Inadvertent Sodium Loading in critically ill patients

S BIHARI
Flinders Medical Centre, Adelaide South Australia

Background 1

- Positive fluid balance – association with poor outcomes
- But strategies to improve fluid balance - not shown to improve mortality- Why?
- Positive fluid balance - ECF expansion - both water and sodium may be important
- IPPV & PEEP - complex neurohumoral responses – Na & water retention
- Serum sodium reflects water balance while total sodium – extra cellular volume
- Are we measuring the wrong thing? – fluid follows the salt - is fluid restriction enough or should be coupled with sodium restriction ?

Background 2

- Sodium administration / balance is rarely separated from fluid overload/balance
- Fluid restriction : often restricted by hypernatremia
- It is easier to remove free water but it is much harder to get the sodium out from the interstitial space & there is minimal obligatory sodium loss in urine
- No study has looked in to effects of excess sodium administration/ balance in the ventilated ICU patients

Historical data

- Recommended daily intake of sodium is 1 – 2 mmol/kg, studies have recommended even lower. I litre of Hartman has close to 2mmol/kg
- Conservative arm of FACTT trial subjects had a mean 3.5 L/day fluid while the liberal fluid arm subjects received **> 4** L/day - over the first week
- Fluid balance in ARDS Network trials and liberal arm of FACTT trial was 7 L +ve in first week, which is essentially approx. 1000 mmol +ve for sodium
- FACTT did not find difference in mortality – was it not powered or sodium was not taken in to account?

General hypothesis

Excessive sodium administration, particularly in mechanically ventilated subjects, may lead to extracellular volume expansion and may be associated with poor outcomes

An analysis of sodium administration in patients with prolonged mechanical ventilation

S. BIHARI , J.J.OU, A.W. HOLT, A.D. BERSTEN

Flinders Medical Centre Adelaide South Australia

Government of South Australia
SA Health

FLINDERS MEDICAL CENTRE

Previous work

Objective

To analyse the amount of sodium administered to patients who required invasive mechanical ventilation for > 5 days in ICU (Group where it might be most important)

Design of Study

A retrospective pilot analysis from case notes and data spread sheets

Inclusion criteria

- Patients admitted to ICU at FMC who were ventilated (invasive) for more than 5days

Exclusion criteria

- Age < 18 years
- Pregnancy
- Chronic haemodialysis
- Traumatic brain injury
- DKA/HHS

Previous work: method

- Retrospective analysis of 20 consecutive patients
- Daily sodium administered per day during mechanical ventilation
- Data sheets, operation notes, TPN sheets was retrieved & reviewed

- Data recorded were
  - Demographics
  - Diagnosis
  - APACHE II score
  - Length of ventilator stay
  - Length of stay in ICU
  - Dialysis
  - Outcome from ICU
  - Daily fluid balance
  - Vasoactive drugs
  - Renal function
  - Daily PO_2/FIO_2 ratio between 8 & 9 am

- All these data were recorded from 24 hours prior to intubation until 24 hours post extubation

Sources of sodium

1. **Resuscitation** sodium - boluses during initial/ ongoing management
2. **Maintenance** sodium - constant infusion during their stay in ICU
3. **Replacement** sodium - replacement to renal/ gastrointestinal loss
4. **Flushes** sodium -central venous and arterial access, we use heparinised

   0.9% saline as flush & we took a rate of 4 ml/hr for every flush based catheter
5. **Infusion** sodium - vehicle for drugs for e.g. sedatives, vasopressor, insulin
6. **Enteral feeds** sodium
7. **Total parental nutrition** sodium
8. **Transfusion** sodium (pure red blood cells, platelets, FFP)
9. **Medications** sodium (sodium present in drugs administered)

Medication	Sodium Content (in mmol)
FLUID	
0.9% Normal Saline	155 mmol/L
4% Dextrose & 0.18% Normal Saline	31 mmol/L
20% Saline	3444 mmol/L
NSA (5% Albumin)	140 mmol/L
20% Albumin	7.4 mmol/100 ml
Gelofusin	154 mmol/L
Hartmann (CSL)	131 mmol/L
TRANSFUSION	
PRC	31.3 mmol/U
FFP	44 mmol/U
Platelet	30.5 mmol/U
NG FEEDS	
Nutrison Concentrated	4.3 mmol/ 100 ml
Nutrison Energy	5.8 mmol/ 100 ml
Nutrison Energy multifibre	5.8 mmol/ 100 ml
Nutrison Low Na	1.1 mmol/ 100 ml
Nutrison Multifibre (default choice of feed in ICU FMC)	4.3 mmol/100 ml
Abbotts Nepro	3.7 mmol/ 100 ml
Nutrison Standard	4.3 mmol/ 100 ml
FLUSH	
Heparin Na	155.2 mmol/L (normal saline)
Daily 2 lines (8ml/hr) Flush @ 4 ml/hr per tranducer	29. 8 mmol/day (normal saline)

MEDICATIONS

Acetazolamide *500 mg*	2.0 mmol/500 mg
Acetylcystein (NAC) *2g*	11.0 mmol/2g
Aciclovir *250 mg*	4.2 mmol/g
Adrenaline *1mg/1 ml*	0.2 mmol/ml (calculated)
Adrenaline *1: 10000 (0.1 mg/ml)*	0.1 mmol/ml (calculated)
Amiodarone *150mg/3 ml*	0 mmol/ml
Aminophylline *250 mg/10 ml*	0 mmol/ml
Amoxacillin *1g*	3.3 mmol/g
Ampicillin *1g*	2.7 mmol/g
Atropine *1mg/10ml*	1.5 mmol/mg (calculated)
Azithromycin *500mg*	5.0 mmol/ 500 mg
Benztropine *2mg/2mL*	0.310 mmol/2 mg
Benzylpenicillin *1.2g/vial*	3.6 mmol/1.2 g
Betamethasone *5.7 mg/ml*	0.1 mmol/ml
Bupivacaine *50 mg/ 20ml vial*	0 mmol/vial
Cephazolin *1g*	2.0 mmol/g
Cefepime *1g*	0 mmol/vial
Cefotaxime *1g*	2.2 mmol/g
Ceftriaxone *1g/vial*	3.6 mmol/g
Chloramphenicol *1.2g*	2.7 mmol/g
Chlorpromazine *50mg/2 ml*	0.2 mmol/ 50 mg
Ciprofloxacin *200 mg/100 ml)*	15.4 mmol/200 mg
Clonazepam *1 mg*	0 mmol
Clonidine *150 ug/1 ml*	0.2 mmol/ 150ug
Desmopressin (DDAVP)	0 mmol/vial
Dexamethasone *8mg/2 ml*	0.1 mmol/ 8 mg
Diazepam *10 mg/2 ml*	0.7 mmol/ 10 mg
Dicloxacillin *1g*	2.2 mmol/g
Digoxin *500 ug/2 ml*	0 mmol/ 500 ug
Dobutamine *250 mg*	0 mmol/ 250 mg
Dopamine *200 mg/ 5 ml*	0 mmol/ 200mg
Ephedine *30 mg/ml*	0.1 mmol/ 30 mg
Erythromycin *1g*	0 mmol
Esmolol *100 mg/10 ml*	0.3 mmol/100 mg
Flucloxacillin *1g*	2.2 mmol/g
Fluconazole *200mg/100ml*	15 mmol/200 mg
Flumazenil *0.5 mg/ 5ml*	0.8 mmol/0.5 mg
Frusemide *250mg/ 25 ml*	0.8 mmol/250mg
Frusemide *20mg/ 2ml*	0.3 mmol/ 20 mg
Gentamicin *80 mg/2ml*	0.1 mmol/80 mg
Glucagon *1 mg*	0 mmol
Glucose IV 50% *(25g/50 ml)*	0 mmol
Glyceryl *50 mg/10 ml*	0 mmol

Haloperidol *5 mg/ml*	0 mmol
Heparin Na	155.2 mmol/L
Hydralazine *20mg*	0 mmol
Hydrocortisone *100*	0.3 mmol/100 mg
Imipenem-Cilastatin	1.6 mmol/500 mg
Ketamine *10 mg/ml*	0.2 mmol/10mg
Lignocaine& Adrenaline	1.1 mmol/ 5ml
Lignocaine *1% 5ml*	0.52 mmol/ 5ml
Lincomycin *600mg/2 ml*	0 mmol
Linezolid *2mg/ml*	5 mmol/300 ml
Meropenem *1g*	4.0 mmol/g
Metoclopramide *10mg*	0.3 mmol/10 mg
Metoprolol *5mg/5ml*	0.8 mmol/5ml
Metronidazole	13.5 mmol/500 mg
Methylprenisolone Na	2 mmol/g
$MgSO_4$ *2.47g/5 ml*	0 mmol
Midazolam *5 mg/ ml*	0.1 mmol/5mg
Milrinone *10 mg/10 ml*	0 mmol
Morphine	0 mmol
Moxifloxacin	34 mmol/400 mg
Naloxone *400 mg/ml*	0.16 mmol/ 400 mg
Nimodipine *100 mg*	0 mmol
Noradrenaline*2mg/ 2 ml*	0.3 mmol/ 2mg

Pantoprazole *40 mg*	0.1 mmol/ 40 mg
Phenobarbitone sodium	< 1 mmol/ml
Phenytoin *250 mg/ 5ml*	1.0 mmol/ 250 mg
Phytomenadine *10 mg*	0 mmol
Piperacillin *2g*	3.7 mmol/ 2g
Piperacillin *4g*+ Tazobactam *500 mg*	11.1 mmol/vial
Potassium	0 mmol
Propofol	0 mmol
Protamine *50mg/5 ml*	0.8 mmol/50 mg
Ranitidine *50 mg/2 ml*	0 mmol/ 50 mg
Rifampicin *600 mg*	0.1 mmol/vial
Rocuronium	< 1 mmol
Sodium Nitroprusside	0.3 mmol/50 mg
Sotalol *40 mg/4ml*	< 1 mmol/100 mg
Suxamethonium*100mg*	0 mmol
Thiamine *100mg/ml*	0 mmol/100 mg
Thiopentone *500 mg*	2.5 mmol/ 500mg
Timentin *3.1g*	31 mmol/ 3.1g
Theophyllin *200mg*	0 mmol
Trimethoprim *80 mg* + Sulfamethoxozole *400 mg*	0 mmol/5ml
Tropisetrone *2 mg*	< 1mmol
Vancomycin	0 mmol
Vasopressin *20 u*	0.2 mmol/ml
Vecuronium	0.1 mmol/10mg
Verapamil *5 mg/2ml*	0.3 mmol/ 5mg
Voriconazole *200mg*	10 mmol

Previous work: results

- Male: 13/20
- Average age (median, range) : 71.9 years(19.8 – 89.2)
- Ventilation days : 10 days (6-20)
- Total ICU stay : 11.6 (6-21)
- Outcome : Died 12, Home 5,
  Readmitted to ICU 2,Other hospital 1
- 7 out of 20 patients required dialysis

Previous work: results

- APACHE II at admission : 29 (18 – 41)
- Avg. daily serum sodium (mean ,SD) : 141 ± 5 mmol/l
  14/20 had serum sodium > 145 mmol/l , 3/20 had > 150mmol/l
- Avg. daily net fluid balance :+ 351mls (- 759 to + 1125) : comparable to conservative group of FACTT
- Avg. daily fluid intake : 2352 mls (1437 – 3798) : less than the conservative group of FACTT

Previous work

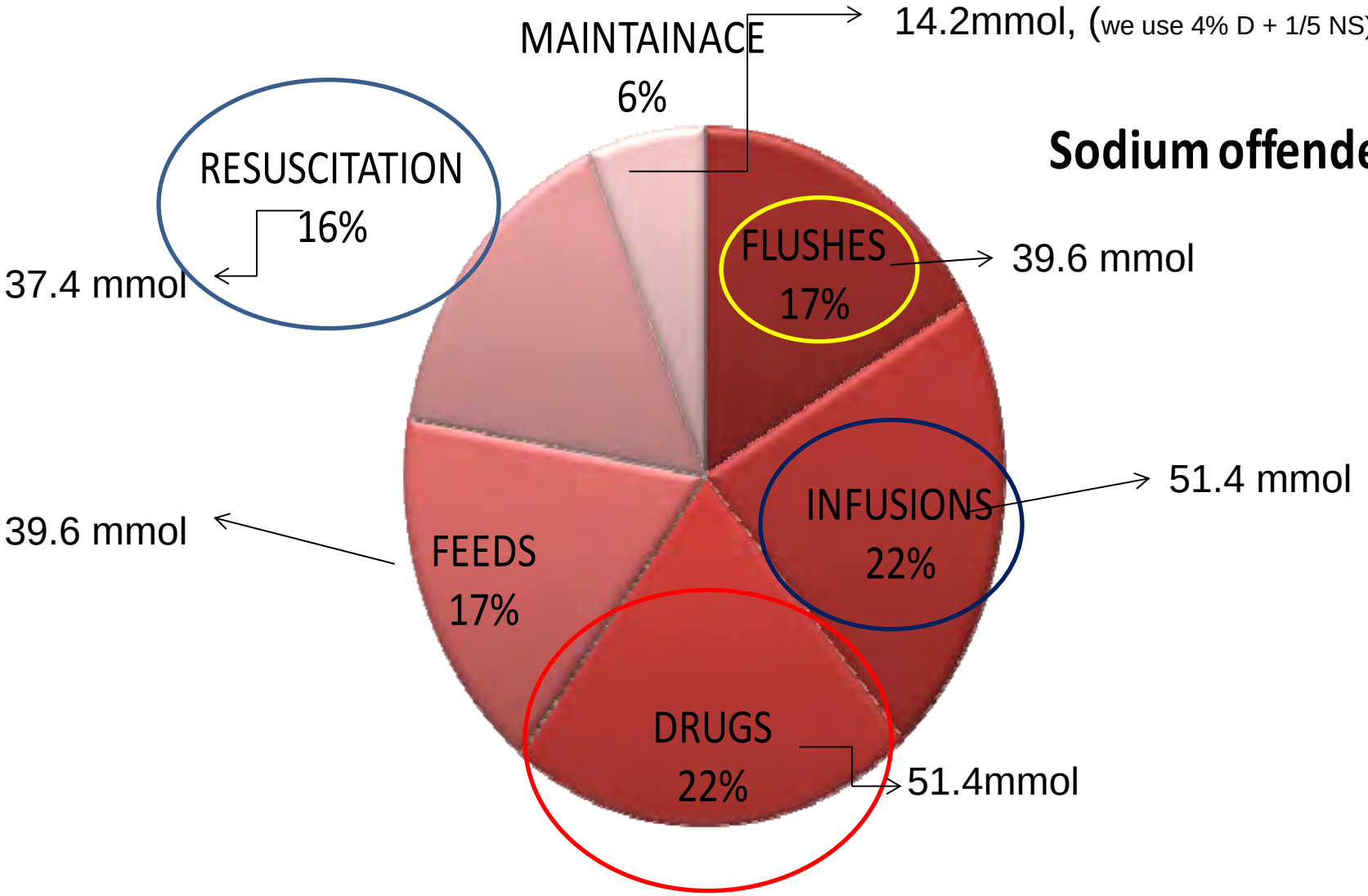
Avg daily sodium administered : 233.5 mmol (151 –355)

VS.

ULTIMATE DOUBLE WHOPPER®

Has less than 100 mmol of sodium

Contribution of sodium



Although these data are consistent with inadvertent sodium loading in critically ill patients it is from a small cohort and a single centre, sodium balance was not estimated and no clinical inference can be made

I propose a program- the proposed destination of which is a definitive trial to test the hypothesis that restriction of sodium intake improves patient centred outcomes

A substantial amount of preliminary work will be necessary to get to this point and determine whether it is warranted to proceed
These steps include

Proposed steps

- **Study 1**: Point prevalence study: Daily sodium administration
- **Study 2:** A prospective study evaluating the effects of daily sodium administration and its balance on volume status, oxygenation and ventilation parameters
- **Study 3:** Comparison of restrictive vs. liberal strategy of sodium administration coupled with conservative fluid strategy in patients who are anticipated to be invasively ventilated for > 2 days(48 hrs)

Study 1

POINT PREVALENCE STUDY: Daily sodium administration.

Hypothesis : *FMC data is an outlier*

Aim**:** To investigate the prevalence of daily sodium administration over a 24 hour period in a large cohort of patients from multiple centres admitted to intensive care units across Australia

Method**:** Data collection will occur over a 24-hour period on Point Prevalence Study Day (defined as a 24 hour period corresponding to each institution's ICU chart day) and will include 24 hour total administered sodium and fluid (from all sources), fluid balance, use of diuretics and dialysis, renal functions and serum sodium

Inclusion criteria:
All patients present in ICU at 10:00 on Point Prevalence study Day

Exclusion criteria:
Patients eating food

Data recorded

- Demographic and baseline information
- ICU admission source, severity scores
- Presence of sepsis , ALI on study day
- Requirement for vasoactive agents & IMV/NIMV
- Duration of MV, ICU length of stay & mortality

- Type /amount of fluid/ feeds administered
- Fluid balance
- All administered drugs
- Dialysis/ diuretics
- Renal function, serum sodium , serum albumin

Trial data collection (12 patients) took 15 minute per patient

Questions

- Measures of fluid status : CVP,BP,HR
- Measures of ventilation : PO_2/FIO_2 , $PaCO_2$, MV, PEEP
- **How best can we get accurate information?**
- Exclude flush / exclude drugs< 20 mls and assume medicines are administered as prescribed but can be incorrect
- Pre-printed sheet @ bed side a day before PPD which is prospectively recorded by bed side nurse of everything he/she administers – more info but more labour intensive and adds to nurses workload – is this an option?

Status

Next PPD : September 2011

Study 2

A prospective study to evaluate the effects of daily sodium administration and balance on volume status, oxygenation and ventilation parameters

S. BIHARI , C. BALDWIN, A.D. BERSTEN

Flinders Medical Centre Adelaide South Australia

HYPOTHESISES:

- High levels of sodium intake will result in sodium accumulation which will increase the extracellular volume of mechanically ventilated patients and will effect their volume status, oxygenation, ventilation and outcome measures
- Sodium input does influence sodium balance

AIM: To study the effects of daily administered sodium and its balance on above parameters in patients who are anticipated to be invasively ventilated for > 2 days

Study 2

***METHOD*:** We plan to measure daily sodium administration and its estimated balance, with its effect on:

- Volume status (measured with bioelectrical impedence spectroscopy recording TBW, ECV, ICV)
- Intravascular filling pressures
- Chest X-ray score
- Peripheral oedema score (central & peripheral)
- Oxygenation and ventilation indices

We will record and measure the above parameters daily for up to 10 days after the patient has been ventilated

Size: 30 patients (pilot study), single centre

Additional insights

This project should improve our knowledge of

- Sodium balance (measuring 24 hour urine sodium)
- Natriuretic effect of diuretics
- Sodium balance of patients on dialysis (measuring afferent and efferent sodium level)

Status

Ethics clearance granted

Study 3 : Pilot Proposal

Comparison of restrictive vs. liberal strategy of sodium administration coupled with conservative fluid strategy in patients who are anticipated to be invasively ventilated for > 2 days (48 hours)

Hypothesises

- We can safely achieve lower sodium administration in ICU patients
- Low sodium administration and achieving a better balance in addition to conservative fluid balance will help in clinical outcomes in patients who are mechanically ventilated in ICU

Research Plan

DESIGN

Prospective, randomised, unblinded multi-centre feasibility study comparing a restrictive sodium administration strategy vs. unrestrictive sodium administration in ICU patients anticipated to require prolonged mechanical ventilation

Both treatment groups will be managed with a conservative fluid strategy

SUBJECTS

Patients admitted to intensive care who require invasive mechanical ventilation will be enrolled

Size: 100 patients (50 in each group)

Statistical analysis

The proposed sample size is based on data from our audit of sodium intake

- Assuming mean daily sodium delivery of 235 in the control group & expecting a 25% reduction in sodium delivery in intervention group
- Power 80% power and 2 tailed α of 0.05 the estimated required sample size per group is 44
- To allow for contingencies we aim to enrol 50 subjects per group

Outcomes:

Primary outcomes

- Difference (25%) in mean daily sodium administration between both the groups to determine process separation for a candidate intervention
- Test the safety of a low sodium strategy in ICU patients
- Protocol refinement
- Sample size &recruitment rate

Secondary outcomes

- Mean daily sodium
- Mean daily serum sodium
- Sodium and fluid balance
- Requirement for additional sodium administration to treat hyponatraemia
- Length of ventilation
- ICU stay and hospital stay
- ICU and hospital mortality

Inclusion criteria

- Age ≥ 18 years
- Receiving invasive mechanical ventilation
- Expected length of invasive ventilation ≥ 48 hours from the time of intubation (based on the treating consultant's prediction)
- Admission Serum sodium 130 to 150mmol/L
- Informed consent

Exclusion criteria

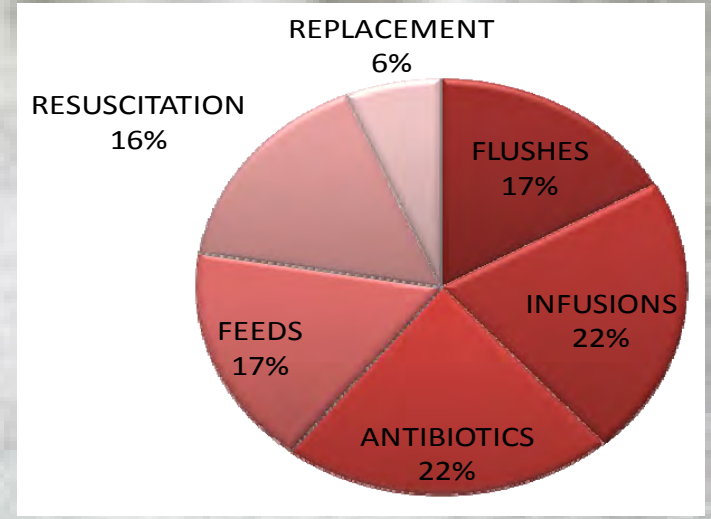
- < 18 years
- Chronic haemodialysis
- Traumatic brain injury
- DKA or HHS
- Treatment clinician feels that sodium and/or volume restriction is contraindicated
- Specific requirement for sodium administration
- Patients in whom a low sodium intake is indicated based on treating clinicians discretion
- Expected death within the next 24 hours or patient not for active treatment
- Suspected or confirmed pregnancy
- Consent refused

Conservative sodium strategy

Unrestricted sodium strategy

- Use 5% dextrose as a vehicle for infusions for all medicines unless contraindicated (by drug solubility requirement)
- Use 5% dextrose as maintenance fluid
- Use 5% dextrose / ½ normal saline as flush for all intravascular catheters
- No added sodium in nutrition
- No change in resuscitation fluid

Sodium administration will be guided by the treating clinician and current unit protocols



Fluid balance

Coupling the above strategy with conservative fluid balance

In both treatment groups, a conservative fluid strategy aiming for a neutral or negative fluid balance will be implemented.

Guidelines: FACTT trial

Data collection

- Baseline demographics (age, sex, weight, height)
- ICU admission diagnosis and APACHE II score
- Elective, emergency and non-surgical category
- Co-morbidities : based on Charlson co-morbidity score
- Length of ventilation
- Length of ICU and hospital stay
- ICU and hospital outcomes

Method

Data will be collected daily for 2 weeks or until 24 hours after extubation (if extubated < 2 weeks)

- Fluid balance
- Sodium administration
- Highest and lowest serum sodium
- Sodium excretion (based on 24 hour urinary sodium concentration) , sodium balance
- Highest daily creatinine and urea
- Lowest PaO_2/FIO_2 ratio
- Lung compliance (if on control mode-static)
- Hemodynamic profile: HR (highest and lowest), MAP (highest and lowest), CVP (highest and lowest), EVLW (highest and lowest)
- Dialysis (Y/N) , dose and measure afferent and efferent sodium levels
- Diuretic (Y/N), type and dose
- Steroid (Y/N), type and dose
- Insulin (Y/N) , type and dose
- Highest and lowest blood sugar level

Discontinuation of study intervention

Study intervention will continue for 2 weeks and will cease earlier if one of the following occurs

- Patient is extubated
- Patient is discharged from ICU
- Treating clinician feels that it is in the patient's best interest to cease the study intervention
- Consent is withdrawn

Safety feature

- The target serum sodium in both treatment groups will be between 130mmol/l and 150mmol/l

- If serum sodium is less than 130 mmol/l then clinicians will be allowed to use aggressive fluid restriction strategy and/or use of frusemide
- Delta sodium: Change in > 10 mmmol in 24 hours

- If serum sodium < 120 mmol/l or patient develops clinical symptoms of hyponatraemia, hypertonic saline administration (rate and concentration decided by treating clinician) will be permitted

- If serum sodium > 150 mmol, 5%Dextrose or water administration will be permitted based on treating clinicians discretion

Time table

1. Conduct PPD (study 1)
2. Refine protocol based on feedback
3. Represent feasibility trial winter CTG
4. Management committee, research coordinator
5. Budget
6. Intensive care foundation
7. Ethics
8. Aim for a January 2012 start
9. Ultimately a large multi-centre trial

Questions

1. Is it feasible?
2. Risk of hyponatremia? What level?
3. Change in serum sodium? (delta serum sodium is > 10 mmmol / 24 hours OK)?
4. At what serum sodium level will be withdraw the patient from study- ?120 ? 155
5. How can we estimate sodium balance better ?
    - Dialysis and sodium : hope to some answers with study 2
    - GI loss – colostomy/ ileostomy / bowel/ vomiting/ Gastric residual volume
6. Flush fluid, what rate ? ½ normal saline/ 5% dextrose – infection rate / BSL?
7. Low sodium feeds (it is 1 kcal /ml)?
8. CXR scoring ? Oedema scoring ?

Show of hands , who is interested?

Acknowledgement

- Sandra Peake
- Steve Webb
- Andrew Bersten
- Andrew Holt

Thank you