

**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 randomisation. 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 \pm 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 receiving 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 receiving 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 |
| 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 inter-quartile range (Q1-Q3) | 68 64 to 81 | 75 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
- 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.

| | |
|-----------------------|----------------------|
| 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 (\pm 868) | 133 (\pm 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 (\pm 2379) | 3259 (\pm 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 10 ⁹ /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 receiving 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>