Clinical trial results:
Forced fluid removal vs. usual care in intensive care patients with high-risk acute kidney injury and severe fluid overload (FFAKI) – A randomized clinical trial

Summary

EudraCT number	2015-001701-13
Trial protocol	DK
Global end of trial date	15 August 2017

Results information

Result version number	v1 (current)
This version publication date	13 May 2018
First version publication date	13 May 2018

Trial information

Trial identification

Sponsor protocol code	FFAKI

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02458157
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nordsjællands Hospital. Dept. of Anaesthesiology and Intensive Care.
Sponsor organisation address	Dyrehavevej 29, Hillerød, Denmark, 3400
Public contact	Dept. of Anaesthesiology, Nordsjællands Hospital, +45 48294829,
Scientific contact	Dept. of Anaesthesiology, Nordsjællands Hospital, +45 48294829,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2017
Global end of trial reached?	Yes
Global end of trial date	15 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this pilot trial was to assess the feasibility of forced fluid removal in high-risk AKI patients with severe fluid overload. Fluid removal was done with furosemide and/or continuous renal replacement therapy aiming at net negative fluid balance > 1 ml/kg ideal body weight/hour until cumulative fluid balance calculated from ICU admission reached less than 1000 ml.

The intervention was compared to standard of care as reflected in the KDIGO guidelines.

Protection of trial subjects:

Patients included in the trial was admitted to the ICU and received all relevant critical care, no other measures were implemented to protect patients during the trial.

Background therapy:

The management of AKI is complex with multiple interventions. These interventions must be provided equally and according to the KDIGO guidelines in both interventions arms. The KDIGO recommendations consist of maintenance of adequate renal perfusion pressure (MAP > 65) through crystalloid fluids and vasopressor use, avoidance of hyperglycaemia, reduction and/or avoidance of further harm by nephrotoxic antibiotics and avoidance of contrast media unless absolutely indicated.

Severe sepsis and septic shock is a frequently associated with AKI, and the management of sepsis should be performed according to the SSC-guidelines [23] in both intervention arms.
Overt fluid losses (e.g. bleeding, diarrhoea, ascites and pulmonary effusion) may be substituted in both intervention arms.

Evidence for comparator:

The primary outcome of the FFAKI trial was cumulative fluid balance 5 days after ramdomisation. This comparator was chosen to reflect both the efficacy of the trial treatment (forced fluid removal) and protocol adherence, since failure of either of these would likely result in failure to remove fluids from the patients and lack of difference in the main outcome.

Actual start date of recruitment	01 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4
From 65 to 84 years	18
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were recruited for the trial in three different Danish ICU's. Nordsjællands Hospital, Rigshospitalet and Aalborg Universitets Hospital. Screening began on October 10th 2015 and the trial was terminated for futility because of very low recruitment rates on June 8th 2017

Pre-assignment

Screening details:

We screened patients for the development of fluid overload during the first 5 days of admission to the ICU and used peak serum creatinine from time of ICU admission ± 24 hours and urine output from the first full ICU-day to determine presence of acute kidney injury and calculate renal recovery score.

Period 1

Period 1 title	Inclusion and randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Forced fluid removal

Arm description:

The eksperimental treatment arm. Patients were allocated to forced fluid removal targeted at a negative fluid balance of at least 1 ml/kg/h using furosemide or CRRT

Arm type	Experimental
Investigational medicinal product name	Furosemide
Investigational medicinal product code	C 03 CA 01
Other name	Furix
Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Furosemide infusion
- Contraindications: anuria, allergy to sulphonamides or furosemide, hepatic coma or pregnancy
- Dose: 40 mg I.V. bolus followed by continuous infusion titrated to achieve the therapeutic goal with a maximum infusion rate of 40 mg/h
- Furosemide is used according to the indication and dosing described in the SmPC. No modification will be made to the packaging or labelling and no placebo will be used in the trial. The preparation of furosemide to be used as a trial drug will be double controlled.
- Start time, end time, hourly infusion rate and any bolus dose of furosemide is registered in the source-data (ICU-observation charts) and will be transferred to the CRF.
- The electronic medicine module EPM will be used to register furosemide used in the trial.

Arm title	Standard Care

Arm description:

Control group recieving standard care.
Renal replacement therapy:
- Supportive therapy with RRT is indicated when life-threatening complications in fluid, electrolyte and acid-base balance occur:
- Hyperkalaemia (p-K+ > 6 mmol/l)
- Severe metabolic acidosis attributable to AKI (pH < 7.25 and SBE < -10 mmol/l) resistant to IV bicarbonate infusion
- Severe respiratory failure with PaO2/FiO2 < 13 kPa and bilateral infiltrates/oedema on the chest x-ray.
- Aside from these absolute indications, RRT may be provided in case of progressive azotaemia and plasma BUN > 25 mmol/l.

Fluid therapy:
Fluid administration at the discretion of the treating clinicians, using hemodynamic goal of choice

Fluid removal:
Pharmacological fluid removal (furosemide) will be done at the discretion of the treating clinicians.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Forced fluid removal	Standard Care
Started	9	14
Completed	7	13
Not completed	2	1
Violation of exclusion criteria	1	-
Violation of inclusion criteria	1	-
Patient discharged within 1 hour of inclusion	-	1

Period 2	
Period 2 title	Intervention
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Forced fluid removal

Arm description:

The eksperimental treatment arm. Patients were allocated to forced fluid removal targeted at a negative fluid balance of at least 1 ml/kg/h using furosemide or CRRT

Arm type	Experimental
Investigational medicinal product name	Furosemide
Investigational medicinal product code	C 03 CA 01
Other name	Furix
Pharmaceutical forms	Solution for injection, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Furosemide infusion
- Contraindications: anuria, allergy to sulphonamides or furosemide, hepatic coma or pregnancy
- Dose: 40 mg I.V. bolus followed by continuous infusion titrated to achieve the therapeutic goal with a maximum infusion rate of 40 mg/h
- Furosemide is used according to the indication and dosing described in the SmPC. No modification will be made to the packaging or labelling and no placebo will be used in the trial. The preparation of furosemide to be used as a trial drug will be double controlled.
- Start time, end time, hourly infusion rate and any bolus dose of furosemide is registered in the source-data (ICU-observation charts) and will be transferred to the CRF.
- The electronic medicine module EPM will be used to register furosemide used in the trial.

Arm title	Standard Care

Arm description:

Control group recieving standard care.
Renal replacement therapy:
- Supportive therapy with RRT is indicated when life-threatening complications in fluid, electrolyte and acid-base balance occur:
- Hyperkalaemia (p-K+ > 6 mmol/l)
- Severe metabolic acidosis attributable to AKI (pH < 7.25 and SBE < -10 mmol/l) resistant to IV bicarbonate infusion
- Severe respiratory failure with PaO2/FiO2 < 13 kPa and bilateral infiltrates/oedema on the chest x-ray.
- Aside from these absolute indications, RRT may be provided in case of progressive azotaemia and plasma BUN > 25 mmol/l.

Fluid therapy:
Fluid administration at the discretion of the treating clinicians, using hemodynamic goal of choice

Fluid removal:
Pharmacological fluid removal (furosemide) at the discretion of the treating clinicians.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Three patients were withdrawn from the trial without receiving the allocated intervention. The reasons for withdrawal was: Violation of inclusion criteria, violation of exclusion criteria and the last patient was discharged within one our from randomization and treated as a failed inclusion. No data were collected from these patients and they were not included in baseline characteristics.
To illustrate this the trial has been divided into two periods with period 2 as baseline period.

Number of subjects in period 2[2]	Forced fluid removal	Standard Care
Started	7	13
Completed	7	13

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Three patients were withdrawn from the trial without receiving the allocated intervention. No data were collected from these patients and they did not contribute to baseline characteristics

Baseline characteristics

Reporting groups	
Reporting group title	Forced fluid removal
Reporting group description:	
The eksperimental treatment arm. Patients were allocated to forced fluid removal targeted at a negative fluid balance of at least 1 ml/kg/h using furosemide or CRRT	
Reporting group title	Standard Care
Reporting group description:	
Control group recieving standard care. Renal replacement therapy: - Supportive therapy with RRT is indicated when life-threatening complications in fluid, electrolyte and acid-base balance occur: - Hyperkalaemia (p-K+ > 6 mmol/l) - Severe metabolic acidosis attributable to AKI (pH < 7.25 and SBE < -10 mmol/l) resistant to IV bicarbonate infusion - Severe respiratory failure with PaO2/FiO2 < 13 kPa and bilateral infiltrates/oedema on the chest x-ray. - Aside from these absolute indications, RRT may be provided in case of progressive azotaemia and plasma BUN > 25 mmol/l. Fluid therapy: Fluid administration at the discretion of the treating clinicians, using hemodynamic goal of choice Fluid removal: Pharmacological fluid removal (furosemide) at the discretion of the treating clinicians.	

Reporting group values	Forced fluid removal	Standard Care	Total
Number of subjects	7	13	20
Age categorical Units: Subjects			
Age continuous Units: years			
median	68	75	
inter-quartile range (Q1-Q3)	64 to 81	70 to 79	-
Gender categorical Units: Subjects			
Female	2	6	8
Male	5	7	12
Septic Shock Units: Subjects			
Yes	6	9	15
No	1	4	5
KDIGO grade Units: Subjects			
KDIGO I	1	1	2
KDIGO II	2	6	8
KDIGO III	4	6	10
Diuresis Units: Subjects			
> 0.5 ml/kg/hour	3	3	6
< 0.5 ml/kg/hour for 6-12 h	1	1	2
< 0.5 ml/kg/hor for > 12 h	2	5	7

< 0.3 ml/kg/h or anuria for > 12 h	1	4	5
Renal replacement therapy Units: Subjects			
Yes	1	4	5
No	6	9	15
Weight			
Patient weight at admission to the ICU			
Units: kilogram(s)			
median	70	73	
inter-quartile range (Q1-Q3)	60 to 91	65 to 80	-
Ideal body weight Units: kilogram(s)			
median	71	66	
inter-quartile range (Q1-Q3)	66 to 71	59 to 75	-
ICU stay prior to randomisation Units: hour			
median	35	42	
inter-quartile range (Q1-Q3)	29 to 41	34 to 45	-
Charlson Comorbidity Index Units: CCI			
median	4	4	
inter-quartile range (Q1-Q3)	2 to 6	4 to 5	-
SOFA score Units: points			
median	8	10	
inter-quartile range (Q1-Q3)	6 to 12	8 to 13	-
Maximum infusion rate of noradrenaline			
Measured in the 24 hours prior to randomisation			
Units: microgram(s)/kilogram/minute			
median	0.35	0.42	
inter-quartile range (Q1-Q3)	0.25 to 1.2	0.35 to 0.78	-
Creatinine Increase			
Increase in creatine from premorbid values			
Units: percent			
median	230	250	
inter-quartile range (Q1-Q3)	150 to 290	210 to 290	-
Renal Recovery Score			
The renal recovery score predicts the chance of recovering renal function within 28 days based upon age, creatinine increase and diuresis within the first 24 hours of admission to the ICU			
Units: percent			
median	46	27	
inter-quartile range (Q1-Q3)	37 to 49	21 to 45	-
Cumulative fluid balance Units: millilitre(s)			
median	10834	8978	
inter-quartile range (Q1-Q3)	9679 to 11703	7220 to 11132	-
Fluid overload			
Calculated as cumulative fluid balance/ideal bodyweight			
Units: percent			
median	15.5	13.0	
inter-quartile range (Q1-Q3)	13.6 to 18.9	10.9 to 16.9	-

End points

End points reporting groups

Reporting group title	Forced fluid removal

Reporting group description:

The eksperimental treatment arm. Patients were allocated to forced fluid removal targeted at a negative fluid balance of at least 1 ml/kg/h using furosemide or CRRT

Reporting group title	Standard Care

Reporting group description:

Control group recieving standard care.
Renal replacement therapy:
- Supportive therapy with RRT is indicated when life-threatening complications in fluid, electrolyte and acid-base balance occur:
- Hyperkalaemia (p-K+ > 6 mmol/l)
- Severe metabolic acidosis attributable to AKI (pH < 7.25 and SBE < -10 mmol/l) resistant to IV bicarbonate infusion
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Fluid therapy:
Fluid administration at the discretion of the treating clinicians, using hemodynamic goal of choice

Fluid removal:
Pharmacological fluid removal (furosemide) will be done at the discretion of the treating clinicians.

Reporting group title	Forced fluid removal

Reporting group description:

The eksperimental treatment arm. Patients were allocated to forced fluid removal targeted at a negative fluid balance of at least 1 ml/kg/h using furosemide or CRRT

Reporting group title	Standard Care

Reporting group description:

Control group recieving standard care.
Renal replacement therapy:
- Supportive therapy with RRT is indicated when life-threatening complications in fluid, electrolyte and acid-base balance occur:
- Hyperkalaemia (p-K+ > 6 mmol/l)
- Severe metabolic acidosis attributable to AKI (pH < 7.25 and SBE < -10 mmol/l) resistant to IV bicarbonate infusion
- Severe respiratory failure with PaO2/FiO2 < 13 kPa and bilateral infiltrates/oedema on the chest x-ray.
- Aside from these absolute indications, RRT may be provided in case of progressive azotaemia and plasma BUN > 25 mmol/l.

Fluid therapy:
Fluid administration at the discretion of the treating clinicians, using hemodynamic goal of choice

Fluid removal:
Pharmacological fluid removal (furosemide) at the discretion of the treating clinicians.

Primary: Cumulative fluid balance at day five

End point title	Cumulative fluid balance at day five

End point description:

Cumulative fluid balance was defined as the sum of daily fluid balance calculated as the difference between total fluid input and total fluid output including estimates of metabolic water (300 ml/day) and perspiration (6-800 ml/day, as estimated by the attending physician)

End point type	Primary

End point timeframe:

5 days after randomisation

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: millilitre(s)				
median (inter-quartile range (Q1-Q3))	-8103 (-9570 to -5116)	516 (-2833 to 917)		

Attachments (see zip file)	Fig4.tif

Statistical analyses

Statistical analysis title	Marginal model
Statistical analysis description: Linear random effects model unconditional on survival status	
Comparison groups	Forced fluid removal v Standard Care
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.01
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	5814
Confidence interval	
level	95 %
sides	2-sided
lower limit	2063
upper limit	9565

Secondary: Mean daily fluid balance at ICU discharge

End point title	Mean daily fluid balance at ICU discharge
End point description:	

End point type	Secondary
End point timeframe: ICU admission	

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: millilitre(s)				
arithmetic mean (standard deviation)	-1269 (± 868)	133 (± 1131)		

Statistical analyses

Statistical analysis title	Linear regression adjusted for observation time
Comparison groups	Standard Care v Forced fluid removal
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.01
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1467
Confidence interval	
level	95 %
sides	2-sided
lower limit	437
upper limit	2497

Secondary: Cumulative fluid balance at ICU discharge

End point title	Cumulative fluid balance at ICU discharge

End point description:

End point type	Secondary

End point timeframe:

ICU stay

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: millilitre(s)				
arithmetic mean (standard deviation)	604 (± 2379)	3259 (± 10721)		

Statistical analyses

Statistical analysis title	Linear regression adjusted for observation time
Comparison groups	Forced fluid removal v Standard Care
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.16
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	3541
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1566
upper limit	8648

Secondary: Achievement of neutral fluid balance during ICU stay

End point title	Achievement of neutral fluid balance during ICU stay
End point description:	
End point type	Secondary
End point timeframe:	
ICU stay	

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: Patients	6	4		

Statistical analyses

Statistical analysis title	Fisher's test
Comparison groups	Forced fluid removal v Standard Care
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.06
Method	Fisher exact

Secondary: Time to neutral fluid balance, median (IQR), days

End point title	Time to neutral fluid balance, median (IQR), days

End point description:

End point type	Secondary

End point timeframe:

ICU stay

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: day				
median (inter-quartile range (Q1-Q3))	7 (6 to 8)	6 (6 to 13.5)		

Statistical analyses

Statistical analysis title	Time to neutral fluid balance
Comparison groups	Forced fluid removal v Standard Care
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	1.3

Secondary: Major protocol violations

End point title	Major protocol violations

End point description:

Number of major protocol violations in each arm, defined as initiation of fluid removal after 12 hours and/or cessation of fluid removal before achieving cumulative fluid balance < 1000 ml.

End point type	Secondary

End point timeframe:

ICU stay

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: Protocol violations	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulated number of SAR's to furosemide

End point title	Cumulated number of SAR's to furosemide

End point description:

Total number of serious adverse reactions to furosemide defined as: Severe electrolyte disturbance (p-K+ < 3.0 mmol/l, p-Na+ < 120 mmol/l, p-Cl- < 90 mmol/l); severe thrombocytopenia (thrombocyte count < 50 x 109/l); anaemia requiring transfusion of red blood cells without bleeding; agranulocytosis; pancreatitis; arrhythmia; circulatory collapse; cramps; Steven Johnsons syndrome; toxic epidermal necrolysis; hearing loss and anaphylaxis). These were registered daily regardless of the patient recieving any furosemide on the given day

End point type	Secondary

End point timeframe:

ICU stay

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: SAR	13	15		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mortality

End point title	Mortality

End point description:

End point type	Other pre-specified

End point timeframe:

90 days

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: Patients	2	6		

Statistical analyses

Statistical analysis title	Fisher's test
Comparison groups	Forced fluid removal v Standard Care
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.64
Method	Fisher exact

Other pre-specified: Days alive and out of hospital

End point title	Days alive and out of hospital

End point description:

End point type	Other pre-specified

End point timeframe:

90 days

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: day				
median (inter-quartile range (Q1-Q3))	0 (0 to 34)	4 (0 to 69)		

Statistical analyses

Statistical analysis title	Mann-Whitney U
Comparison groups	Forced fluid removal v Standard Care
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.35
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Days alive and without mechanical ventilation

End point title	Days alive and without mechanical ventilation

End point description:

End point type	Other pre-specified

End point timeframe:

90 days

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: day				
median (inter-quartile range (Q1-Q3))	85 (0 to 87)	25 (2 to 84)		

Statistical analyses

Statistical analysis title	Mann-Whitney U
Comparison groups	Forced fluid removal v Standard Care
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.36
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Days alive and without renal replacement therapy

End point title	Days alive and without renal replacement therapy

End point description:

End point type	Other pre-specified

End point timeframe:

90 days

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: day				
median (inter-quartile range (Q1-Q3))	36 (0 to 76)	42 (1 to 89)		

Statistical analyses

Statistical analysis title	Mann-Whitney U
Comparison groups	Forced fluid removal v Standard Care
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.48
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Days alive and without vasopressors/inotropes

End point title	Days alive and without vasopressors/inotropes

End point description:

End point type	Other pre-specified

End point timeframe:

90 days

End point values	Forced fluid removal	Standard Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: day				
median (inter-quartile range (Q1-Q3))	86 (2 to 87)	53 (2 to 88)		

Statistical analyses

Statistical analysis title	Mann-Whitney U
Comparison groups	Forced fluid removal v Standard Care

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.82
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

ICU stay up to a maximum of 90 days

Adverse event reporting additional description:

The presence of adverse events was assessed daily during ICU stay

Assessment type	Systematic

Dictionary used

Dictionary name	none
Dictionary version	1

Reporting groups

Reporting group title	Forced fluid removal

Reporting group description:

The eksperimental treatment arm. Patients were allocated to forced fluid removal targeted at a negative fluid balance of at least 1 ml/kg/h using furosemide or CRRT

Reporting group title	Standard Care

Reporting group description:

Control group recieving standard care.
Renal replacement therapy:
- Supportive therapy with RRT is indicated when life-threatening complications in fluid, electrolyte and acid-base balance occur:
- Hyperkalaemia (p-K+ > 6 mmol/l)
- Severe metabolic acidosis attributable to AKI (pH < 7.25 and SBE < -10 mmol/l) resistant to IV bicarbonate infusion
- Severe respiratory failure with PaO2/FiO2 < 13 kPa and bilateral infiltrates/oedema on the chest x-ray.
- Aside from these absolute indications, RRT may be provided in case of progressive azotaemia and plasma BUN > 25 mmol/l.

Fluid therapy:
Fluid administration at the discretion of the treating clinicians, using hemodynamic goal of choice

Fluid removal:
Pharmacological fluid removal (furosemide) at the discretion of the treating clinicians.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Patients in this trial were admitted to the ICU. All ICU patients experience numerous non-serious adverse events daily during their critical illness. These were not recorded as an entity, but the most important SAEs and SAE's directly related to fluid removal have been captured in the exploratory outcome measures and in the daily SOFA- scoring. Patient charts will contain daily registrations of clinical data, which can be obtained on request from the medical authorities.

Serious adverse events	Forced fluid removal	Standard Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	6 / 13 (46.15%)	
number of deaths (all causes)	2	6	
number of deaths resulting from adverse events	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 7 (28.57%)	5 / 13 (38.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 20	
deaths causally related to treatment / all	0 / 2	0 / 6	

Myocardial ischaemia	Additional description: Verified acute myocardial infarction resulting in intervention with PCI/thrombolysis or antithrombotic treatment		
subjects affected / exposed	1 / 7 (14.29%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 6	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 6	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Forced fluid removal	Standard Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 13 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2016	The inclusion criterium: Renal recovery score < 50% was changed to Renal Recovery Score < 60%

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29664109