 days.

Exploratory outcomes

There were no significant differences in cerebral or muscle oximetry measurements between groups (Table E10). Other exploratory outcomes will be reported in a separate manuscript.

Sepsis subgroup

In the subgroup of patients with sepsis (N=72), severity of illness and use of vasopressors and RRT were greater at baseline in patients in the intervention arm than the usual care arm (Table E11). Mortality at 28 days was higher in the intervention group (14 of 40 patients, 35%) than the usual care group (4 of 32 patients, 12.5%), P=0.03 (Figure E5), however no significant differences in other clinical outcomes were present between treatment arms (Table E12). A statistically significant interaction between sepsis subgroup and treatment arm was not present (P=0.25).

ARDS subgroup

In the subgroup of patients with ARDS (N=30), there were no differences in 30-day mortality or other clinical outcomes between intervention and usual care arms (Table E13).

Additional analyses

After adjustment for baseline variables, treatment group assignment was not significantly associated with 28-day mortality, duration of mechanical ventilation for survivors, or duration of ICU stay for survivors (Table E14).

A pre-planned per-protocol analysis was undertaken where 12 patients in the intervention group who did not receive the protocol-directed deresuscitation intervention on at least 50% of days were excluded. These results were consistent with the primary analysis (Table E15). In a second per-protocol analysis (N=92), patients from the intervention group were included only if the target negative fluid balance of 1000-3000 mL was achieved, and patients in the usual care group who received diuretics were excluded. Results from this analysis were again similar to those in the primary intention-to-treat analysis (Table E16).

Discussion

In this open-label randomised clinical trial of critically ill adult patients, a strategy of conservative fluid administration and active deresuscitation using combination diuretic therapy or ultrafiltration to reduce fluid overload was feasible and reduced fluid accumulation compared to usual care.

Fluid management strategies in critically ill patients have been the subject of considerable discussion in recent years. The association between both the volume of fluid administered and accumulation of a positive fluid balance with adverse outcomes is well-recognised [6, 7]. Deresuscitation is widely practiced in an attempt to mitigate this potential harm [14]. However, although several randomised trials have investigated restrictive fluid resuscitation [11, 24-26], an approach which shows considerable promise, this is one of the first randomised trials to investigate an active deresuscitation fluid strategy in a broad cohort of critically ill patients.

The Fluids and Catheter Treatment Trial [16] randomised patients with ARDS to a conservative fluid group which achieved a near-neutral fluid balance at the end of the 7-day intervention period or a liberal fluid group who accumulated a 7 litre positive fluid balance, and reported more ventilator-free and ICU-free days among patients in the conservative fluid arm. However, both conservative and liberal fluid strategies relied on static measures of intravascular filling to guide treatment and were not targeted at clinically evident fluid overload or a positive fluid balance.

The RADAR-2 study was designed to enrol patients whose initial fluid resuscitation was already complete. While no specific parameters were mandated to define fluid repletion, and occult hypovolaemia during the intervention could not be entirely excluded, clinicians were able to administer intravenous fluid boluses or withhold deresuscitation as directed by clinical judgment if there was evidence of hypoperfusion, increasing vasopressor support, or hypotension. The first stage of the intervention was intended to limit the accumulation of fluid from maintenance fluid administration and ongoing fluid bolus administration beyond the point where fluid responsiveness was unlikely to be present [27]. The second, active deresuscitation, phase was designed only to be initiated when fluid overload was present and hemodynamic stability had been attained, and was subject to daily review. The study was powered to detect a difference of 750mL between groups for the primary outcome, based on extrapolation of existing evidence and accepted practice [14, 15, 28]. Furosemide is the most widely used diuretic in critically ill patients and was the main element of the deresuscitation strategy, while indapamide and spironolactone were used to provide 'sequential nephron blockade' and thus to increase natiuresis and diuresis while minimising the side effects of any single agent [29, 30]. The primary endpoint of 24-hour fluid balance from the beginning of study day 2 to the beginning of study day 3 was designed to test the feasibility of separating fluid balance early in the ICU stay, at a timepoint at which fluid balance is strongly associated with mortality [9].

We demonstrated that minimizing fluid balance once hemodynamic stability had been achieved was feasible. Although lower volumes of intravenous bolus and maintenance fluid were administered in the intervention group, the difference in fluid balance between arms was mediated primarily by greater diuresis or ultrafiltration, as expected. Potential side effects of diuretic drugs include hypovolaemia, electrolyte abnormalities such as dysnatraemias and hypokalaemia, and metabolic alkalosis. There was no evidence of renal or cardiovascular compromise with deresuscitation, and rates of serious adverse events were similar between groups, although non-serious adverse events, particularly metabolic alkalosis, were more frequent in the intervention group. Alternative diuretic combinations to minimise metabolic alkalosis could be considered in future trials. Overall there was no evidence of clinical benefit from the intervention, albeit the study was underpowered for clinical outcomes, magnifying the effect of baseline imbalances.

In patients with sepsis, the intervention strategy was associated with increased mortality. This finding should be interpreted with caution in the context of the small sample size and baseline imbalances between groups, with greater severity of illness and organ support requirements for patients in the intervention group. Unfortunately the small number of patients in this group precluded meaningful adjustment for severity of illness. Trends in other clinical outcomes including duration of ICU stay in survivors, duration of mechanical ventilation, and change in SOFA scores, were not consistent with

this finding. The mortality rate in the intervention group is similar to that in other recent sepsis trials [31, 32], while that in the standard care group is unexpectedly low. Furthermore, other recent trials in critically ill patients have suggested comparable or better outcomes resulting from restrictive fluid strategies [11, 25, 33]. The likelihood that this finding represents a type 1 error is therefore high. Nevertheless, the possibility of harm from a deresuscitative fluid strategy in patients with sepsis must be considered, and this finding should be considered carefully when future trials of fluid management strategies are contemplated. This finding also highlights the broader possibility that subgroups of critically ill patients may respond differently to alternative fluid management strategies, whether defined by biological phenotype [34] or by more clinically defined subpopulations (medical, post-operative, neurosurgical) for which benefits and risks may vary.

Limitations

This study has a number of important limitations. First, this study was designed to assess feasibility, and is underpowered to detect differences in clinical outcomes. The results are consistent with clinically important benefit or harm, and larger trials are needed to ascertain the effects of fluid strategies on clinical outcomes. Secondly, despite randomisation, imbalances in measured baseline characteristics were present between usual care and intervention groups, with a greater requirement for supportive measures in the intervention arm. Further baseline differences in unmeasured characteristics such as sedation use, which may impact on cardiovascular stability, cannot be excluded. Thirdly, eligibility criteria for deresuscitation were broad, and based on parameters (recorded fluid balance from ICU admission and clinician-defined pitting oedema) which, despite face validity, are imprecise measures of volume status. It may be that patients with greater or lesser degrees of fluid accumulation would be more likely to benefit from deresuscitation, although this remains uncertain. Fourthly, failure to comply with the protocolised intervention was common due to lack of clinician equipoise. Finally, in keeping with most clinical trials, only a small proportion (16.8%) of patients meeting inclusion criteria were randomised, limiting external validity.

Conclusions

In critically ill adult patients, conservative fluid administration and deresuscitation using combination diuretic therapy or ultrafiltration to minimise fluid overload is feasible. Given the wide variability in practice, and widespread use of deresuscitation in contemporary practice, large randomised trials, powered to detect differences in patient-centred outcomes, are warranted to determine the clinical effectiveness of conservative fluid administration and deresuscitation, and should consider the possibility of a differential effect on patients with and without sepsis.

Table 1. Baseline patient characteristics.

Characteristics		Intervention (N=89)	Usual care (N=90)
Age, Mean (SD), y		57.0 (17.2)	57.1 (16.9)
Sex, N (%)	Female	34 (38.2)	31 (34.4)
	Male	55 (61.8)	59 (65.6)
Type of Admission, N (%)	Elective	3 (3.4)	4 (4.44)
	Emergency	86 (96.6)	86 (95.6)
Primary Diagnosis, N (%)	Cardiovascular	12 (13.5)	8 (8.9)
	Gastrointestinal	25 (28.1)	13 (14.4)
	Neurological	15 (16.9)	21 (23.3)
	Respiratory	17 (19.1)	21 (23.3)
	Other	20 (22.5)	27 (30.1)
Operative Status, N (%)	Non-operative	57 (64.0)	64 (71.1)
	Operative	32 (36.0)	26 (28.9)
ARDS, N (%)		19 (21.4)	11 (12.2)
Sepsis, N (%)		40 (45.0)	32 (35.6)
Traumatic Brain Injury, N (%)		2 (2.3)	7 (7.8)
APACHE II Score, Mean (SD)		17.5 (6.9)	16.8 (6.40)
Baseline SOFA Score, Mean (SD)		8.4 (3.3)	7.7 (2.9)
KDIGO Stage, N (%)	0	45 (50.6)	48 (53.3)
	1	14 (15.7)	16 (17.8)
	2	8 (9.0)	11 (12.2)
	3	22 (24.7)	15 (16.7)
Vasopressors, N (%)		50 (56.2)	41 (45.6)
Serum Lactate, Mean (SD), mmol/L		1.2 (1.3)	1.2 (0.6)
Renal Replacement Therapy, N (%)		15 (16.9)	6 (6.7)
PaO_2 / FiO_2 ratio, Mean (SD), mmHg		255 (93)	269 (105)
Pitting Oedema > 1 Site, N (%)		51 (57.3)	39 (43.3)
Cumulative Fluid Balance at randomisation (mL) Mean (SD) Median (IQR)		 +2779 (2262) +2241 (+1290,+3865)	 +2430 (2282) +2166 (+960, +3811)

Table 2. Outcomes.

	Intervention (N=89)	Usual care (N=90)	P
Fluid balance from beginning of study day 2 to beginning of study day 3: Mean (SD) Median (IQR)	 -840 (1756) -836 (-2168, +524)	 +130 (1401) +24 (-636, +971)	 <0.01*
Cumulative fluid balance at Day 3: Mean (SD) Median (IQR)	 +2099 (3333) +1880 (+66, +3538)	 +2967 (3527) +2620 (+708, +4738)	 0.04*
Cumulative fluid balance at Day 5: Mean (SD) Median (IQR)	 +397 (4173) +288 (-2106, +2320)	 +3692 (4415) +3082 (+751, +5778)	 <0.01*
Cumulative fluid balance at ICU discharge: Mean (SD) Median (IQR)	 -465 (6527) -921 (3930, 1715)	 +1179 (6626) +498 (-2627, 4284)	 0.07
Serious adverse events, N (%)	6 (6.7)	5 (5.6)	0.78
Adverse events, number of patients (%) Adverse events, number of events Hypernatraemia# Metabolic alkalosis^ Other	31 (34.4) 39 13 9 17	17 (18.9) 22 8 0 14	0.03
Change in SOFA score from baseline to day 3, mean (SD)	-1.3 (2.9)	-1.4 (2.7)	0.45
Change in SOFA score from baseline to day 5, mean (SD)	-2.7 (3.3)	-2.2 (3.1)	0.25
Change in SOFA subscores from baseline to day 5: SOFA-Respiratory, mean (SD) SOFA-Cardiovascular, mean (SD) SOFA-Renal, mean (SD)	 -0.01 (0.9) -1.49 (2.0) -0.26 (0.7)	 -0.01 (1.0) -1.11 (1.7) 0.22 (0.8)	 0.84 0.13 0.82
Death within 28 days, N (%)	19 (21.4)	14 (15.6)	0.32
Death within 180 days, N (%), N=176	25 (54.4)	21 (52.5)	0.86
Ventilator-free days (of 28)+, mean (SD)	16.6 (11.1)4.0 (7.0)	17.9 (10.5)	0.68
Duration of mechanical ventilation in survivors (n=145), median (IQR)	4 (2, 9.3)	3 (2, 9)	-
ICU-free days (of 28)+, mean (SD)	13.8 (10.1)6.0 (10.0)	14.9 (9.9)	0.43

Duration of ICU stay in survivors (n=145), median (IQR)	8 (5, 13)	7 (4, 12.5)	-
New acute kidney injury (uncorrected), N (%)	4 (4.5)	5 (5.6)	0.75
New acute kidney injury (corrected for changes in fluid balance), N (%)	3 (3.4)	5 (5.6)	0.48
New or worsening acute kidney injury~, N (%)	14 (15.7)	12 (13.3)	0.65
Cognitive dysfunction at 180 days, N (%), N=40	7 (33.3)	9 (47.4)	0.37
ED-5Q-5L score, mean (SD), N=38	0.6 (0.3)	0.5 (0.4)	0.83
ED-5Q-5L visual analogue score, mean (SD), N=38	61.0 (22.6)	55.3 (32.4)	0.78
Anxiety, N (%), N=34	4 (22.2)	7 (46.7)	0.14
Depression, N (%), N=37	2 (10.0)	8 (50.0)	<0.01
Post-traumatic stress disorder, N (%), N=35	11 (57.9)	9 (60.0)	0.90

*Kruskal-Wallis rank sum test #Hypernatraemia defined as serum sodium >150 mmol/L, protocol-mandated suspension of intervention. ^Metabolic alkalosis defined as pH>7.5 and Bicarbonate >35mmol/L, protocol-mandated suspension of intervention. ~Post-hoc analysis. [+]Post-hoc analyses in place of planned analyses using 'duration of mechanical ventilation in survivors' and 'duration of ICU stay in survivors'.

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