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HYDration and Bicarbonate to Prevent Acute Renal Injury After Endovascular Aneurysm Repair With Suprarenal Fixation: Pilot/Feasibility Randomised Controlled Study (HYDRA Pilot Trial)

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WHAT THIS PAPER ADDS

Almost a quarter of patients undergoing elective endovascular aneurysm repair (EVAR) develop acute kidney injury (AKI). This impacts on cost, and short and long-term morbidity and mortality. However, there is no high quality randomised evidence regarding prevention of EVAR related AKI. A novel AKI prevention strategy specifically for EVAR was developed based on best evidence and expert consensus meetings. This pilot trial confirms that using a high dose of sodium bicarbonate immediately before EVAR is a safe AKI prevention strategy.

Objective/Background: Up to 25% of patients undergoing elective endovascular aneurysm repair (EVAR) develop acute kidney injury (AKI), which is associated with short and long-term morbidity and mortality. There is no high quality randomised evidence regarding prevention of EVAR related AKI.

Methods: A novel AKI prevention strategy for EVAR was devised, based on best evidence and an expert consensus group. This included a bolus of high dose sodium bicarbonate ($NaHCO_3$) immediately before EVAR (1 mL/kg of 8.4% $NaHCO_3$) and standardised crystalloid based hydration pre- and post-EVAR. A pilot/feasibility randomised controlled trial (RCT) was performed in two centres to assess the safety of the intervention, potential impact on AKI prevention, and feasibility of a national RCT; the primary end point was the proportion of eligible patients recruited into the study. AKI was defined using "Kidney Disease Improving Global Outcomes" and "Acute Kidney Injury Network" criteria based on National Institute for Health and Clinical Excellence AKI recommendations, using serum creatinine and hourly urine output.

Results: Fifty-eight patients (84% of those screened; median age 75 years [range 57—89 years], 10% female) were randomised to receive the standardised intravenous hydration with (intervention) or without (control) $NaHCO_3$. Groups were comparable in terms of AKI risk factors; 56 of 58 participants had a device with suprarenal fixation. Overall, 33% of patients in the control arm developed AKI versus 7% in the intervention arm (as treated analysis). None of the patients receiving $NaHCO_3$ developed a serious intervention related adverse event; five patients did not attend their 30 day follow-up.

Conclusion: Bolus high dose $NaHCO_3$ and hydration is a promising EVAR related AKI prevention method. This trial has confirmed the feasibility of delivering a definitive large RCT to confirm the efficacy of this novel intervention, in preventing EVAR related AKI.

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Keywords: Acute kidney injury (AKI), Randomised controlled trial (RCT), Endovascular aneurysm repair (EVAR)

INTRODUCTION

Currently, most patients having abdominal aortic aneurysm (AAA) surgery undergo endovascular aneurysm repair (EVAR), a minimally invasive alternative to open repair.[1]

One of the most common complications of EVAR is acute kidney injury (AKI). It has previously been shown that AKI can develop in almost 25% of patients having elective EVAR.[2—4] Peri-operative AKI is independently associated with higher short-term morbidity, increased length of hospital stay, cost, and mortality.[5—7] Some series have also

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shown that peri-operative AKI impacts on long-term outcomes.[4,8] AKI after EVAR results in a significant increase in both short and long-term complications and impacts on long-term renal function.[2–4,9,10]

There is no high quality evidence regarding strategies to prevent peri-operative AKI in EVAR. This is partly owing to the complexity of the mechanisms underlying renal injury in EVAR.[10] Given the major differences between both patient and procedure characteristics, prevention strategies applicable to other surgical or radiological interventions cannot be extrapolated for use in EVAR. To address this, an EVAR specific reno-protective strategy of urinary alkalisation with a bolus dose (1 mL/kg) of intravenous (IV) 8.4% sodium bicarbonate ($NaHCO_3$) was developed together with pre-/post-operative intravascular volume expansion. This was based on best available evidence,[10–12] using the latest National Institute for Health and Care Excellence (NICE) guidance and British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients, and a thorough consultation between surgeons, nephrologists, and anaesthetists in a series of focus groups aimed to inform trial design.

The aim of this two centre pilot randomised controlled trial (RCT) was to confirm the ability to efficiently recruit patients in a definitive large RCT, evaluate the safety of this novel EVAR specific AKI prevention strategy, and assess its impact on renal physiology.

METHODS

Patient population

Patients scheduled to undergo elective EVAR for an infrarenal AAA were prospectively recruited from two tertiary vascular surgery units in England (actual patient recruitment dates: 1 May 2016–26 February 2017). The study started recruiting in April 2016 and finished recruiting in April 2017. After written informed consent was obtained, patients were randomised in a 1:1 ratio to receive either standardised aggressive hydration (control arm) or aggressive hydration together with a single bolus $NaHCO_3$ infusion (intervention arm) on a 1:1 ratio as per a computer generated randomisation schedule using variable block randomisation and stratification by centre. Ethical approval was given by the West Midlands Research Ethics Committee in February 2016 (reference number: 16/WM/0008) and Health Research Authority (https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/hydra-p/). The trial was reviewed and approved by the Medicines and Healthcare products Regulatory Agency (December 2015) and registered accordingly (186752/882996/19/777). The study conduct followed the principles of the Declaration of Helsinki and was publically registered (ISRCTN reference number: ISRCTN12291961). Study design and delivery were supported by the Oxford Surgical Intervention Trials Unit.

Exclusion criteria

Exclusion criteria were emergency EVAR; established severe cardiac failure defined as functional status New York Heart Association stage 4; allergy to $NaHCO_3$; juxtarenal or suprarenal aneurysm; solitary kidney; administration of intravenous or intra-arterial contrast <2 days prior to EVAR; previous open AAA or iliac aneurysm repair; surgery or trauma within 1 month before EVAR; metabolic or respiratory alkalosis; chemotherapy, radiotherapy, or steroid therapy; patient undergoing renal dialysis for established renal failure; patient receiving nephrotoxic medication (non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers) for 48 h prior to EVAR; pulmonary oedema; systolic blood pressure > 200 mm Hg at baseline.

Study interventions

To develop an EVAR specific AKI prevention strategy (August 2015–December 2015) an expert consensus group was set up, which included a panel of vascular anaesthetists, vascular surgeons, nephrologists with an interest in AKI, a medical biochemist, and clinical research methodologists. The literature was reviewed systematically to identify the best evidence, and the most recent NICE guidance relating to AKI prevention was used, as well as the British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients.[2,10–13] A nationwide remote survey was carried out, completed by 131 anaesthetists, to confirm acceptability of the proposed intervention. Overall, the consensus group met three times and a Delphi process was followed both for the group meetings and the survey.[14]

Patients in both groups received the following fluid regime: 10 mL/kg Hartmann's solution given over 1 h before the induction of anaesthesia. Intra-operative fluid and vasopressor administration aimed to maintain mean arterial pressure within 80% of the baseline for >90% of time. Post-operatively, 2 mL/kg/hour of IV crystalloid was given for 12 h. In terms of contrast agent, patients received 51.03% w/v of iomeprol equivalent to 25% iodine or 250 mg iodine/mL.

The intervention arm also received a bolus of 1 mmol/kg or 1 ml/kg of an 8.4% $NaHCO_3$ solution starting upon induction of anaesthetic and administered via a large bore peripheral cannula over 1 h.

The anaesthetists administering the trial intervention were not blinded.

Definitions

Development of AKI was defined using NICE guidance (minimum of stage 1 "Kidney Disease Improving Global Outcomes" and "Acute Kidney Injury Network" criteria)[11] using serum creatinine (SCr) and hourly urine output measurements. AKI was defined as either a rise in SCr ≥ 26 μmol/L within 48 h of surgery or ≥50% rise in SCr within 48 h of surgery or a fall in urine output to <0.5 mL/kg/hour for six consecutive hours or more. This is a widely accepted definition of AKI, based on the latest expert consensus statements and adopted in several trials worldwide.[11]

All anatomy and outcome definitions followed reporting criteria for EVAR set by Chaikof et al. and the latest Clavien

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Dindo classification statement.[15,16] A patient with >50% of the circumference of their proximal AAA neck covered with thrombus was considered as having a significant degree of neck thrombus (see Table 1). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula,[17] based on SCr measurements; SCr was measured on the day of admission immediately prior to EVAR, to calculate baseline eGFR and define AKI post-operatively.

End points

In order to inform a large definitive RCT, the willingness of participants to be randomised and the willingness of clinicians to recruit patients in this pilot RCT over the course of 1 year (April 2016—April 2017) were investigated. The primary end point was therefore the proportion of eligible patients recruited into the study. The aim was to recruit a minimum of 50% of patients eligible to participate in the RCT over 1 year.

Secondary outcome measures included: (i) incidence of AKI; (ii) tolerability of the intervention by the patients (number of patients withdrawing from the study); (iii) adequacy of the standardised hydration regimen in the two arms—if the proposed fluid regimen failed to maintain an intra-operative central aortic pressure of at least 90% of baseline and bioimpedance indicated that post-operative hydration levels were <90% of baseline; (iv) levels of serum bicarbonate during and after the EVAR; (v) adverse events and complications 30 days after EVAR (all clinical events between recruitment and completion of follow-up were recorded during inpatient hospital stay and outpatient visits).

Outcome assessors were blinded to the study intervention. Reporting follows the 2010 CONSORT statement.[18]

Statistical analysis

Formal sample size calculations were not performed for this pilot phase as the results will allow the power calculations for the full scale RCT to be updated accordingly, and allow for adjustment of the interventions and planning of the number of centres required to participate. Analysis of all outcomes was performed on an "as treated" population (analysing patients according to the intervention they actually received and not based on their randomisation allocation), given that this was a pilot study and following a consensus discussion between the research team and a senior medical statistician with experience in delivering clinical trials of surgical interventions. For continuous variables, mean ± SD or median (interquartile range) is reported for each group. For categorical variables, the number (%) of patients in each category is reported for each group. The effect size is reported in terms of mean or median difference and relative risk together with the corresponding 95% confidence interval (CI). No test was used to assess the association between compliance and allocated group.

RESULTS

Overall, 84% of eligible patients with an infrarenal AAA treated in the two participating centres were randomised in this pilot at an average recruitment rate of 4.8 (95% CI 3.2—6.4) patients per month. Only three patients who were eligible for the study declined to participate. Overall, 58 participants (mean age 75 years; 10% female) were recruited and randomised during the 1 year study period. Characteristics of the intervention and control groups are summarised in Table 1. Fig. 1 provides a summary of trial recruitment and follow-up. A total of 42 potential participants did not take part in the study for clinical reasons: 38 had a juxta- or suprarenal aneurysm, and four patients had an angiogram 24 h before the EVAR (requiring contrast administration).

Bolus bicarbonate was not used for two participants randomised to the active arm, who as a result received standard hydration only; this was owing to unavailability of the study medication at the time. The patients were randomised out of hours and the clinical trials pharmacy did not have sufficient time to prepare the study medication. No participant withdrew consent and no protocol violations were reported.

All EVAR procedures were completed successfully with no evidence of type 1 endoleak on the completion angiogram. All but two patients (56 of 58 participants, one in each group) received a device with suprarenal fixation. No renal artery related complications were recorded peri-operatively and no renal arteries were covered. Nephrotoxic medications were stopped in all cases 48 h before and after EVAR.

A total of 33% of those who received hydration only (control arm) developed AKI versus 7% of those who received hydration and $NaHCO_3$ (intervention arm). All patients with AKI developed stage 1 AKI and none required dialysis. Only two patients developed AKI based only on urine output drop (one in each group).

The aim was to keep the patients' blood pressure within 80% of the baseline for >90% of time during EVAR, which was achieved in all participants. Patients in the intervention arm received 29 ± 11 min of inotropic support during the EVAR versus 27 ± 12 min in the control arm. Post-operatively, only six patients required inotropic support (three in each group), all during the first 12 h after surgery.

Table 2 provides a summary of results and parameters relating to renal injury. Twelve complications were recorded within 30 days of surgery (Table 3). Two patients with AKI developed acute heart failure (one of whom had a non-ST elevation myocardial infarction). The heart failure in the case of the patient with the myocardial infarction was attributed to cardiogenic shock. The other patient had significant relevant pre-existing comorbidities (New York Heart Association 3 heart failure and chronic kidney disease level 3). Both patients were admitted to the intensive care unit for 48 h, where they received IV diuretics and were eventually discharged within a week with no further sequelae (Clavien Dindo class 4). None of the patients receiving $NaHCO_3$ had a complication exceeding Clavien Dindo class 2.

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Table 1. Baseline characteristics.

Demographics	Standard hydration ($n = 28$)	Standard hydration + bolus bicarbonate ($n = 30$)	Total ($n = 58$)
Demographics			
Median (range) age (y)	75.5 (70–80)	74.5 (73–80)	75 (71–80)
IQR	57–89	66–89	57–89
Sex			
Male	25 (89.3)	27 (90.0)	52 (89.7)
Female	3 (10.7)	3 (10.0)	6 (10.3)
AAA anatomy			
Median (range) maximal diameter (cm)	6.2 (5.9–6.6)	6.7 (5.8–8.1)	6.3 (5.8–6.9)
IQR	5.6–8.9	3.8–9.7	3.8–9.7
Proximal aneurysmal neck length	2.1 (1.5–2.6)	2.0 (1.6–2.6)	2.0 (1.6–2.6)
IQR	1.0–4.0	1.0–4.5	1.0–4.5
Significant proximal neck calcification	4 (14.3)	3 (10.0)	7 (12.1)
Thrombus (>50%)	4 (14.3)	3 (10.0)	7 (12.1)
Cardiovascular and renal injury risk factors			
Previous stroke	1 (3.6)	1 (3.3)	2 (3.5)
Previous MI	7 (25.0)	9 (30.0)	16 (27.6)
Previous TIA	3 (10.7)	7 (23.3)	10 (17.2)
Atrial fibrillation	4 (14.3)	3 (10.0)	7 (12.1)
Angina	7 (25.0)	12 (40.0)	19 (32.8)
Statin use	26 (92.9)	29 (96.7)	55 (94.8)
β blocker use	16 (57.1)	20 (66.7)	36 (62.1)
Aspirin use	21 (75.0)	21 (70.0)	42 (72.4)
Clopidogrel use	2 (7.1)	4 (13.3)	6 (10.3)
Warfarin use	2 (7.1)	1 (3.3)	3 (5.2)
ACE inhibitor use	11 (39.3)	9 (30.0)	20 (34.5)
NSAIDs	0 (0.0)	0 (0.0)	0 (0.0)
Diuretic use	8 (28.6)	14 (46.7)	22 (37.9)
Diabetes	4 (14.3)	4 (13.3)	8 (13.8)
Current smoker	3 (10.7)	1 (3.3)	4 (6.9)
Ex-smoker (>1 year ago)	14 (50.0)	23 (76.7)	37 (63.8)
Antihypertensive treatment	22 (78.6)	17 (56.7)	39 (67.2)
Previous abdominal surgery	12 (42.9)	7 (23.3)	19 (32.8)
Previous abdominal radiation	1 (3.6)	0 (0.0)	1 (1.7)
BMI > 30	4 (14.3)	4 (13.3)	8 (13.8)
Peripheral arterial disease	6 (21.4)	9 (30.0)	15 (25.9)
Renal artery stenosis	0 (0.0)	0 (0.0)	0 (0.0)
Contrast received in the last 2 wk	2 (7.1)	4 (13.3)	6 (10.3)
CKD stage >2	2 (7.1)	4 (13.3)	6 (10.3)
Basic observations			
Median (range) pre-operative BP			
Systolic	139 (126.5–146.5)	144.5 (130–155)	142 (130–152)
IQR	110–162	106–165	106–165
Diastolic	82.5 (77–89)	81 (73–87)	82 (76–88)
IQR	62–92	65–95	62–95
Median (range) pre-operative HR (bpm)	65 (62–77.5)	68.5 (64–80)	68 (63–78)
IQR	52–96	51–91	51–96
Median (range) pre-operative oxygen saturation (%)	97 (96–98)	97 (96–98)	97 (96–98)
IQR	94–100	94–99	94–100
Missing	1	0	1
Median (range) weight (kg)	82 (77.5–89)	80.5 (78–88)	82 (78–88)
IQR	48–132	63–110	48–132
Height (cm)	172 (169.5–179)	173.5 (168–176)	172.5 (168–178)
IQR	148–193	151–181	148–193
Blood tests			
Median (range) serum creatinine (μmol/L)	96.5 (81–115.5)	86 (81–102)	90 (81–109)
IQR	47–197	32–157	32–197
Missing	0	1	1
Median (range) haemoglobin (g/dL)	13.5 (12.4–14.9)	14.0 (12.7–14.5)	13.7 (12.4–14.6)

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Table 1-*continued*

Demographics	Standard hydration ($n = 28$)	Standard hydration + bolus bicarbonate ($n = 30$)	Total ($n = 58$)
IQR	10.7—15.8	10.9—16.4	10.7—16.4
Median (range) eGFR[a]	66.5 (51—115)	65 (50—116)	65.5 (50—116)
IQR	51—121	50—122	50—122
Bio-impedance reading			
Median (range) extracellular (%)	28 (24—31)	23.4 (21—30)	26 (22—30)
IQR	19.4—34	18—50.2	18—50.2
Missing	0	1	1
Median (range) intracellular (%)	27.7 (22—30)	24 (21—28)	26.9 (21.5—29.5)
IQR	16—37.5	18—38.9	16—38.9
Missing	0	2	2
Median (range) fat (%)	28.5 (23.5—32)	30 (24—34)	29 (24—32.2)
IQR	17.5—49	21—49	17.5—49
Missing	0	1	1

Note. Data are *n* (%) unless otherwise indicated. IQR = interquartile range; AAA = abdominal aortic aneurysm; MI = myocardial infarction; TIA = transient ischaemic attack; ACE = angiotensin converting enzyme; NSAID = non-steroidal anti-inflammatory drug; BMI = body mass index; CKD = chronic kidney disease; BP = blood pressure; HR = heart rate; bpm = beats per min; eGFR = estimated glomerular filtration rate.
[a] eGFR calculated using the CKD-EPI formula.

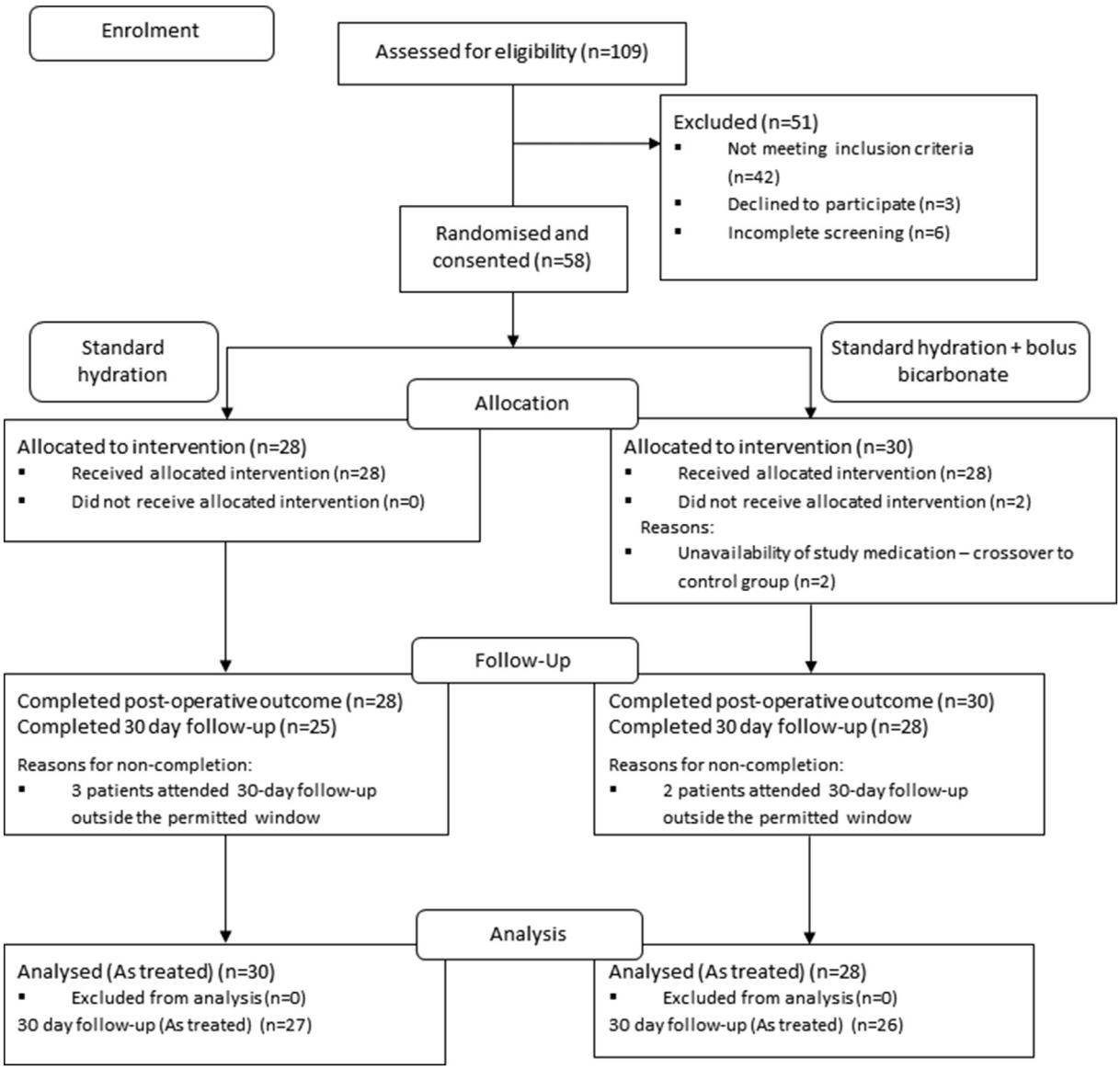

Figure 1. CONSORT diagram (trial flowchart).

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Table 2. Results.

End point	Standard hydration ($n = 30$)	Standard hydration + bolus bicarbonate ($n = 28$)	Effect size (95% CI)
AKI[a]	10 (33.3)	2 (7.1)	0.21 (0.05–0.89)
Serum bicarbonate (difference)[b]	−1.5 ± 1.8	0.6 ± 1.8	2.1 (1.1–3.0)
Missing (*n*)	1	1	
At start of procedure	24.3 ± 1.6	24.6 ± 1.5	
Missing (*n*)	1	1	
At end of procedure	22.8 ± 2.0	25.2 ± 1.8	
pH (difference)[b]	0.0 ± 0.1	0.0 ± 0.5	0.0 (0.0–0.1)
Missing (n)	1	1	
At start of procedure	7.4 ± 0.5	7.4 ± 0.5	
Missing (*n*)	1	1	
At end of procedure	7.4 ± 0.7	7.4 ± 0.6	
Median (IQR) duration of EVAR (min)[c]	154 (130–185)	150 (120–180)	5 (−16 to 30)
Contrast volume[b]	132.7 (62.2)	119.0 (65.6)	−13.7 (−47.3, 19.9)
Median (IQR) duration of post-operative inotropic support[d]	12 (8–17)	10 (1–16)	2 (−8 to 16)
AKI stage > 2[a]	0 (0.0)	0 (0.0)	–
Urine output drop > 6 h[a]	8 (26.7)	1 (3.6)	0.13 (0.02–1.00)
Fluid deficit over 48 h (urine produced − IV fluid)	−110.5 ± 50	90 ± 70	1.17 (1.00–1.77)

Note. CI = confidence interval; AKI = acute kidney injury; IQR, interquartile range; EVAR = endovascular aneurysm repair; IV = intravenous.

[a] Binary outcomes, *n* (%) reported, effect size = relative risk.

[b] Continuous outcomes, mean ± SD reported; effect size = difference in means.

[c] Duration variables, median (IQR) reported; effect size = difference in medians.

[d] Only three patients per group received post-operative inotropic support.

DISCUSSION

The pilot phase has confirmed the safety of this EVAR specific AKI prevention strategy and has shown that recruitment to a large trial investigating the efficacy of this intervention is feasible, with 84% of eligible patients recruited and no trial withdrawals recorded. A definite trial is therefore being planned to definitively test the clinical effectiveness of this intervention.

Table 3. Complications within 30 days of the aneurysm repair.

	Study group Standard hydration ($n = 30$)	Standard hydration + bolus bicarbonate ($n = 28$)
Complications reported		
Yes	7	5
No	22	21
Failed to attend 30 day visit	3	2
Type (non-exclusive)		
Endoleak type 1	0	0
Endoleak type 2	2	3
Other endoleak	0	0
Re-intervention	0	0
Dialysis	0	0
MI	1	0
Stroke/TIA	0	0
Acute heart failure	2	0
UTI	1	0
Buttock claudication	1	0

Note. MI = myocardial infarction; TIA = transient ischaemic attack; UTI = urinary tract infection.

One of the most common complications of EVAR is AKI.[2] AKI is independently associated with short-term morbidity, length of hospital stay, cost, and mortality.[5–7] A series of cohort studies suggest that AKI after EVAR leads to a significant increase in both short and long-term complications and impacts on long-term renal function.[2–4,9,10] Based on previously published data, 20–25% of patients undergoing elective infrarenal EVAR and 28% of those having fenestrated EVAR will develop AKI.[3,4,9,10,19]

Despite the above, there is no high quality evidence regarding prevention of AKI in EVAR. This is partly owing to the complexity of the mechanisms underlying renal injury in EVAR. Contrast induced nephropathy is one of the main mechanisms.[2] However, there are several other factors contributing to AKI during and after EVAR, such as ischaemic nephropathy from renal microemboli caused by EVAR stent graft deployment in the peri-renal aorta;[20] renal macrovascular injury, such as dissection or ostial coverage of renal arteries, leading to renal ischaemia;[21] ischaemia–reperfusion syndrome due to lower limb ischaemia;[22] and hypovolaemia due to blood loss.

As a result, previously reported prevention strategies applicable to general surgery or simpler radiological interventions cannot be extrapolated for use in EVAR. To address this, a novel EVAR specific reno-protection strategy was developed, employing urinary alkalisation with a bolus dose of IV $NaHCO_3$ and a pre-/post-operative intravascular volume expansion regimen. This was chosen because of strong laboratory evidence for the unique scenario of EVAR related AKI: the administration of crystalloid minimises pre-renal injury (hypovolaemia/dehydration); $NaHCO_3$ acts upon the two main insults to the kidney during AAA repair,[23–25]

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as a free radical scavenger (inflammation and reperfusion injury)[23] and by reducing renal tubular ischaemia (contrast injury).[26]

More than 300 studies have reported on the value of $NaHCO_3$ in preventing AKI after sepsis, admission to intensive care, and radiological procedures, including several meta-analyses. Early trials evaluating $NaHCO_3$ versus normal saline (NaCl) hydration in radiological procedures have shown that $NaHCO_3$ is superior.[27] However, $NaHCO_3$ has not been shown to lead to a benefit in all settings with some trials in patients undergoing coronary intervention showing conflicting results.[28,29] Some meta-analyses have also been conflicting, mostly owing to the fact that they pool together data from studies investigating diverse populations, for example septic patients together with patients undergoing coronary procedures. NICE AKI guidance also suggests offering $NaHCO_3$ for patients who are deemed at high risk of AKI if they receive contrast.[11] However, NICE guidance also points out the lack of evidence for major endovascular procedures, such as EVAR. It is also important to note that this guidance and most of the current $NaHCO_3$ evidence relates to slow hydration with $NaHCO_3$ solutions. The vast majority of the currently available studies have used $NaHCO_3$ instead of simple NaCl to substitute the patients' IV fluid infusion and not a rapid infusion of $NaHCO_3$, as proposed in this trial. Rapid $NaHCO_3$ infusion to rapidly alkalinise the urine has recently been found to be superior to NaCl hydration alone.[30] The benefit of this approach is that IV volume expansion can still be given in the standard way, without the need for a slow infusion that substitutes the routine crystalloid infusion. This can prove beneficial in EVAR where AKI develops owing to both contrast toxicity and dehydration/pre-renal injury.

Some small studies have assessed specific methods of reno-protection in EVAR, such as IV volume expansion; ischaemic preconditioning;[31] targeted renal therapy, which involves the administration of vasodilatory agents directly into the renal artery through a catheter;[32] administering $NaHCO_3$ before EVAR (one small study with limited follow-up reported on this);[33] and *N*-acetylcysteine before EVAR (one pilot study reported on 20 patients).[34] These studies have been reported on in a recent systematic review.[10] Unfortunately, all were underpowered and did not use a consistent AKI definition.

In this pilot trial >50% of patients with an infrarenal AAA who presented at the two participating centres over 1 year were successfully recruited. No major adverse events relating to $NaHCO_3$ administration were documented. There were no protocol deviations regarding fluid administration. Two patients did not receive $NaHCO_3$ owing to the fact that the clinical trials pharmacy was unable to provide the trial medication out of hours. The AKI rates differed considerably between the two arms: 7% for those receiving $NaHCO_3$ versus 33% for those in the control arm; however, given that this pilot was not powered to show such a difference, this intervention cannot yet be adopted into clinical practice. A full scale and adequately powered RCT is therefore needed to confirm this potential benefit and detect a specific difference. These results provide sufficient evidence that the proposed intervention is acceptable to both patients and clinicians and may prevent AKI. Furthermore, this study confirms the strong association between major post-operative complications and AKI; all major events occurred in patients who had developed AKI. With regard to planning the future definitive trial, this pilot has confirmed that the incidence of AKI is high after this procedure (33% in the non-intervention arm), which will be the basis of the power and sample size calculations for the definitive trials. Also, it has been confirmed that at least 50% of eligible patients can be recruited into a trial of this nature. Other forms of reno-protection, such as CO_2 imaging, are occasionally applied in EVAR, and the future trial will have to account for that; furthermore, improved imaging in the future, such as exclusive use of a hybrid operating theatre with fusion techniques, may also decrease the incidence of AKI. As a result, it is hoped to include 10 centres from across the UK in the subsequent definitive study.

Challenges encountered such as the out of hours randomisation and attendance of the 30 day visit within a reasonable time window will be carefully considered in the set up of the main trial, which is necessary to fully prove the efficacy of this AKI prevention strategy in EVAR.

Limitations

This was a pilot trial and as such it cannot prove the efficacy of this EVAR specific AKI prevention protocol. Also, two patients allocated to $NaHCO_3$ did not have the medication owing to issues with out of hours randomisation. The anaesthetist administering the medication was not blinded; however, the AKI definition was based on post-operative SCr measurements and urine output, and not on a clinical assessment. Hence, unblinding of the anaesthetist to the intervention should not bias the results of AKI incidence. The fluid strategy was also identical in the two groups. The vast majority of patients (56 of the 58 participants) had an EVAR device with suprarenal fixation. This type of proximal fixation has previously been implicated in the pathogenesis of renal injury in EVAR and this may affect the generalisation of the findings.[35,36] However, suprarenal fixation was not an inclusion criterion and this population reflects contemporary EVAR practice. As far as contrast volumes are concerned, this pilot study was not designed to assess the impact of baseline risk factors on subsequent AKI development. The volume of contrast used in both arms was, indeed, somewhat higher than the reported average in contemporary series. This may be partially explained by the fact that a portable C-arm and not a hybrid operating suite was used in this trial. Finally, no associations between long-term renal function and AKI can be made as this pilot only included 30 day follow-up.

CONCLUSION

Bolus high dose $NaHCO_3$ and hydration is a promising EVAR related AKI prevention method. This trial confirmed the safety and acceptability of this intervention, as well as the

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feasibility of delivering a definitive large RCT to confirm its efficacy in preventing EVAR related AKI.

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CONFLICT OF INTEREST

None.

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