

openheart The use of the RenalGuard system in cardiac surgery with cardiopulmonary bypass: a first in man prospective, observational, feasibility pilot study

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ABSTRACT

Objectives As proof of concept, this prospective, observational study assessed the feasibility and early clinical outcomes of performing on-pump cardiac surgery with the RenalGuard system.

Background Acute kidney injury (AKI) is reported in up to 30% of patients undergoing cardiac surgery and is a recognised independent predictor of both morbidity and mortality. Forced diuresis with the RenalGuard system reduces the incidence of AKI during percutaneous coronary intervention procedures but its use in cardiac surgery has not been explored.

Methods Ten consecutive patients who were at risk of developing AKI during cardiac surgery were selected. The RenalGuard system was used to facilitate forced diuresis using weight-adjusted intravenous furosemide while maintaining neutral fluid balance by matched intravenous fluid replacement. This regimen was initiated preoperatively in all patients and continued for 6–12 hours postoperatively. Serum creatinine, electrolytes and need for renal replacement were documented in all patients.

Results The RenalGuard system functioned successfully in all patients and facilitated high perioperative urine outputs, even when patients were placed on cardiopulmonary bypass (CPB). There were no incidences of significant (A) electrolyte imbalance, (B) changes in haemoglobin levels or (C) pulmonary oedema. No patients developed AKI within 36 hours of surgery despite one patient developing cardiac tamponade 8 hours postoperatively and one patient developing paralytic ileus. One patient, however, was 'electively' haemofiltered on day 2 after developing acute right ventricular failure. The median intensive care stay was 1.5 (1, 5) days.

Conclusion The RenalGuard system can be used successfully in patients undergoing cardiac surgery with CPB and may reduce the incidence of AKI in at-risk patients.

Trial registration NCT02974946; Pre-results.

INTRODUCTION

Acute kidney injury (AKI) is reported in 2%–30% of patients undergoing cardiac surgery.¹ This variability is due to a spectrum of definitions used to classify AKI. It is now customary to use

KEY MESSAGES

What is already known about this subject?

Acute kidney injury (AKI) causes significant morbidity and mortality when it occurs after cardiac surgery. As it is due to multiple factors, so far, there has not been any major treatment strategy to prevent it from occurring.

What does this study add?

This pilot study assessed if it was feasible to use the RenalGuard system in patients undergoing cardiac surgery when the cardiopulmonary bypass machine is used. In this small series feasibility was demonstrated as well as a possible clinical benefit in reducing AKI after cardiac surgery.

How might this impact on clinical practice?

This pilot study has led the way to set up a randomised control trial to assess the clinical benefit and safety of the use of the RenalGuard system. If clinical benefit is proven, using the RenalGuard system will improve cardiac surgery morbidity and mortality significantly by reducing AKI.

the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE),^{2,3} or the Acute Kidney Injury Network (AKIN) consensus criteria.⁴ The development of AKI in the postop cardiac surgery setting is associated with significant morbidity,^{5,6} mortality,⁵ prolonged intensive care unit (ICU) and in-hospital stays,⁷ increased treatment costs and poorer long-term survival and quality of life.^{7–9} As yet, no satisfactory strategy has been successful in preventing AKI despite identifying patients who are at risk of developing AKI.

Previous experience

Pharmacological interventions to reduce AKI have produced inconsistent results and include the use of preoperative hydration, dopamine, mannitol and

dexamethasone.¹⁰ Evidence for the use of furosemide alone has also been conflicting. Diuretics reduce renal oxygen consumption and high urine outputs can be achieved with intravenous furosemide during cardiac surgery.¹¹ Continuous intravenous furosemide infusion has been shown to reduce the need for post-operative haemofiltration but contrasting studies have even shown detrimental effects of using peri-operative furosemide.¹² Importantly, forced diuresis with furosemide can lead to volume depletion if adequate fluid replacement is not achieved which may adversely impact on renal perfusion. It is therefore not yet clear whether forced diuresis with simultaneous balancing of urine output with intravenous fluid infusion (to prevent hypovolaemia) would be of benefit in reducing AKI. Forced diuresis to achieve high urine flow rate of >150 mL/hour has shown to reduce serum creatinine levels.¹³ However, use of high dose of diuretics (furosemide >1 mg/kg) and associated hypovolaemia resulted in high incidence of AKI.^{14 15} The RenalGuard system uses low dose of diuretics to initiate the forced diuresis and maintains intravascular volume by infusing maintenance fluids to match the urine output.

New intervention

The use of the RenalGuard system (RenalGuard, PLC Medical Systems, Milford, Massachusetts, USA) has been investigated at reducing AKI in patients at risk of contrast-induced nephropathy when undergoing either percutaneous coronary intervention (PCI) or transcatheter aortic valve implantation (TAVI).^{13 16–18} These studies showed that in patients with chronic kidney disease, the RenalGuard System reduced the incidence of AKI by 60%–75% as compared with controls. The RenalGuard system uses forced diuresis with low dose (0.25–0.5 mg/kg) of furosemide along with administration of intravenous fluids matched in real time to urine output to prevent inadvertent volume depletion. It should be noted, however, that AKI in these situations is due to contrast nephropathy

but in the setting of cardiopulmonary bypass (CPB), the aetiology of the AKI is likely to be multifactorial.

The RenalGuard system

The various components of this system have previously been reported.¹⁷ Essentially, it includes a closed-loop fluid management system, a high-volume fluid pump, a high-accuracy dual weight measuring system, motion-detection artefact reduction, a single-use intravenous set and urine collection system that interfaces with a standard Foley catheter, real-time display of urine and replacement fluid volume, timely alerts to drain the urine bag or to replace the hydration fluid bag, and safety features such as automatic air and occlusion detection. The console measures the volume of urine in the collecting set (also calculates the urine flow rate) and infuses an equal volume of hydration fluid to match the urine output. The console allows the user to set to achieve a net fluid gain or loss above matched hydration. The console also allows infusion of a bolus of fluids at the user's request.

The use of the RenalGuard system in patients undergoing cardiac surgery has not been investigated. We describe our initial first-in-man experience with this system in cardiac surgery patients and evaluate: (A) the feasibility and safety of using the device, particularly during CPB, (B) the impact of its use on electrolytes, fluid balance and haemoglobin levels and (C) its effect on kidney function in the postoperative phase.

METHODS

Patient's selection for being at risk of developing AKI was based on our unit's own experience,⁷ and previous report.¹ For the purpose of this pilot study, the RIFLE definition for AKI was used. Creatinine was used as the marker for AKI rather than cystatin-c or neutrophil gelatinase-associated lipocalin. Ten consecutive patients (under the care of a single surgeon—HL) who were at risk of developing AKI were selected. During that same period 41 patients underwent cardiac surgery under the

Table 1 The patients' preop characteristics

Ptnum	Gender	Age, years	Diabetes	PVD	Priority	CABG	Valve	LogEuroscore
1	Male	51	NIDDM	No	Urgent	Yes	No	0.88
2	Female	76	Non	No	Elective	Yes	Yes	6.19
3	Male	71	NIDDM	No	Elective	Yes	No	1.94
4	Male	82	Non	No	Elective	Yes	Yes	10.38
5	Male	74	Non	Yes	Urgent	Yes	No	14.1
6	Male	66	Non	No	Urgent	Yes	No	2.11
7	Male	63	Non	No	Elective	Yes	No	6.24
8	Male	76	NIDDM	No	Elective	Yes	No	2.69
9	Male	57	NIDDM	Yes	Elective	Yes	No	2.54
10	Male	74	NIDDM	Yes	Elective	Yes	No	4.45

CABG, coronary artery bypass grafting; IDDM, Insulin dependent diabetes; NIDDM, non-insulin dependent diabetes; Ptnum, patient number; PVD, peripheral vascular disease.

Table 2 The serum creatinine and eGFR between preop and postop values

Ptnum	preop eGFR	Preop creatinine	Discharge eGFR	Creat D1	Creat D2	Creat D3	Max % change in Creat
1	90	72	90	95	72	75	31%
2	49	97	N/A	120	123	97	27%
3	89	72	90	61	82	66	14%
4	36	170	30	143	155	172	1%
5	44	135	40	157	142	146	16%
6	33	180	28	186	202	213	18%
7	27	217	24	273	279	242	29%
8	86	72	90	77	76	74	4%
9	61	105	63	98	114	103	9%
10	57	110	51	138	152	136	27%

eGFR, estimated glomerular filtration rate (Cockcroft-Gault); Creat D1, creatinine level on day 1 postop; Creat D2, creatinine level on day 2 postop; Creat D3, creatinine level on day 3 postop (serum creatinine in $\mu\text{mol/L}$ (to convert to mg/dL , divide by 88.4)); Ptnum, patient number.

care of the same surgeon. The patients were anaesthetised by the same anaesthetist (RG).

This project was reviewed and ethically agreed by the Hospital's 'Patients Safety Investigation Group (PSIG)' as an initial evaluation of the device (Reference T:PSIG/JAN2016, meeting date 15 January 2016). All patients gave written consent for the use of the device and patients were treated according to the Declaration of Helsinki 1964 (amended Edinburgh 2000).

In previous reports, when used in patients undergoing PCI or TAVI, the RenalGuard system was started around 90 min preprocedure in order to achieve a urine output rate of 300 mL/hour prior to contrast injection. It was then continued during the procedure and for 4 hours after last contrast injection.^{16,17} We aimed to apply a similar protocol for our patient group but elected to continue for longer (6–12 hours on ICU) in recognition of the late renal damage seen in previous studies in cardiac surgery.¹⁹ Patients were commenced on intravenous Hartmann's solution controlled by the RenalGuard system.

Furosemide (20 mg) was administered intravenously to achieve an optimal urine flow of 300 mL/

hour. Controlled hydration by the RenalGuard system continued during the procedure and for 6–12 hours after the patient was transferred to the cardiac intensive care unit (CICU). Urine flow was monitored and maintained at the target value throughout and additional furosemide doses were given when urine flow fell below this target value. Real-time matched hydration was facilitated by the RenalGuard system in all patients, that is, any volume of urine produced was matched by infusion with the same volume of Hartmann's solution instantaneously.

CPB was carried out using the centrifugal pump in a non-pulsatile mode aiming for a flow of 2.4 L/min/m² at mild hypothermia (34°C for coronary artery bypass grafting (CABG) and 32°C for aortic valve replacement (AVR)). For patients undergoing CABG, the proximal anastomoses were performed with the cross-clamp still in situ (ie, a single clamp technique).

Table 3 Urine and Hartmann's replacement volumes during RenalGuard use

Ptnum	Furosemide bolus	Additional furosemide	Total urine (mL)	Total intravenous Hartmann's solution (mL)	Total time (hours)	Weight (kg)	BSA	Urine (ml/hour/BSA)
1	20 mg	20 mg × 5 bolus	9350	9848	18	77	1.89	275
2		20 mg × 3 bolus	2947	3206	13	80	1.75	130
3	40 mg	20 mg bolus	7226	7478	18	104	2.32	173
4	40 mg	20 mg bolus	4539	4538	12	98	2.08	182
5	40 mg	5 mg infusion	4964	4895	12	70	1.77	234
6	20 mg	5 mg infusion	3972	3974	11	76	1.92	188
7	40 mg	5 mg infusion	2076	2076	11	94	2.08	91
8	40 mg	5 mg infusion	5358	5361	13	108	2.23	185
9	20 mg	10 mg infusion	5372	5373	10	74	1.8	298
10	40 mg	10 mg infusion	5051	5051	10	71	1.85	273

BSA: body surface area; Ptnum, patient number.

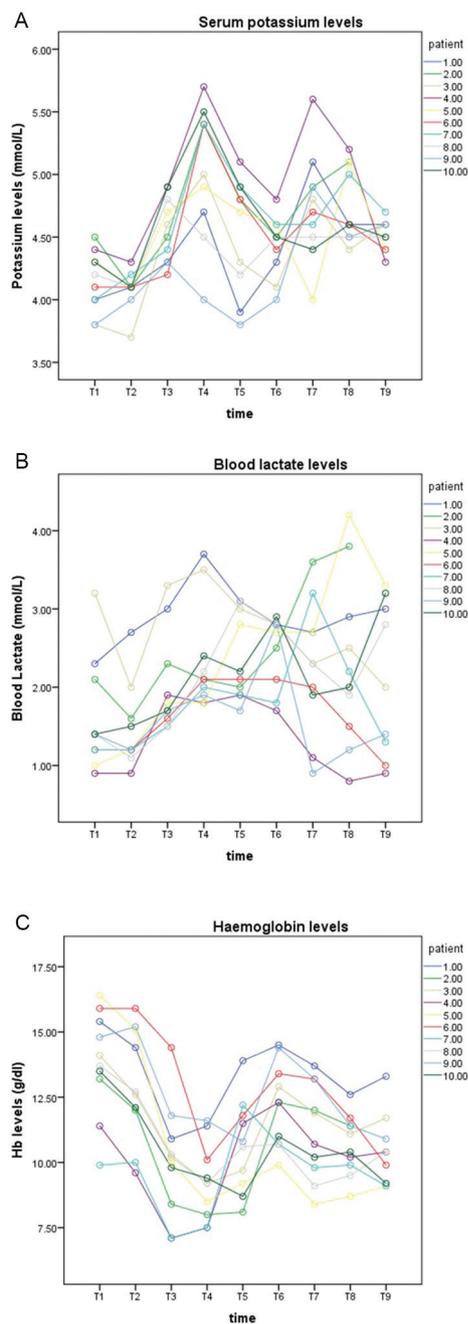


Figure 1 (A) Serum potassium levels for each patient at various time intervals. (B) Serum lactate levels for each patient at various time intervals. (C) Haemoglobin levels for each patient at various time intervals. Time intervals: T1—prestart of RenalGuard system—baseline; T2—poststart of RenalGuard system/pre-cardiopulmonary bypass (CPB) start. T3—within 15 min after CPB initiation. T4—60 min postinitiation of CPB. T5—post-CPB. T6—on admission to CICU. T7—4 hours post-CICU admission. T8—8 hours post CICU admission. T9—16 hours post CICU admission.

Categorical data are expressed as percentage. Continuous variables are expressed as mean (SD) or median (range) for Gaussian and skewed distributed data, respectively.

RESULTS

The patients' characteristics are summarised in [table 1](#).

For the first three patients, the RenalGuard system was initiated 1 hour prior to the patient being transferred to the anaesthetic room (around 2 hours prior to skin incision). Thereafter, for the remaining seven patients, the system was initiated in the anaesthetic room (around 1 hour prior to skin incision) after induction of anaesthesia. For the first five patients, the RenalGuard system was continued for 12 hours post-transfer to CICU while for the latter five patients the system was discontinued after 6 hours post-CICU transfer. These adjustments were made as we learnt more about the way the device functioned in patients undergoing cardiac surgery.

During this assessment period, matched diuresis with the RenalGuard system was achieved in all patients, even during CPB when reduced urine output might be anticipated. The changes in the serum creatinine and estimated Glomerular filtration rate (eGFR) between preop and postop values are shown in [table 2](#) and urine as well as Hartmann's replacement volumes are depicted in [table 3](#).

The changes in electrolytes (potassium), lactate and haemoglobin levels for each patient along the various time points are illustrated in [figure 1A-C](#).

Only one patient required continuous venovenous haemofiltration (CVVHF) on day 2 after developing acute right ventricular failure. The other patients did not have any significant deterioration in renal function despite one patient developing cardiac tamponade 8 hours post-operatively and one patient developing paralytic ileus. Other postoperative complications are listed in [table 4](#).

Two patients died, one of sudden acute right ventricular failure and the other due to a stroke 1 week postoperatively. Both of these were not thought to be related to the use of the RenalGuard system.

Median CICU stay was 1.5 (1, 5) days and median in-hospital stay was 6 (3, 36) days. The long duration of in-hospital stay related to (A) patient '5' who developed several episodes of intermittent acute bowel obstruction on a background of previous abdominourlogical surgery (cystectomy for bladder cancer and formation of an ileal urostomy) and (B) patient '8' who developed a stroke a week postop requiring CICU readmission and re-intubation.

DISCUSSION

The RenalGuard system can be used successfully and safely in patients undergoing cardiac surgery with the CPB machine.

During our experience, the device set-up was modified as compared when used in patients undergoing PCI and TAVI. The initiation of the device is feasible after induction of anaesthesia and a urine output of 200–300 mL/min is acceptable during the whole process. Lower urine outputs on the CICU might be an early indicator of reduced renal perfusion. Indeed, in two patients who developed postoperative mechanical complications (one developed severe right ventricular dysfunction and the

Table 4 Perioperative and postoperative data

Ptnum	CPB time (mins)	ICU stay (days)	AF	Confusion	Stroke	GI comp	CVVHF	Postoperative stay (days)
1	109	1	No	No	No	No	No	3
2	93	–	No	No	No	No	Yes	–
3	90	1	AF	No	No	No	No	7
4	131	1	AF	No	No	No	No	9
5	95	5	No	No	No	Ileus	No	36
6	102	1	No	No	No	No	No	4
7	120	2	No	No	No	No	No	7
8	152	3	AF	No	Yes	Ileus	No	–
9	76	3	No	No	No	No	No	5
10	97	2	No	No	No	No	No	5

CPB time, duration of cardiopulmonary bypass; ICU, intensive care unit; AF, atrial fibrillation; GI, gastrointestinal; CVVHF, continuous venovenous haemofiltration; Ptnum, patient number.

other developed tamponade requiring surgical intervention), reduced urine flow was the first indicator of physiological compromise despite otherwise normal haemodynamic measurements at that point in time.

The urine flow decreased soon after induction of anaesthesia and returned to the desired level (200–300 mL/min) provided the mean arterial pressure was maintained at >65 mm Hg. In hypertensive patients, this level can be as high as 75 mm Hg. After knife-to-skin and prior to initiation of CPB, similar changes were noted. Hence, this part of the procedure can be an important contributing factor to the development of AKI and is often overlooked.

When the CPB was initiated, the urine flow was dependent on the mean perfusion pressure, the flow rate as set by the CPB machine and the presence of pulsatility. The latter was more evident in the patient with chronic kidney disease (CKD) (patient 7). His urine flow was zero throughout the whole CPB run despite increasing mean arterial pressure (MAP). Interestingly despite starting with a preoperative creatinine of 217 micromol/L (eGFR 41) and having no urine output during the 120 min of the CPB run, he maintained a good urine output in the postop period. He did not develop AKI as per RIFLE criteria with his creatinine peaking at 279 micromol/L and his ICU stay was only 2 days. He did not require CVVHF.

Previous studies of furosemide in cardiac surgery (without matched hydration) have shown the ability to achieve polyuria but this has not consistently translated into renal protection.²⁰ A randomised study comparing furosemide infusion with placebo showed a threefold increase in urine outputs with furosemide without any significant reduction in 12-hour postoperative serum creatinine. However, only 25% extra intravenous fluid was used in the furosemide group which may have led to relative hypovolaemia and limited any benefits of forced diuresis.²⁰ The RenalGuard system therefore ensures that neutral fluid balance is maintained throughout despite forced diuresis and may mitigate against the risks of hypovolaemia and consequent renal damage.

Finally, should this device be proven to be beneficial to the patients in the cardiac surgery setting, then appropriate cost-analysis studies will be required to assess the

cost of the device as offset to the cost of treating AKI, especially bearing in mind the cost of CVVHF and prolonged ICU stay.

This study was performed and reported as per the STROBE recommendations.²¹

Limitations

This is a small report of 10 patients assessing the feasibility and potential benefit of the RenalGuard system. It is limited by the small number in the group and the lack of a randomised comparison group. Moreover, the patients selected were those who were felt to be at risk of developing AKI. Thus the findings of this study cannot be generalised as yet until further information from a randomised control trial is available.

CONCLUSION

This first-in-man assessment of the RenalGuard system in patients undergoing cardiac surgery with the CPB machine has shown that this is feasible. The clinically significant benefits as well as any cost savings will need to be investigated by a randomised control trial. This has been set up (ClinicalTrials.gov: NCT02974946). Recruitment has started and the study will report in around 18 months.

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Contributors This study was conceptualised by HL, RG and BW. The project was set up by all of the authors listed. Data were collected by HL, RG, BW and A-MH. Data were analysed by AN. All authors contributed to the writing up of the manuscript and agreed to the current final version being submitted for publication.

Competing interests None declared.

Ethics approval Institutional Approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data for this pilot study are available for review by contacting the main author.

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