


Balanced forced-diuresis as a renal protective approach in cardiac surgery: Secondary outcomes of electrolyte changes

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Funding information

National Institute of Healthcare Research, Grant/Award Number: NIHR CRN No 32769; RenalGuard Solutions

Abstract

Objectives: Forced-diuresis during cardiopulmonary bypass (CPB) can be associated with significant electrolyte shifts. This study reports on the serum electrolyte changes during balanced forced-diuresis with the RenalGuard® system (RG) during CPB.

Methods: Patients at risk of acute kidney injury (AKI)—(history of diabetes &/or anaemia, e-GFR 20–60 ml/min/1.73 m², anticipated CPB time >120 min, Log Euro-Score >5)—were randomized to either RG (study group) or managed as per current practice (control group).

Results: The use of RG reduced AKI rate (10% for RG and 20.9% in control, $p = .03$). Mean urine output was significantly higher in the RG group during surgery (2366 ± 877 ml vs. 765 ± 549 ml, $p < .001$). The serum potassium levels were maintained between 3.96 and 4.97 mmol/L for the RG group and 4.02 and 5.23 mmol/L for the controls. Median potassium supplemental dose was 60 (0–220) mmol (RG group) as compared to 30 (0–190) mmol for control group over first 24 h ($p < .001$). On Day 1 post-op, there were no significant differences in the serum sodium, potassium, calcium, magnesium, phosphate, and chloride levels between the two groups. Otherwise, postoperative clinical recovery was also similar.

Conclusions: Balanced forced-diuresis with the RG reduced AKI rates after on-pump cardiac surgery compared to controls. Although the RG group required higher doses of IV potassium replacement in the postoperative period, normal serum levels of potassium were maintained by appropriate intravenous potassium supplementation and the clinical outcomes between groups were similar.

KEYWORDS

acute kidney injury, balanced forced diuresis, cardiac surgery

Abbreviations: AKI, acute kidney injury; CICU, cardiac intensive care unit; CIN, contrast induced nephropathy; CONSORT, Consolidated Standards of Reporting Trials; CPB, cardiopulmonary bypass machine; CVP, central venous pressure; e-GFR, estimated-glomerular filtration rate; i.v., intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; KIDNEY, study Kidney protection using the RenalGuard® system in cardiac surgery; MAP, mean arterial pressure; NKCC2, sodium potassium chloride co-transporter; OR, operating room; RG, RenalGuard® system; RIFLE, Risk, Injury, Failure, Loss of kidney function, End-stage renal disease; R & D, Research & Development; SD, standard deviation; TAL, thick ascending limb.

Institution where work was performed: Heart & Lung Centre, Wolverhampton, UK

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1 | INTRODUCTION

The development of acute kidney injury (AKI) after cardiac surgery has been reported to be associated with significant postoperative morbidity and mortality both in the short-term and the long-term.^{1,2} Many strategies have been described to reduce AKI³ and the use of the RenalGuard® system (RG) (RenalGuard Solutions Inc.) has recently been reported to reduce AKI rates after cardiac surgery.⁴

The principles and components of RG have been extensively described in previous reports.^{4,5} In brief, it is a closed-loop fluid management system which allows forced-diuresis to be induced with low dose (0.25–0.5 mg/Kg) furosemide while inadvertent volume depletion is prevented by the administration of intravenous (i.v) fluids at a rate which can be matched in real-time to the urine output. Its components include a high-volume fluid pump, a high-accuracy dual weight measuring system, a single-use i.v set and a urine collection system that interfaces with standard Foley urinary catheter. There are, also, (a) real-time displays of fluid replacement and urine volumes, (b) safety features such as automatic air and occlusion detection and (c) alerts to drain the urine bag or to replace hydration fluid bag. The RG console measures the volume of urine in the collecting set, then calculates urine flow rate and finally, infuses a pre-set volume of hydration fluid to match the urine output, as decided by the treating physician. The console allows the user to set either an overall equal fluid balance (zero balance) or a net fluid gain above or loss below matched hydration as well as allowing the user to infuse fluid boluses.

It is well recognised that diuresis, especially by loop diuretics, is associated with electrolyte losses. The loop diuretics block the NKCC2 (sodium potassium chloride co-transporter) channels present on the apical membrane of the thick ascending limb of the loop of Henle causing sodium and potassium excretion in the urine.⁶ Other effects of loop diuretics include metabolic alkalosis, hypocalcaemia, hypomagnesemia and hypochloroemia. Moreover, the use of the cardiopulmonary bypass machine (CPB) during cardiac surgery also causes significant volume and electrolytes shifts.⁷ These changes can lead to arrhythmias, cardiac dysfunction, brain oedema and in severe cases, neuronal demyelination.⁸ These effects are modulated due to alterations in cellular metabolism, cell membrane potentials and energy transformations. It is therefore imperative that the electrolytes levels are monitored during cardiac surgery and replenished appropriately and in a timely fashion.

This randomised control trial assessed the electrolyte changes (secondary outcomes) between patients treated with balanced forced-diuresis (RG group) compared to controls, during cardiac surgery and within the first 24-h post-op, along with the clinical impact during the in-hospital stay.

2 | MATERIALS AND METHODS

2.1 | Ethical approval

The KIDNEY study (Kidney protection using the RenalGuard® system in cardiac surgery) was reviewed and approved by the

Institutional Research Committee (16CARD13) before seeking Ethical committee (16/NI/0246, 2nd December 2016) approval and was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) website (NCT02974946). The study was also supported by the National Institute of Healthcare Research, Clinical Research Network, United Kingdom (NIHR ID: 32769). All recruited patients gave written informed consent to partake in the study. Trial patients were treated according to the Declaration of Helsinki 2013.

2.2 | Aims and objectives

The primary aim of the study assessed the impact of the RG system on the reduction of AKI (RIFLE—Risk, Injury, Failure, Loss of kidney function, End-stage renal disease—criteria definition—50% increase in pre-op “baseline” serum creatinine within first 3 days of surgery) in patients undergoing cardiac surgery. Baseline creatinine was defined as latest creatinine level available before surgery. Secondary aims included the electrolyte changes during surgery and within 24-h post-op as well as their impact on clinical outcomes during hospital stay. The primary outcome has already been published⁴ and the secondary objectives are being reported in this study.

2.3 | Inclusion criteria

The inclusion criteria for recruited patients were one or more of the following: (i) diabetics (insulin or noninsulin dependent diabetes mellitus), (ii) eGFR of 20–60 ml/min/1.73 m², (iii) Logistic Euroscore of 5 or above, (iv) haemoglobin level of 12.5 g/dl or below and (v) cardiac procedures when CPB time was likely to exceed 120 min.

2.4 | Interventions

A research-independent person based in the Research & Development department devised and managed a sealed opaque envelope system for randomisation of consented patients. In patients randomised to the RG system, balanced forced diuresis was started in anaesthetic room after patient intubation and continued throughout the cardiac procedure in the operating room (OR) and for up to 6 h after cardiac intensive care unit (CICU) admission. Forced-diuresis was initiated with 20 mg bolus of IV furosemide. In some patients, the urine output rate was maintained by a furosemide infusion which was titrated to 10 mg/hour during surgery, with the aim of achieving a urine output of at least 200 ml/hour. This infusion was stopped in the OR at the end of procedure. In this study, patients were managed at a zero balance i.e. volume of urine output was matched in real-time to the volume of Hartmann's fluid replacement infusion given through the RG system. On CICU, the RG system was continued for 6 h (matching Hartmann's i.v infusion rate to urine output rate). Additional furosemide bolus (20 mg i.v) was administered whenever the urine output fell below the 200 ml/hour threshold within the first 6-h

postadmission to CICU. Control group patients were managed as per current medical practice. They did not receive i.v furosemide in the OR. Otherwise, the management of the patients was similar including the anaesthetic technique and cardiopulmonary bypass run including the need for inotropic support to maintain a mean arterial pressure (MAP) >65 mmHg. CPB-flow was calculated and maintained at a cardiac index of 2.4 l/min/m². Bypass was performed at mild to moderate (32–34°C) hypothermia and patients were warmed to nasopharyngeal temperature of 36.5–37°C and bladder temperature of >35°C before discontinuation of CPB. The cardioplegia solution (Harefield Hospital formulation) had the following constituents: sodium—147 mmol/l, potassium—84 mmol/l, calcium—2 mmol/l, magnesium—80 mmol/l, procaine—5 mmol/l and chloride 400 mmol/l. This was mixed with cold blood in a ratio 1:4 for myocardial protection during surgery.

2.5 | Statistical analysis

To achieve the primary end-point with a power of 0.8 and an alpha of 0.05, 110 patients per group were deemed adequate as per the power calculations. Categorical data are expressed as percentages and differences between the two groups assessed using the chi square (χ^2) test of independence. Continuous variables are expressed as median (minimum, maximum) or mean (SD) for skewed and Gaussian distributed data, respectively. Group comparison was carried out using two-tailed *t* test or Mann–Whitney *U* test accordingly. Repeated measures were analysed via the generalised linear model for the changes in the variables (electrolytes, lactate, haemoglobin levels) across the various time points between the two groups and adjusted for any differences by the Bonferroni corrections. The tests were considered significant at $p < .05$. SPSS version 26.0 (IBM SPSS statistics 26) was used for statistical analyses.

Patients' recruitment was from 1st March 2017 to 4th September 2019. All patients' data were analysed on an intention to treat basis.

3 | RESULTS

A total of 220 patients were randomised to the study (110 patients per group). Pre and intraoperative patients' data were not significantly different between the two groups (Table 1). The primary outcome of postoperative AKI was significantly lower in the RG group as compared to controls (10% vs. 20.9%, $p = .025$).

The secondary aims of mean volumes of urine produced during surgery (2366 ± 877 ml vs. 765 ± 549 ml) and within first 24-h post-op on CICU (3310 ± 1303 ml vs. 2052 ± 804 ml) were significantly higher in RG group ($p < .001$).

The median volumes of cold blood cardioplegia used were 2070 (995, 5381) ml and 1933 (1000, 5339) ml, respectively ($p = .8$). Patients in RG group received a median dose of 28 (0, 92) mg i.v furosemide in the OR. On the CICU 61% of study group (median dose

20 [0, 160] mg) and 53% of control group (median dose 20 [0, 180] mg) received i.v furosemide within the first 24 h of CICU admission ($p = .99$). There were no statistically significant differences between the groups in terms of the MAP and CVP during surgery and on the CICU. Similarly, there was no significant difference between (a) the haemoglobin levels during and after surgery (Figure 1) and (b) the postoperative blood transfusion rates (27% vs. 19%, $p = .16$), inclusive of intraoperative transfusions.

Patients in the study group required significantly higher doses of i.v potassium supplementation to maintain normal serum levels, with median potassium supplemental dose being 60 (0–220) mmol for RG as compared to 30 (0–190) mmol for control group over 24 h ($p < .001$). The serum potassium levels were maintained between 3.96 and 4.97 mmol/L for the RG group and 4.02 and 5.23 mmol/L for the controls. The changes in the strong ion difference ($[Na^+ + K^+ + Ca^{2+} + Mg^{2+}$ levels] minus $[Cl^- + lactate$ levels]) are shown in Figure 2. The changes in serum electrolytes (sodium, potassium), lactate and pH levels are depicted in Figure 3. On the first postoperative day, there were no significant differences in the sodium, potassium, calcium, magnesium, phosphate and chloride serum levels, between the two groups (Table 1).

There was no significant difference in incidence of atrial fibrillation rate, infections (chest, surgical site infection, sepsis), postoperative cerebro-vascular events rate and median durations of CICU stays between the two groups. The median in-hospital stay was 6 days for both groups.

One patient in RG group and two patients in control group died before hospital discharge. Causes of death were not related to the use of device and included cardiogenic shock, cardiac failure and sepsis (pneumonia) respectively.

4 | DISCUSSION

The primary aim of this study was confirmed⁴ as AKI rate was reduced when the RG system was used perioperatively in cardiac surgery. The study also found that there were statistically significant electrolyte shifts during the use of the CPB and when it is combined with forced-diuresis provided by the RG system. However, these changes did not impact on clinical outcomes.

Polderman reported electrolytes depletion in patients undergoing surgery with the CPB machine. The author suggested that these could be due to the intracellular shifts of electrolytes which are induced by hypothermia as well as urinary excretion of these electrolytes which was independent of the use of perioperative diuretics.⁹ The current study confirmed similar electrolyte shifts. However, clinically there was no significant difference in the patients' recovery as the levels of these electrolytes were closely monitored and supplementation of any electrolyte depletion was carried out in a timely manner.

Another important aspect which could influence electrolyte shifts is the acid–base status of the patient in particular, alkalosis.⁷ The latter is also assessed regularly during cardiac surgery and in the

	RG group (n = 110)	Control group (n = 110)	p value
Age ^a , years	67.8 (9.3)	67.0 (9.2)	.33
Male (n, %)	87, 79%	84, 76%	.63
Nondiabetics (n, %)	30, 27%	30, 27%	.66
Pre-op CVA (n, %)	11, 10%	8, 7%	.63
Urgent surgery (n, %)	34, 31%	24, 22%	.13
STS mortality score ^b	0.96 (0.24, 6.63)	0.88 (0.20, 6.95)	.15
Pre-op creatinine ^a , micromol/L	99.0 (28.2)	98.3 (34.7)	.29
Pre-op haemoglobin ^a , g/L	135 (16)	134 (18)	.72
Operative procedures			.38
Isolated CABG (n, %)	53, 48%	59, 54%	
Isolated valve (n, %)	15, 15%	19, 18%	
Combined procedures (n, %)	40, 37%	31, 28%	
Day-1 sodium level ^a , mmol/L	139 (3)	139 (2)	.35
Day-1 potassium level ^a , mmol/L	4.7 (0.2)	4.7 (0.3)	.79
Day-1 calcium level ^a , mmol/L	1.2 (0.3)	1.3 (0.4)	.06
Day-1 magnesium level ^a , mmol/L	1.1 (0.2)	1.1 (0.2)	.41
Day-1 phosphate level ^a , mmol/L	1.1 (0.2)	1.1 (0.2)	.21
Day-1 bicarbonate level ^a , mmol/L	24 (2)	24 (2)	.92
Day-1 chloride level ^a , mmol/L	105 (2)	105 (3)	.79
Day-1 Haemoglobin ^a , g/L	99 (15)	102 (16)	.29

Abbreviations: CABG, coronary artery bypass surgery; CICU, cardiac intensive care unit; CVA, cerebro-vascular accident; e-GFR, estimated glomerular filtration rate; STS, Society of Thoracic Surgery.

^aDenotes mean (SD).

^bDenotes median (minimum, maximum).

postoperative phase. There was no significant difference between the two groups in terms of bicarbonate and pH levels. Correction of acid-base disturbances can be through respiratory, renal or pharmacological routes.

The use of CPB circuit is recognized to lead to metabolic acidosis possible as a consequence of bicarbonate dilution.¹⁰ As per the Stewart calculations,¹¹ metabolic acid-base status is a function of two independent variables interacting in intravascular and interstitial compartments: the strong ion difference and the concentration of nonvolatile weak acid. The former is the net charge of all fully dissociated ions (sum of Na⁺, K⁺, Ca²⁺, Mg²⁺ levels minus the sum of Cl⁻ and lactate levels). As for the weak-acid, it consists of albumin and phosphate in the extracellular fluid, whereas within erythrocytes, it is primarily haemoglobin. An isolated increase in weak-acid or a decrease in strong ion difference creates a metabolic acidosis. Changes in opposite directions, respectively, cause a metabolic alkalosis. In normal individuals not undergoing surgery a strong ion difference of around 40–45 mEq/L is considered normal¹² whereas during a CPB run, a crystalloid strong ion difference of 24 mEq/L produces a balanced CPB with normal acid-base status.¹³ In this study the mean

TABLE 1 Peri-op characteristics of patients in the two groups

strong ion difference between the RG group and control group was similar at most time-points except during the period of 6–12 h post ICU admission (Figure 2). Nevertheless, it was maintained between 30 and 45 mEq/L throughout the perioperative period.

The CPB circuit also causes significant haemodilution, hypomagnesaemia, and hyponatraemia. Haemodilution, as also discussed, causes acid-base changes. The degree of haemodilution can be minimized by using the retrograde autologous priming technique (RAP) where the priming volume is kept to around 1 L.¹⁴ This approach was used during this study and despite large volume diuresis and volume replacement in the RG group, the transfusion rate was similar between both groups as were the haemoglobin levels around the perioperative period. Precipitous hyponatraemia on CPB initiation can lead to osmotic demyelination syndrome causing cerebral injury and paralysis.⁸ Moreover, forced diuresis can exacerbate the degree of sodium ion loss. Thus it is important that the electrolytes are monitored appropriately. Last but not least, low magnesium levels have been reported during and after CPB.¹⁵ This can translate into clinical episodes of cardiac arrhythmias. In this study, both groups had similar and normal levels of magnesium.

Peri-operative haemoglobin levels ($p > 0.05$)

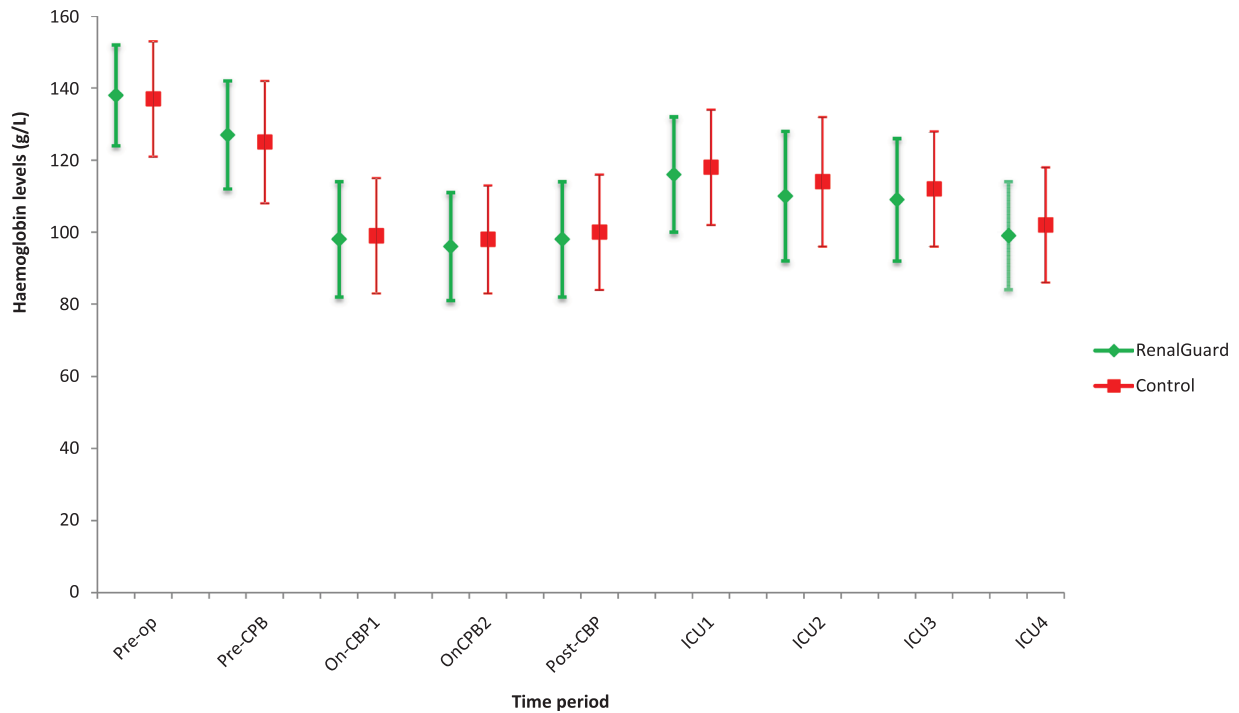


FIGURE 1 Haemoglobin levels in the perioperative period. Pre-op: in anaesthetic room, Pre-CBP: before initiation of cardiopulmonary bypass. On-CBP1: on cardiopulmonary bypass for 15 min, On-CBP2: before stopping cardiopulmonary bypass, Post-CBP: poststopping cardiopulmonary bypass for 15 min. ICU1: on arrival to ICU, ICU2: on ICU for 6 h, ICU3: On ICU for 12 h, ICU4: On ICU for 24 h. ICU, intensive care unit

Strong ion difference levels ($p > 0.05$, except at ICU-6hr* & ICU-12hr*)

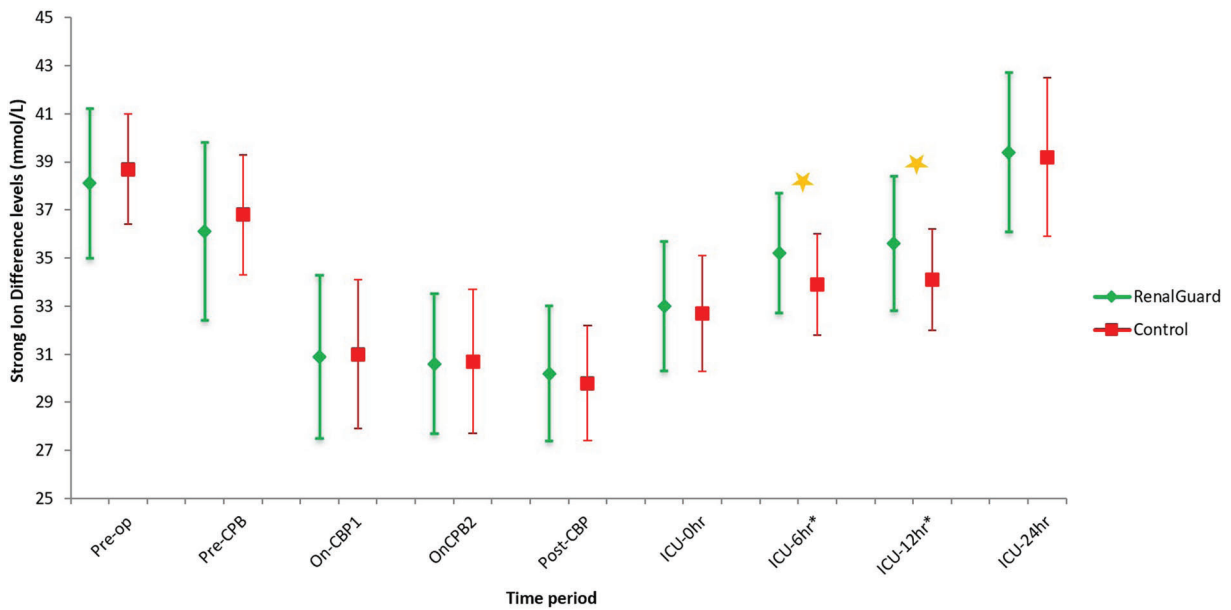


FIGURE 2 The strong ion difference levels (not significantly different except at ICU2* & ICU3* periods) at various time periods—Pre-op: In anaesthetic room, Pre-CBP: before initiation of cardiopulmonary bypass. On-CBP1: on cardiopulmonary bypass for 15 min. On-CBP2: before stopping cardiopulmonary bypass, post-CBP: poststopping cardiopulmonary bypass for 15 min. ICU-0 h: on arrival to ICU, ICU-6 h: on ICU for 6 h, ICU-12 h: on ICU for 12 h, ICU-24 h: on ICU for 24 h. ICU, intensive care unit

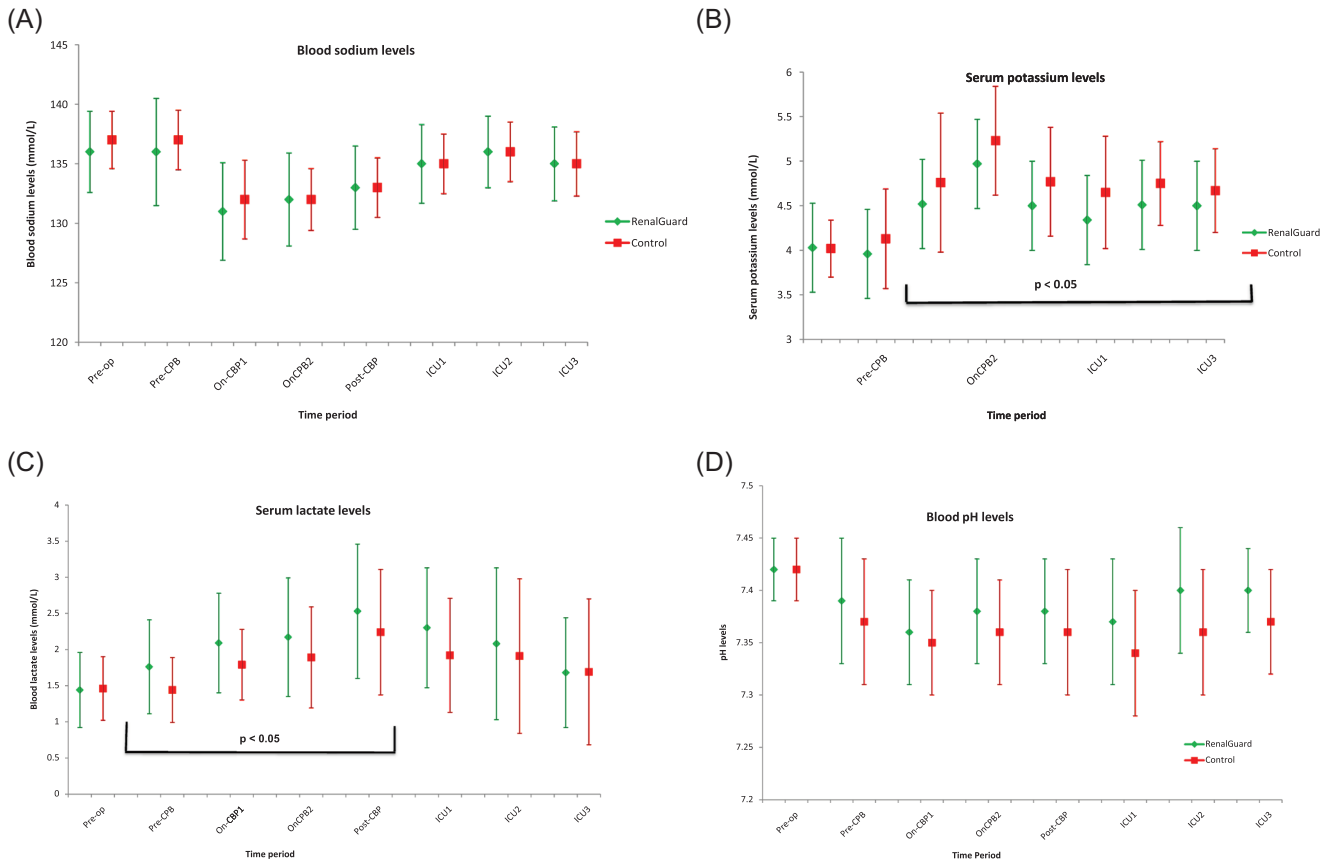


FIGURE 3 Electrolytes (A) sodium, (B) potassium, (C) lactate, and (D) pH levels in the perioperative period—pre-op: in anaesthetic room, pre-CPB: before initiation of cardiopulmonary bypass. On-CPB1: on cardiopulmonary bypass for 15 min. On-CPB2: before stopping cardiopulmonary bypass, post-CPB: poststopping cardiopulmonary bypass for 15 min. ICU1: on arrival to ICU, ICU2: on ICU for 6 h, ICU3: on ICU for 12 h. ICU, intensive care unit

4.1 | Limitations

This was a single centre study. Moreover, as the study was not blinded, the management of the control group could have been influenced by some aspects of the Hawthorne effect.

5 | CONCLUSION

In patients at-risk for AKI, undergoing cardiac surgery with CPB, balanced forced-diuresis as provided by the RG system significantly reduced the incidence of AKI. Compared to the control group, serum potassium levels were lower in the RG group. However, normal levels could be maintained by administration of IV potassium replacement in the postoperative period, thus maintaining similar clinical outcomes, with no adverse safety concerns.

ACKNOWLEDGEMENTS

We sincerely acknowledge the assistance of anaesthetic, surgical, and CICU staff at Heart and Lung Centre, Wolverhampton, UK. This work was supported by a research grant from RenalGuard Solutions and by

the National Institute of Healthcare Research (NIHR), Clinical Research Network, UK (Ref: NIHR CRN No 32769)

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Concept and design: Heyman Luckraz, Ramesh Giri, Benjamin Wrigley, Lawrence Beare, Alan Nevill. *Data analysis and interpretation:* Alan Nevill, Heyman Luckraz, Ramesh Giri, Benjamin Wrigley, Lawrence Beare. *Drafting article:* Heyman Luckraz, Ramesh Giri, Benjamin Wrigley, Kumaresan Nagarajan, Eshan Senanayake, Emma Sharman, Lawrence Beare, Alan Nevill. *Critical revision of article:* Heyman Luckraz, Ramesh Giri, Benjamin Wrigley, Kumaresan Nagarajan, Eshan Senanayake, Emma Sharman, Lawrence Beare, Alan Nevill. *Approval of article:* Heyman Luckraz, Ramesh Giri, Benjamin Wrigley, Kumaresan Nagarajan, Eshan Senanayake, Emma Sharman, Lawrence Beare, Alan Nevill. *Statistics:* Alan Nevill. *Funding secured by:* Heyman Luckraz, Ramesh Giri, Benjamin Wrigley. *Data collection:* Kumaresan Nagarajan, Eshan Senanayake, Emma Sharman, Lawrence Beare. *Project administration:* Heyman Luckraz, Ramesh Giri, Benjamin Wrigley, Emma Sharman.

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How to cite this article: Luckraz H, Giri R, Wrigley B, et al. Balanced forced-diuresis as a renal protective approach in cardiac surgery: Secondary outcomes of electrolyte changes. *J Card Surg.* 2021;1-7. <https://doi.org/10.1111/jocs.15925>