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Complete List of Authors:	Rehman, Naveed; Aga Khan University, Pediatrics and Child Health; AGA KHAN UIVERSITY HOSPITAL, PEDIATRIC AND CHILD HEALTH Merchant, Quratulain; Aga Khan University, Pediatrics and Child Health Hasan, Babar; Aga Khan University, Pediatrics and Child Health Rizvi, Arjumand; Aga Khan Medical University, Pediatrics and Child Health Amanullah, Muneer; Aga Khan University, Surgery Rehmat, Amina; Aga Khan University, Haq, Anwar; Aga Khan University, Pediatrics and Child Health
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Comparison of **E**nteral versus **I**ntravenous **P**otassium **S**upplementation in hypokalemia in post cardiac surgery Pediatric Cardiac Intensive Care patients – Open label Randomized control trial **(EIPS)**

Authors: Naveed ur Rehman Siddiqui*, Quratulain Merchant*, Babar S. Hasan, Arjumand Rizvi, Muneer Amanullah, Amina Rehmat, Anwar ul Haq.

Institution: Aga Khan University Hospital, Stadium Road P.O Box 3500, Karachi, Pakistan.

*These authors contributed equally and will share first authorship. **EIPS is a non-funded trial. Reprints will not be ordered. No extra data is available.**

Corresponding author: Babar Hasan MD FAAP, Associate Professor, Head of Section, Pediatric Cardiology

Email address: babar.hasan@aku.edu

Address: Department of Pediatrics and Child Health, Aga Khan University Hospital, Stadium Road 75500, Karachi

Quratulain Merchant MD

Email address: annie.merchant@hotmail.com

Naveed ur Rehman Siddiqui, FCPS MBBS Fellow, Pediatric Critical Care Medicine

Email address: naveed.rehman@aku.edu

Arjumand Rizvi, MSc, Statistician, Department of Pediatrics and Child Health

Email address: arjumand.rizvi@aku.edu

Muneer Amanullah, FRCS MBBS Associate Professor, Department of Surgery

Email address: muneer.amanullah@aku.edu

Amina Rehmat, BscN Head nurse, PCICU

Email address: amina.rehmat@aku.edu

Anwar ul Haq, MD, Diplomat Amercican Board of Pediatric Critical Care, Associate Professor, PICU

Email address: anwar.haq@aku.edu

Article Summary

1) EIPS is the first prospective randomized control trial comparing the routes (enteral versus intravenous) for potassium replacement in the post cardiac-surgery pediatric patients in the PCICU.
2) Previously, a retrospective review has shown comparable efficacy between the two routes.
3) Research from this trial will lead the way for further research in this field, possibly bringing about a change in the management of hypokalemia in post-op patients and subsequently lower complications and morbidity associated with intravenous potassium replacement.
4) EIPS is not a blinded study, which may lead to a procedure bias. Blinding could not be carried out in this trial owing to different routes of administration of the same supplementation (enteral versus intravenous) and different time interval for checking serum levels in each arm (1 h after intravenous replacement and 2 h after enteral replacement).
5) Confounding factors, such as concomitant use of diuretics and inotropic agents during the episode, have been identified and will be adjusted in the analysis.

Abstract:

Objectives: Primary Objective was to compare the efficacy of enteral potassium replacement (EPR) and intravenous potassium replacement (IVPR). Secondary objectives included comparison of adverse effects and doses required to resolve episode of hypokalemia.

Trial design: EIPS trial is designed as a randomized control trial with two treatment arms.

Study Setting: Study was conducted at Pediatric Cardiac Intensive care Unit (PCICU) of Aga Khan University Hospital, Karachi.

Participants: 41 post-cardiac surgery patients (1 month- 25 year) admitted to PCICU were recruited (23 IVPR arm and 18 EPR arm).

Intervention: Intervention arms were block randomized as alternate week for IVPR and EPR.

Outcome measure: Change in serum potassium levels in (mmol/L) and % change after each event of potassium replacement by Intravenous and Enteral routes.

Results: Both groups (41 patients) had similar baseline characteristics. Mean age was 4.7 (SD +/-4) years and most common surgical procedure was VSD repair (12 patients 29.3%). No mortality was observed in either arm. 4 episodes of vomiting and one arrhythmia were seen in EPR group. After adjusting for age, potassium concentration at beginning of episode, average urine output, inotropic score and diuretic dose, there was no statistically significant difference in change in potassium levels after enteral and intravenous replacement (p=0.86 intention to treat).

Conclusion: EPR may be an equally efficacious alternative in treating hypokalemia in selective post-operative congenital heart disease patients.

Ethics and Dissemination: This study has been approved by Ethics Review Committee at AKU.

Trial Registration: Clinical Trials.Gov. Registration number: NCT02015962.

Funding: None

Key words: Hypokalemia, potassium replacement, pediatric post-surgical patients, intravenous potassium replacement, enteral potassium replacement.

Introduction:

Hypokalemia is frequently encountered in daily clinical practices of pediatric cardiac intensive care unit (PCICU). Activation of renin-angiotensin-aldosterone system, the presence of enhanced sympathetic tone and use of potassium-wasting diuretics for positive fluid balance increases the occurrence and consequences of severe hypokalemia [1]. Hypokalemia is a strong independent predictor of mortality in heart failure patients [2-4]. Potassium replacement remains the cornerstone therapy for hypokalemia. There is mounting evidence that the serum potassium level should be maintained between 3.5 - 4.5 mmol/L[5] or even higher in acute cardiac injury settings [6-7]. Thus it is desirable to avoid hypokalemia by close monitoring and subsequent replacement of potassium.

Although intravenous potassium replacement (IVPR) in hypokalemia is the preferred route in most intensive care settings, it is associated with known safety risks. Inappropriately administered, IVPR can lead to arrhythmias, cardiac arrest and death [2,8,9]. Given these risks, IVPR is considered a “high-alert medication” by Institute of Safe Medication practice [10,11]. Though low concentration of IVPR can be done via a peripheral intravenous route, the need of a central line for higher concentrations of potassium can lead to central line related infection due to frequent access of the line during IVPR. Additionally a larger volume of fluid is required during IVPR for delivery of the desired dose of potassium through the peripheral lines. This may not be preferred in post-surgical cardiac patients in whom a negative fluid balance is being desired. Given all the above mentioned issues with IVPR, enteral potassium replacement (EPR), with its equal or superior safety profile may be a better alternative to IVPR. A retrospective review showed that the efficacy of EPR was comparable to IVPR in pediatric patients

after congenital heart disease [9].

We sought to explore this comparison between EPR and IVPR in a randomized trial.

This trial was registered at the Clinicaltrials.gov. Registration number: NCT02015962. Details of the trial protocol and design have been previously published [12].

Objectives:

Primary objective was to compare the efficacy (measured as change in serum potassium levels in mmol/L and percentage change in level after potassium replacement) of EPR versus IVPR for treatment of hypokalemia. The secondary objectives were: i) compare the adverse effects (hyperkalemia, diarrhea, GI bleeds, nausea and vomiting) after EPR and IVPR, ii) compare number of dose/s required in achieving resolution of hypokalemia (as described per protocol) for each episode of hypokalemia, and iii) determine the efficacy of EPR versus IVPR for various degrees of severity of hypokalemia i.e. mild, moderate or severe hypokalemia.

Trial design:

Trial protocol and design have been published previously [12]. Briefly, the EIPS trial was designed as a randomized, non-blinded trial with two arms. Arm A (IVPR) received intravenous potassium replacement while Arm B (EPR) received enteral potassium replacement as a treatment of hypokalemia. Intervention arms were block randomized as alternate week for IVPR and EPR for the sake of convenience and to minimize error in drug delivery.

Methods

Definitions used for the study:

Hypokalemia: Hypokalemia was defined as serum Potassium <4.4mmol/L

Event and episode of hypokalemia: Serum potassium <4.4 mmol/L was considered as hypokalemia. This marked beginning of EPISODE of hypokalemia. Each potassium replacement was considered an EVENT of hypokalemia irrespective of whether hypokalemia was completely resolved or not. The EPISODE of hypokalemia ended when the potassium level returned to the normal range as described above.

Study setting:

The study was conducted at PCICU of Aga Khan University Hospital, Karachi, Pakistan.

Eligibility Criteria:

Inclusion criteria:

This trial included patients, 1 month to 25 years of age, undergoing surgical repair/palliation of congenital heart lesion at Aga Khan University Hospital and admitted to PCICU for post-operative management. Patients/Parents willingness to participate in this study, serum potassium levels (<4.4 mmol/l) immediate post operatively, ability to tolerate oral or nasogastric administration of medication for EPR and presence of a central line for IVPR were also included in eligibility criteria.

Exclusion Criteria:

We excluded patients with acute renal failure (clearance creatinine - ecCr <75%, urine output <0.3 ml/kg/h × 16 hrs.)[13]. Also those with paralytic ileus, necrotizing enterocolitis, gastrointestinal bleeding, nausea, vomiting or diarrhea were excluded, as

they could not be given EPR. However, patients were not excluded if vomiting or diarrhea developed after initial recruitment. Patients with critically low serum potassium <2.0 mmol and patients with symptomatic hypokalemia were also not recruited.

Consent Procedure:

Informed consent and assent was taken by investigators, from each patient (or parent in case of age <16 years) before going for cardiac surgery.

Study Recruitment, procedure and Monitoring:

Detailed description about recruitment, study procedure, and monitoring had been previously published in protocol [12]. Patients were enrolled and potassium levels were checked routinely, once they were shifted to PCICU post-operatively. In case, when they developed hypokalemia, they received treatment according to intervention arm and was followed till he/she had reached optimal potassium levels or shifted from PCICU to step down unit. Repeat serum potassium was sent 1 hour after replacement in IVPR group and 2 hours after replacement in EPR group. Further patient serum electrolyte monitoring was determined by patient's clinical status.

In cases, where patient stayed in PCICU beyond one week and block changed, patient continued to follow the route they were originally assigned. EPR patients who developed side effects (e.g. vomiting GI upset) or who develop critically low levels of potassium <2mmol (exclusion criteria) were allowed to cross over and receive IVPR subsequently. An intention to treat analysis was performed to account for cross over patients.

During pre-recruitment trial period, it was recognized that patients, who were given

enteral potassium supplementation couldn't tolerate enteral formulation and ended up vomiting due to sour taste of formulation. Thus it was decided to use nasogastric (NG) tube, placed intra-operatively under anesthesia, in mechanically ventilated patients and administer enteral potassium through NG tube. Once patients were extubated and started tolerating oral feeds, enteral potassium supplementation was administered with apple juice to improve the taste and palatability of medicine. These measures were adopted throughout the trial to improve tolerance and compliance to EPR.

Study Drugs, Drug management:

Drug dosing protocol for potassium replacement, details about maximum concentration and dose in each arm and drug management can be reviewed in previously published protocol [12].

Adverse Events:

Adverse effects of potassium supplementation that were monitored are; hyperkalemia (potassium levels > 5 mmol/L), arrhythmias, diarrhea, gastrointestinal bleeds, nausea and vomiting, during or within 2 hours of potassium replacement.

The adverse events were monitored and documented on hourly bases by PCICU nursing staff and notified to on-call physician and PI.

Sample size calculation:

Sample size was calculated using equivalence test of mean procedure, considering equal efficacy of both interventions (EPR and IVPR) with standard deviation of 4%. Equivalence limit assumed to be +/- (15%), using a power of 90% and level of significance 5%, a total of 155 events were required in each arm to reject the null

hypothesis which states that there is no difference in the efficacy (change in Serum Potassium levels) of IVPR and EPR. Sample size was calculated using PASS software.

Statistical Analysis:

The primary objective of study was to compare the efficacy of EPR and IVPR for treatment of hypokalemia. End points (primary outcome) used were change in serum potassium levels in mmol/L and percentage change in serum potassium levels after each event of potassium replacement by both methods

Data was analyzed using two approaches; Intention to treat (ITT) and actual treatment (AT) received analysis. Intention to treat (ITT) was considered the primary analysis. Mean (+/-SD) was calculated for continuous parametric variables while median was used to describe continuous non-parametric variables. Categorical variables are presented as frequencies. To explore bivariate associations, independent student-t and Mann-Whitney U-tests were used for parametric and non-parametric continuous variables respectively, while Chi Square was used for categorical variables. Change in potassium concentration over time, was assessed by mixed effects regression modeling. It incorporated a random intercept trend. This analytic approach included all children that have data available on at-least one time point. A hierarchical model developed that nests event within episode and patients through random intercept model to adjust inter-individual and episode related variation in change in potassium concentration. The analysis included linear time effect with main effect of treatment to examine whether the experimental condition (EPR) resulted in greater changes in potassium than the control (IVPR) over time. Age of children, potassium concentration at beginning of episode, average urine output, diuretic

dose and inotrope score were incorporated in model as confounding factors and results were reported as coefficients with 95% CI's. Data was analyzed using STATA version 12 through xtmixed command. Fit of the models assessed through Akaike information criteria (AIC) and Bayesian information criteria (BIC). Generally the smallest the statistical value the better the model fits the data

An interim analysis was performed after 155 events (cumulative in both arms) to ensure protocol compliance and monitor adverse effects. Analysis did not reveal any major adverse effects and validated comparable efficacy between two arms. Thus, no major changes were made to protocol and trial was continued to achieve final sample size.

Data collection, storage and record keeping:

The data abstraction form was used to abstract patient data for study.

Data was collected by investigators (NR, QM, AR) throughout the duration of study and was kept safe under lock and password protected e-files at all times.

Ethics committee and regulatory approval:

This study was approved by ERC and Clinical Trials Unit at Aga Khan University Hospital.

Results:

Patients were recruited from December 2013 to May 2014. Forty-one patients were approached and consented to participate in trial. There were no dropouts. Of all the participants recruited, 10 patients were considered a part of pre-trial period and not included in the final analysis. During the trial period, 4 patients could not be included; 2

participants were excluded as they developed critically low levels of potassium while the other 2 participants did not fulfill the inclusion criteria i.e. they never developed an episode of hypokalemia during their PICU stay. The most common cardiac lesion in both groups was found to be Ventricular Septal Defect (VSD) and most common surgical procedure was VSD closure. After randomization, 18 patients were recruited in IVPR arm while 23 patients in EPR arm. The mean age of the patients was 4.8 (SD+/- 4) in IVPR group and 4.6 (SD+/-4.0) in EPR group (table 2A). Five patients from EPR arm crossed over to IVPR arm (figure 1) due to development of adverse events i.e. 4 vomiting and one arrhythmia. The median length of CICU stay was 2 (0.63-14) days and 1.95 (0.58-8) days (p= 0.26) in IVPR and EPR respectively. The median length of hospital stay in IVPR was 7 (3-19) days while in EPR was 6 (4-18) days (p=0.83). A total of 97 episodes of hypokalemia were recorded (48 and 49 in IVPR and EPR arm respectively). From these episodes a total of 460 events of hypokalemia were recorded (234 and 226 in IVPR arm and EPR arm respectively). There was no difference in episode (IVPR 2.7 SD +/- 2.1; EPR 2.1 SD +/- 1.3) and events (number of doses) (IVPR 5.0 SD+/-4.9; EPR 4.6 SD+/- 4.2) per child between the two arms (table 2B). Baseline characteristics of patients in both arms are presented in table 2A. Both groups had similar baseline characteristics; however, the IVPR arm had a higher inotropic score when compared to EPR arm at both ITT (8.5 ± 9.1 vs 4.6 ± 4.1, p= 0.01, respectively) and AT (8.4 ± 8.8 vs 4.1 ± 3.3, p= 0.004, respectively) analysis.

Mode of supplementation and response to therapy:

There was no difference between IVPR and EPR arm in mean serum potassium levels at the beginning (3.67 ± 0.42 vs 3.62± 0.48, p=0.45, respectively) and at the end of episode

of hypokalemia (4.47 ± 0.62 vs 4.48 ± 0.60, p=0.94, respectively) (figure 2).

Univariate analysis showed no difference in response to therapy (number of doses required, dosage of potassium replaced, absolute change (IV 0.82±0.7; 95% CI:0.62-1.01 vs. Oral 0.86±0.8 ;95% CI: 0.62-1.10 p=0.8) and percentage change (IV 24±20 ;95% CI: 18-30 vs. Oral 26±30; 95% CI: 18-35 p=0.59) in potassium levels in both arms at initial episode (table 2b).

Actual treatment received analysis was also performed and findings were not significantly different from intention to treat analysis.

Using repeated measure analysis, after adjusting for age of patient, potassium concentration at beginning of episode, average urine output, inotropic score and diuretic dose, change in absolute potassium level for each event of hypokalemia, after EPR and IVPR was equal with no statistically significant difference between two arms at ITT (β=0.01; 95% CI: -0.08 to 0.10, p=0.86) and AT analysis. Similar results were seen when analysis was performed for using percentage change in potassium levels after supplementation at ITT (β=0.30; 95% CI: -3.42 to 4.03, p =0.87) and AT (table 3, S2, S3).

Adverse events:

No mortality occurred in either of the arms. Total of 5 adverse events in EPR and none in IVPR arm were recorded. Out of these 5 cases, 4 were episodes of vomiting within two hours of enteral potassium replacement. A single atrial arrhythmia occurred in a 4.5 month old patient who underwent complete repair for tetralogy of Fallot. Abnormal rhythm was noticed an hour after enteral supplementation for treating mild hypokalemia.

Rhythm was evaluated to be a run of ectopic atrial tachycardia. This patient was also noted to have such episodes of tachycardia immediately post-operatively before the enteral supplementation was started. Rhythm improved after patient was placed on oral amiodarone.

Discussion:

Our trial portrays comparable efficacy between both the modes of supplementation, intravenous and enteral, for correction of hypokalemia in post-cardiac surgery pediatric patients in PCICU setting. Through this trial we were able to establish that enteral potassium supplementation is an equally efficacious and safe mode of potassium replacement during hypokalemia in selected patient with congenital heart disease in the immediate post-operative period.

Pediatric patients after congenital heart disease repair are particularly susceptible to hypokalemia in post-operative period due to administration of high doses of loop diuretics and inotropes [1, 7]. In immediate postoperative period, body does not conserve potassium efficiently thus making potassium supplementation a requirement for many such pediatric cardiac patients [1]. Potassium supplementation has a narrow therapeutic range and thus a guarded safety profile. Although serious adverse effects with either mode of supplementation are quite rare, inappropriate administration of potassium in these patients may lead to worsening of heart failure, cardiac arrest, hyperkalemia, arrhythmias and death [2, 8, 9]. Given all the above mentioned factors, efficient potassium replacement through a safe route holds pivotal importance in post cardiac surgery pediatric patients.

A comparable efficacy between enteral versus intravenous potassium supplementation was initially demonstrated in a recent retrospective study [9]. This retrospective study conducted by Moffet BS et al. included 66 post congenital heart surgery pediatric patients, who received 399 blouses of potassium (266 intravenous and 233 enteral). As a change of practice was advocated to encourage the use of enteral potassium supplementation before data collection for this retrospective study, authors believe that physician's clinical experience and judgment may have skewed administration of enteral potassium to less critically ill patients. Also, limitations associated with a retrospective review reduced the generalizability of the findings of this study. Keeping above mentioned limitations in consideration; a prospective study with pre-defined protocol practices in place to reduce the clinician to clinician variability was warranted.

Although equally efficacious in improving potassium levels, IVPR requires stringent monitoring by PCICU staff and presence of a central line [9]. Correcting potassium levels back to normal usually requires multiple replacements, making repeated access to central line, a necessity. This may lead to central line related infections [9, 14]. Also, transition to enteral supplementation from IVPR poses a challenge in some patients and central lines have to be kept in place longer than required otherwise, for intravenous potassium supplementation [14]. Another downside of using IVPR is that a large volume of fluid is required for delivery of the desired dose of potassium which is not preferable in post-operative cardiac patients in whom clinicians aim to achieve a negative fluid balance. On other hand, enteral supplementation, with comparable efficacy offers many advantages. It is easier to transition post-operative pediatric congenital heart disease patients directly to enteral supplementation and if required they can be discharged home on these

supplementation. Moreover, use of enteral potassium supplementation can lead to significant reduction in fluid administration, which is of great advantage as hypokalemia is frequently a consequence of administration of loop diuretics to treat fluid overload in this patient population. Although, pediatric data regarding pharmacokinetics of enteral potassium supplementation is lacking, safety and efficacy of enteral supplementation of potassium in adult population has been well established previously. One more potential advantage of administrating enteral potassium supplementation for treatment of hypokalemia is its cost effectiveness [9]. Along with being ten times more costly at our institution, IVPR also require central line utilization, increased nursing time and syringe pump utilization that further adds to overall cost of potassium supplementation. Adverse events seen in enteral arm mainly comprised of episodes of vomiting seen in some participants in the beginning of the trial. This can be attributed to sour taste of formulation or inappropriately fast administration through NG tube. The former can be taken care of by feeding through NG tube or mixing enteral potassium formulation with fruit juices. Other than these few episodes of vomiting, participants in this trial tolerated enteral supplementation of potassium. Given its equal efficacy, low adverse event profile and a potential benefit, EPR was shown to be an excellent alternative to IVPR in our patient cohort.

Generalizability:

EIPS included cardiac surgery patients after being received in PCICU post-operatively. Mean age of participants was 4.7 years with the youngest child being 1 month and the oldest child being 14 years, while predominant surgical procedure was VSD repair surgery. We believe that results of our study can be generalized to this patient population.

However, there were only two patients with severely low potassium levels (see definition) and patients with critically low potassium i.e. <2.0 mmol/L were excluded from trial thus results from this trial should be generalized with caution in patients with severely and critically low potassium levels. Further investigation is warranted to determine safety profile of enteral potassium in these patients. Also, EIPS is a single-center randomized study, with alternate week patient randomization, leading to potential significant selection and allocation bias and limiting generalizability of the findings.

Limitations:

EIPS is a single-center, non-blinded study that may lead to observer bias. Blinding was not feasible in this trial owing to different routes of administration of same supplementation (enteral versus intravenous) and different time interval for checking serum levels in each arm (1 hour after intravenous replacement and 2 hours after enteral replacement). Confounding factors, such as concomitant use of diuretics and inotropic agents during the episode may have affected potassium metabolism. These factors were identified and were adjusted in analysis.

Auto-analyzer, located in PCICU, was used to measure point of care potassium levels in this trial. This might have been a potential limiting factor in our study. Central lab values, although being gold standard, could not be used, as turnover time for each sample at our institution is about 4 hours. Central lab values were obtained only when a critically low or high value was seen on the auto analyzer testing. Strong correlation between two values had previously been established during daily practice at our PCICU.

Another limitation was that some participants got shifted out of PCICU before

completion of episode of hypokalemia. Patients could not be followed once they moved out of PCICU to step-down unit or ward as stringent monitoring for trial and point of care potassium levels was not available in ward settings. This does affect generalizability of study. Routinely, patients who had been moved to step down units or wards in our institutions receive oral potassium supplementation. Lastly, our trial was also underpowered to detect difference in frequency of adverse effects between both arms.

Conclusion: There is no difference in EPR or IVPR in treating hypokalemia in post-operative congenital heart disease pediatric patients. EPR may be an equally efficacious alternative to treat hypokalemia in these patients.

Trial Registration:

This trial is registered at Clinical Trials.Gov. Registration number: NCT02015962.

Protocol:

Merchant Q, Rehman Siddiqui NU, Rehmat A, Amanullah M, Haq AU, Hasan B. Comparison of Enteral versus Intravenous Potassium Supplementation in hypokalemia in post-cardiac surgery paediatric cardiac intensive care patients: prospective open label randomized control trial (EIPS). British Medical Journal Open. 2014 Sep; 4(9): -. Cited in PubMed; PMID: 25190615.

Abbreviations:

PCICU: Pediatric cardiac intensive care unit. ERC: Ethical Review Committee. CTU: Clinical Trials Unit. IVPR: intravenous potassium replacement. EPR: enteral potassium replacement.

Conflict of Interest:

All authors declare no support from any organization for submitted work, no financial relationships with any organizations that might have an interest in submitted work in previous three years and no other relationships or activities that could appear to have influenced submitted work.

Author's contributions:

NR, QM, MA, AH and BH: contributed equally to the research idea, study design, protocol writing, initiation, data acquisition, analysis and manuscript writing. AR and AR contributed in data acquiring, analysis of data and manuscript writing. BH was the senior author on this project involved in study idea genesis, design, data analysis and interpretation and manuscript writing. All authors have read and approved final manuscript.

Data sharing statement: No additional data available.

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None

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Figure Legends:

Figure 1: Recruitment flow chart EIPS

Figure 2: Change in potassium concentration at the beginning and end of episode

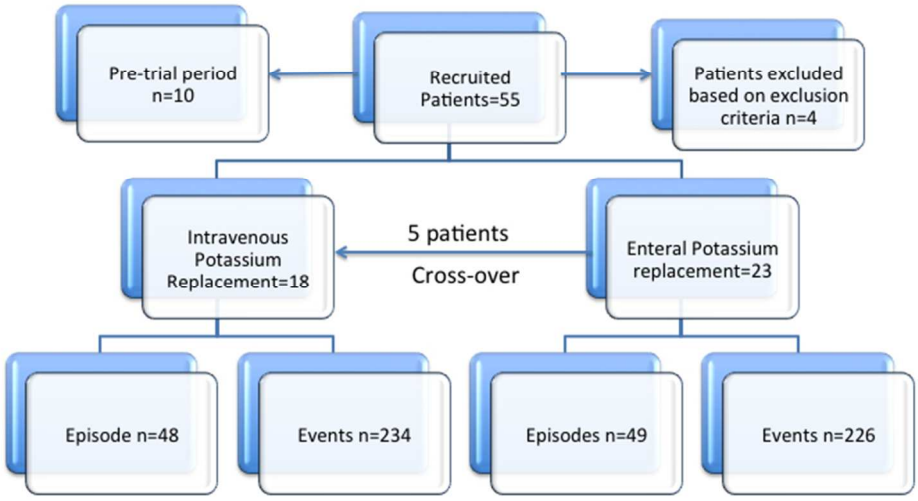

Figure 1: Recruitment flow chart EIPS

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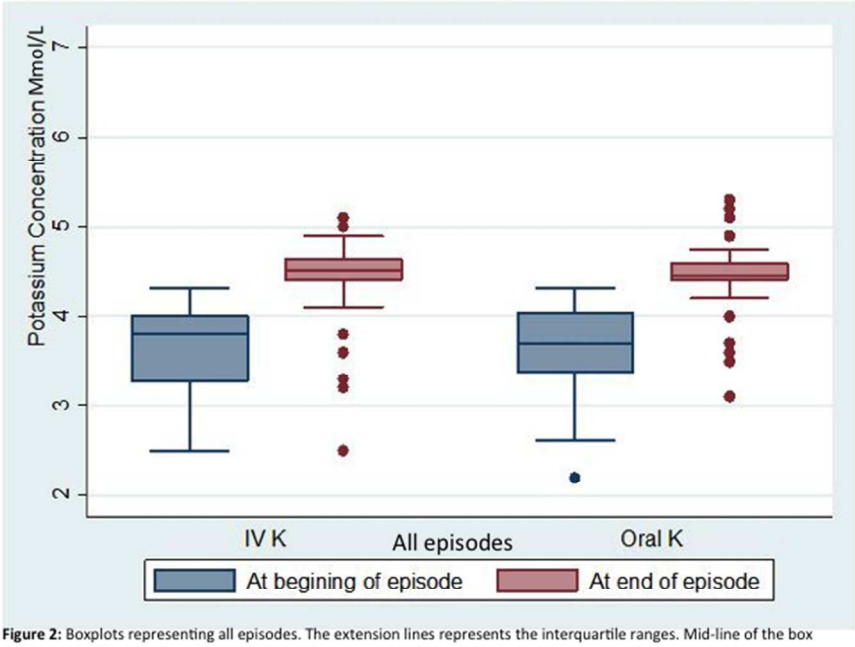

Figure 2: Boxplots representing all episodes. The extension lines represents the interquartile ranges. Mid-line of the box represents median while the top and bottom line represents first and third quartile respectively

Figure 2: Change in potassium concentration at the beginning and end of episode

254x190mm (72 x 72 DPI)

Table 1 Potassium replacement dosing.

Serum Potassium level (mmol/L)	Potassium replacement (I/V and Enteral)
4.0 – 4.4	0. 1 mmol/kg/dose
3.5 -3.9	0.3 mmol/kg/dose
3.0 -3.4	0.5 mmol/kg/dose
2.5 – 2.9	0.7 mmol/kg/dose
2.1- 2.4	1 mmol/kg/dose and call physician

Intravenous Potassium Chloride
Maximum dose: 3mmol/kg/day;
Dilution and infusion rate: 8mmol/100ml, 10mmol/hour for peripheral line, 15mmol/100ml, 15mmol/hour for central line.

Oral Potassium Chloride
Maximum dose 240mmol/24 hours . Maximum per dose 60mmol.
Concentration 13.33mmol/5ml

Table 2a: Baseline characteristics of enrolled children in IVPR and EPR arms

	Intention to treat(ITT)			Actual treatment received(AT)		
	IV K (n=18)	Oral K (n=23)	p-value	IV K (n=23)	Oral K (n=18)	p-value
Age at randomization (count,%)						
<1 year	5(27.8%)	4(17.4%)	0.54	6(26.1%)	3(16.7%)	0.61
1-5 year	5(27.8%)	10(43.5%)		7(30.4%)	8(44.4%)	
5-15 year	8(44.4%)	9(39.1%)		10(43.5%)	7(38.9%)	
Mean Age(years) *	4.8 ± 4.0	4.6 ± 4.0	0.91	4.8±4.2	4.6±3.8	0.87
Indicators at beginning of episode						
Potassium level (count,%) ‡						
Mild	33(71.7%)	31(63.3%)	0.47	41(74.5%)	23(57.5%)	0.14
Mod	13(28.3%)	17(34.7%)		14(25.5%)	16(40.0%)	
Severe	--	1(2.0%)		--	1(2.5%)	
Mean potassium*	3.7 ± 0.5 (3.5-3.8)	3.6 ± 0.5 (3.5-3.8)	0.71	3.7 ± 0.5 (3.6-3.8)	3.6 ± 0.5 (3.4-3.7)	0.23
Average Urine output*	3.9 ± 2.1 (3.4-4.6)	4.3 ± 2.5 (3.6-5.0)	0.44	4.1 ± 2.2 (3.5-4.7)	4.2 ± 2.5 (3.4-5.0)	0.81
Diuretic average dose (mg/kg)*†	0.4 ± 0.5 (0.3-0.6)	0.4 ± 0.6 (0.2-0.5)	0.57	0.5±0.6 (0.3-0.6)	0.3±0.4 (0.2-0.4)	0.15
Inotrope Score*	8.5 ± 9.1 (5.5-10.7)	4.6 ± 4.1 (3.4-5.8)	0.01	8.4±8.8 (5.6-10.5)	4.1±3.3 (3.0-5.1)	0.004
Total episodes	48	49		57	40	

* Values reported as Mean ±SD (95% CI)

† Diuretics were given either at bolus every 6 hrs or as a continuous infusion. Average dose was calculated as total diuretic (mg) received in 6hrs/ weight (kg) of the patient/6 to get mg/kg/hour.

‡ Severity of hypokalemia defined as potassium level of Mild: 3.5 -4.4 mEq/L, Moderate: 2.5 -3.4 mEq/L, Severe: 2.1- 2.4 mEq/L

Table 2b: Episodes, events and mean percent change in potassium concentration in IVPR and EPR arms

	Intention to treat(ITT)			Actual treatment received(AT)		
	IV K	Oral K	p-value[3]	IV K	Oral K	p-value[3]
Events	234	226		279	181	
Episode per child(N)	18	23		23	18	
Mean±SD	2.7 ± 2.1	2.1 ± 1.3	0.32	2.5±1.9	2.2±1.4	0.63
Event per episode(N)	48	49		57	40	
Mean±SD	5.0 ± 4.9	4.6 ± 4.2	0.70	5.0±4.8	4.5±4.2	0.64
Change in Potassium(N) [1]	48	49		57	40	
Mean±SD **95% CI**	0.82±0.7 (0.62-1.01)	0.86±0.8 (0.62-1.10)	0.80	0.78±0.6 (0.65-0.95)	0.93±0.8 (0.64-1.21)	0.34
Relative percentage change in Potassium(N) [2]	48	49		57	40	
Mean±SD **95% CI**	24±20 (18-30)	26±30 (18-35)	0.59	22±20 (17-27)	29±30 (19-39)	0.20
Relative percentage change in Potassium first episode(N) [2]	18	23		23	18	
Mean±SD **95% CI**	25±20 (16-34)	30±20 (19-41)	0.51	24±20 (16-31)	33±30 (20-46)	0.18

All values reported as Mean ±SD (95% CI)

1- Change in potassium concentration calculated as 'last event K-first event K' of an episode

2- Relative percent change calculated as (first K value of the episode –Last K value of the episode)/first K value of the episode * 100.

3- Mann-Whitney U test was used for comparison of episodes and events due to skewed distribution while change in potassium concentration and relative percent change were compared using independent sample t-test

Table 3: Repeated measure analysis of change in serum potassium concentration in IVPR and EPR arms(ITT)

	Unadjusted				Adjusted*			
	Coef.	SE	95% CI	p-value	Coef.	SE	95% CI	p-value
Potassium Concentration								
Intervention								
Oral K	0.02	0.05	-0.08 to 0.13	0.66	0.01	0.05	-0.08 to 0.10	0.86
IV K	Ref				Ref			
Percent Change in Potassium Concentration*								
Intervention								
Oral K	0.10	1.89	-3.60 to 3.80	0.95	0.30	1.90	-3.42 to 4.03	0.87
IV K	Ref				Ref			
Percent Change (per hour) in Potassium Concentration*								
Intervention								
Oral K	-3.01	1.55	-6.11 to -0.003	0.05	1.16	1.50	-1.76 to 4.08	0.44
IV K	Ref							

* Percent change calculate as (previous K –current K)/previous K * 100

Linear mixed effect regression analysis, adjusted for episode level variations and controlled for covariates of age, potassium levels at the beginning of episode, inotropic score, average urine output and average diuretic dose. The β co-efficient is the standardized coefficient' showing the degree of impact of intervention on the outcome.

Table SI : Unadjusted repeated measure analysis of change in serum potassium concentration and percent change in potassium concentration.

	change in serum potassium concentration				percent change in potassium concentration			
	Coef.	**SE**	**95% CI**	**p-value**	**Coef.**	**SE**	**95% CI**	**p-value**
Time	0.01	0.001	0.008 to 0.01	<0.0001	0.25	0.02	0.21-0.29	<0.0001
Intervention(ITT)								
IV K	0.02	0.05	-0.08 to 0.13	0.66	0.10	1.89	-3.60 to 3.80	0.95
Oral K	Ref				Ref			
Intervention(ATT)*								
IV K	0.05	0.05	-0.06 to 0.16	0.37	0.68	1.93	-0.31 to 4.50	0.72
Oral K								
Average Urine output	-0.04	0.01	-0.06 to -0.02	<0.0001	-0.47	0.36	-1.21 to 0.26	0.20
inotrope score	0.13	0.05	0.03 to 0.22	0.007	-0.39	1.77	-0.38 to 3.08	0.83
Diuretic average dose	-0.07	0.04	-0.14 to 0.01	0.08	-1.13	1.40	-3.86 to 1.59	0.41
Age groups								
<1 yrs	-0.21	0.06	-0.33 to -0.08	0.01	0.82	2.40	-0.38 to 5.45	0.72
1-5 yrs	-0.13	0.07	-0.27 to 0.005	0.06	0.83	2.68	-4.43 to 6.10	0.75
5-15 yrs	Ref				Ref			
Potassium level at beginning of episode								
mild	0.41	0.29	-0.18 to 0.97	0.17	-24.1	11.7	-46.9 to -1.20	0.04
mod	0.26	0.29	-0.32 to 0.83	0.38	-20.3	11.7	-43.2 to 2.69	0.08
sever	Ref							

*Hierarchical effect of patient and episode incorporate in the model as random intercept

Table S2: Multivariate repeated measure analysis of change in serum potassium concentration by ITT and AT in IVPR and EPR arms.

	Intention to treat(ITT)				Actual treatment received(AT)			
	Coef.	SE	95% CI	p-value	Coef.	SE	95% CI	p-value
Intervention								
IV K	0.01	0.05	-0.08 to 0.10	0.86	0.04	0.05	-0.05 to 0.13	0.39
Oral K	Ref				Ref			
Average Urine output	-0.02	0.01	-0.04 to -0.01	0.01	-0.02	0.01	-0.04 to -0.00	0.01
inotrope score	0.15	0.04	0.06 to 0.23	0.00	0.14	0.04	0.06 to 0.23	0.00
Age groups								
<1 yrs	-0.14	0.06	-0.25 to -0.02	0.02	-0.14	0.06	-0.25 to -0.02	0.02
1-5 yrs	-0.12	0.06	-0.24 to 0.00	0.06	-0.13	0.06	-0.25 to -0.01	0.04
5-15 yrs	Ref				Ref			
Potassium level at beginning of episode								
mild	0.55	0.25	0.07 to 1.03	0.03	0.58	0.25	0.09 to 1.06	0.02
mod	0.40	0.25	-0.08 to 0.88	0.11	0.42	0.25	-0.06 to 0.90	0.09
sever	Ref				Ref			

*Analysis performed to examine effect of oral and IV on potassium concentration adjusting for age, potassium levels at the beginning of episode, inotropic score, average urine output and average diuretic dose. All of the variables treated as fixed effect. Hierarchical effect of patient and episode incorporate in the model as random intercept .

Table S3: Multivariate Repeated measure analysis of percentage change in serum potassium concentration by ITT and AT. Percent change calculate as (previous K –current K)/previous K * 100

	Intention to treat(ITT)				Actual treatment received(AT)			
	Coef.	**SE**	**95% CI**	**p-value**	**Coef.**	**SE**	**95% CI**	**p-value**
Time	0.24	0.02	0.21-0.29	<0.0001	0.24	0.02	0.21-0.29	<0.0001
Intervention								
IV K	0.30	1.90	-3.42 to 4.03	0.87	0.50	1.90	-3.27 to 4.30	0.79
Oral K	Ref							
Potassium level at beginning of episode								
Mild	-23.94	11.71	-46.88 to -1.00	0.04	-23.8	11.7	-46.76 to -0.79	0.04
Mod	-20.09	11.77	-43.17 to 2.98	0.09	-19.9	11.8	-43.04 to 3.15	0.09
Sever	Ref							

* Hierarchical effect of patient and episode incorporate in the model as random intercept.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	-
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	12
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	-

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Clinicaltrials.gov
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Table 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13-14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-17
Other information			
Registration	23	Registration number and name of trial registry	18
Protocol	24	Where the full trial protocol can be accessed, if available	18
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Comparison of Enteral versus Intravenous Potassium Supplementation in hypokalemia in post cardiac surgery Pediatric Cardiac Intensive Care patients – Open label Randomized control trial (EIPS)

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Comparison of **E**nteral versus **I**ntravenous **P**otassium **S**upplementation in hypokalemia in post cardiac surgery Pediatric Cardiac Intensive Care patients – Open label Randomized control, equivalence trial **(EIPS)**

Authors: Naveed ur Rehman Siddiqui*, Quratulain Merchant*, Babar S. Hasan, Arjumand Rizvi, Muneer Amanullah, Amina Rehmat, Anwar ul Haq.

Institution: Aga Khan University Hospital, Stadium Road P.O Box 3500, Karachi, Pakistan.

*These authors contributed equally and will share first authorship. **EIPS is a non-funded trial. Reprints will not be ordered. No extra data is available.**

Corresponding author: Babar Hasan MD FAAP, Associate Professor, Head of Section, Pediatric Cardiology

Email address: babar.hasan@aku.edu

Address: Department of Pediatrics and Child Health, Aga Khan University Hospital, Stadium Road 75500, Karachi

Quratulain Merchant MD

Email address: annie.merchant@hotmail.com

Naveed ur Rehman Siddiqui, FCPS MBBS Fellow, Pediatric Critical Care Medicine

Email address: drnrsvd@hotmail.com

Arjumand Rizvi, MSc, Statistician, Department of Pediatrics and Child Health

Email address: arjumand.rizvi@aku.edu

Muneer Amanullah, FRCS MBBS Associate Professor, Department of Surgery

Email address: muneer.amanullah@aku.edu

Amina Rehmat, BscN Head nurse, PCICU

Email address: amina.rehmat@aku.edu

Anwar ul Haq, MD, Diplomat Amercican Board of Pediatric Critical Care, Associate Professor, PICU

Email address: anwar.haq@aku.edu

Abstract

Objectives: Primary objective was to compare the efficacy of enteral potassium replacement (EPR) and intravenous potassium replacement (IVPR). Secondary objectives included comparison of adverse effects and doses required to resolve episode of hypokalemia.

Trial design: EIPS trial is designed as a randomized, equivalence trial between two treatment arms.

Study Setting: Study was conducted at Pediatric Cardiac Intensive care Unit (PCICU) of Aga Khan University Hospital, Karachi.

Participants: 41 post-cardiac surgery patients (1 month- 25 year) admitted to PCICU were recruited (23 IVPR arm and 18 EPR arm).

Intervention: Intervention arms were block randomized as alternate week for IVPR and EPR.

Outcome measure: Change in serum potassium levels in (mmol/L) and % change after each event of potassium replacement by Intravenous and Enteral routes.

Results: Both groups (41 patients) had similar baseline characteristics. Mean age was 4.7 (SD +/-4) years and most common surgical procedure was ventricular septal defect (VSD) repair (12 patients 29.3%). No mortality was observed in either arm. 4 episodes of vomiting and one arrhythmia were seen in EPR group. After adjusting for age, potassium concentration at beginning of episode, average urine output, inotropic score and diuretic dose, there was no statistically significant difference in change in potassium levels as well as percentage change in potassium level after enteral and intravenous replacement

(p=0.80 & 0.51 respectively, intention to treat).

Conclusion: EPR may be an equally efficacious alternative in treating hypokalemia in selective post-operative congenital heart disease patients.

Ethics and Dissemination: This study has been approved by Ethics Review Committee at AKU.

Trial Registration: Clinical Trials.Gov. Registration number: NCT02015962.

Funding: None

Key words: Hypokalemia, potassium replacement, pediatric post-surgical patients, intravenous potassium replacement, enteral potassium replacement.

Article Summary

1) EIPS is the first prospective randomized control, equivalence trial comparing the routes (enteral versus intravenous) for potassium replacement in the post cardiac-surgery pediatric patients in the PCICU.
2) Previously, a retrospective review has shown comparable efficacy between the two routes.
3) Research from this trial will lead the way for further research in this field, possibly bringing about a change in the management of hypokalemia in post-op patients and subsequently lower complications and morbidity associated with intravenous potassium replacement.
4) EIPS is not a blinded study, which may lead to a procedure bias. Blinding could not be carried out in this trial owing to different routes of administration of the same supplementation (enteral versus intravenous) and different time interval for checking serum levels in each arm (1 h after intravenous replacement and 2 h after enteral replacement).
5) Confounding factors, such as concomitant use of diuretics and inotropic agents during the episode, have been identified and will be adjusted in the analysis.

Introduction:

Hypokalemia is frequently encountered in daily clinical practices of pediatric cardiac intensive care unit (PCICU). Activation of renin-angiotensin-aldosterone system, the presence of enhanced sympathetic tone and use of potassium-wasting diuretics for positive fluid balance increases the occurrence and consequences of severe hypokalemia [1]. Hypokalemia is a strong independent predictor of mortality in heart failure patients [2-4]. Potassium replacement remains the cornerstone therapy for hypokalemia. There is mounting evidence that the serum potassium level should be maintained between 3.5 - 4.5 mmol/L[5] or even higher in acute cardiac injury settings [6-7]. Thus it is desirable to avoid hypokalemia by close monitoring and subsequent replacement of potassium.

Although intravenous potassium replacement (IVPR) in hypokalemia is the preferred route in most intensive care settings, it is associated with known safety risks. Inappropriately administered, IVPR can lead to arrhythmias, cardiac arrest and death [2,8,9]. Given these risks, IVPR is considered a “high-alert medication” by Institute of Safe Medication practice [10,11]. The need of a central line for higher concentrations of potassium can lead to central line related infection due to frequent access of the line during IVPR. Inability to use high concentration potassium through peripheral lines may lead to a larger volume of fluid for delivery of the desired dose of potassium thus disturbing the fluid balance in these patients. This may not be preferred in post-surgical cardiac patients in whom a negative fluid balance is being desired. Given all the above mentioned issues with IVPR, enteral potassium replacement (EPR), with its equal or superior safety profile may be a better alternative to IVPR. A retrospective review showed that the efficacy of EPR was comparable to IVPR in pediatric patients after

congenital heart disease [9].

We sought to explore this comparison between EPR and IVPR in a randomized, equivalence trial to determine if EPR can be used as an alternative to IVPR.

This trial was registered at the Clinicaltrials.gov. Registration number: NCT02015962. Details of the trial protocol and design have been previously published [12].

Objectives:

Primary objective was to compare the equivalence of efficacy (measured as change in serum potassium levels in mmol/L and percentage change in level after potassium replacement) between EPR versus IVPR for treatment of hypokalemia. The secondary objectives were: i) compare the adverse effects (hyperkalemia, diarrhea, GI bleeds, nausea and vomiting) after EPR and IVPR, ii) compare number of dose/s required in achieving resolution of hypokalemia (as described per protocol) for each episode of hypokalemia, and iii) determine the efficacy of EPR versus IVPR for various degrees of severity of hypokalemia i.e. mild, moderate or severe hypokalemia.

We hypothesize that EPR will be equally efficacious in treatment of hypokalemia as IVPR.

Trial design:

Trial protocol and design have been published previously [12]. Briefly, the EIPS trial was designed as a randomized, non-blinded, equivalence trial with two arms. Arm A (IVPR) received intravenous potassium replacement while Arm B (EPR) received enteral potassium replacement as a treatment of hypokalemia. Intervention arms were block

randomized as alternate week for IVPR and EPR for the sake of convenience and to minimize error in drug delivery.

Methods

Definitions used for the study:

Hypokalemia: Hypokalemia was defined as serum Potassium <4.4mmol/L

Event and episode of hypokalemia: Serum potassium <4.4 mmol/L was considered as hypokalemia. This marked beginning of EPISODE of hypokalemia. Each potassium replacement was considered an EVENT of hypokalemia irrespective of whether hypokalemia was completely resolved or not. The EPISODE of hypokalemia ended when the potassium level returned to the normal range as described above.

Study setting:

The study was conducted at PCICU of Aga Khan University Hospital, Karachi, Pakistan.

Eligibility Criteria:

Inclusion criteria:

This trial included patients, 1 month to 25 years of age, undergoing surgical repair/palliation of congenital heart lesion at Aga Khan University Hospital and admitted to PCICU for post-operative management. Patients/Parents willingness to participate in this study, serum potassium levels (<4.4 mmol/l) immediate post operatively, ability to tolerate oral or nasogastric administration of medication for EPR and presence of a central line for IVPR were also included in eligibility criteria.

Exclusion Criteria:

We excluded patients with acute renal failure (clearance creatinine - ecCr <75%, urine output <0.3 ml/kg/h × 16 hrs.)[13]. Also those with paralytic ileus, necrotizing enterocolitis, gastrointestinal bleeding, nausea, vomiting or diarrhea were excluded, as they could not be given EPR. However, patients were not excluded if vomiting or diarrhea developed after initial recruitment. Patients with critically low serum potassium <2.0 mmol and patients with symptomatic hypokalemia prior to being recruited were also excluded.

Consent Procedure:

Informed consent and assent was taken by investigators, from each patient (or parent in case of age <16 years) before going for cardiac surgery.

Study Recruitment, procedure and Monitoring:

Detailed description about recruitment, study procedure, and monitoring had been previously published in protocol [12]. Patients were enrolled and potassium levels were checked routinely, once they were shifted to PCICU post-operatively. In case, when they developed hypokalemia, they received treatment according to intervention arm and were followed till he/she had reached optimal potassium levels or shifted from PCICU to step down unit. Repeat serum potassium levels were sent 1 hour after replacement in IVPR group and 2 hours after replacement in EPR group. Further patient serum electrolyte monitoring was determined by patient's clinical status.

In cases, where patient stayed in PCICU beyond one week and block changed, patient

continued to follow the route they were originally assigned. EPR patients who developed side effects (e.g. vomiting GI upset) or who develop critically low levels of potassium <2mmol (exclusion criteria) were allowed to cross over and receive IVPR subsequently. An intention to treat analysis was performed to account for cross over patients.

During pre-recruitment trial period, it was recognized that patients, who were given enteral potassium supplementation couldn't tolerate enteral formulation and ended up vomiting due to sour taste of formulation. Thus it was decided to use nasogastric (NG) tube, placed intra-operatively under anesthesia, in mechanically ventilated patients and administer enteral potassium through NG tube. Once patients were extubated and started tolerating oral feeds, enteral potassium supplementation was administered with apple juice to improve the taste and palatability of medicine. These measures were adopted throughout the trial to improve tolerance and compliance to EPR.

Study Drugs, Drug management:

Drug dosing protocol for potassium replacement as shown in Table 1, details about maximum concentration and dose in each arm and drug management can be reviewed in previously published protocol [12].

Table 1 Potassium replacement dosing.

Serum Potassium level (mmol/L)	Potassium replacement (I/V and Enteral)
4.0 – 4.4	0. 1 mmol/kg/dose
3.5 -3.9	0.3 mmol/kg/dose
3.0 -3.4	0.5 mmol/kg/dose
2.5 – 2.9	0.7 mmol/kg/dose

2.1- 2.4	1 mmol/kg/dose and call physician

Intravenous Potassium Chloride
Maximum dose: 3mmol/kg/day;
Dilution and infusion rate: 8mmol/100ml, 10mmol/hour for peripheral line, 15mmol/100ml, 15mmol/hour for central line.

Oral Potassium Chloride
Maximum dose 240mmol/24 hours . Maximum per dose 60mmol.
Concentration 13.33mmol/5ml

Adverse Events:

Adverse effects of potassium supplementation that were monitored are; hyperkalemia (potassium levels > 5 mmol/L), arrhythmias, diarrhea, gastrointestinal bleeds, nausea and vomiting, during or within 2 hours of potassium replacement.

The adverse events were monitored and documented on hourly bases by PCICU nursing staff and notified to on-call physician and PI.

Sample size calculation:

Sample size was calculated using equivalence test of mean procedure, considering equal efficacy of both interventions (EPR and IVPR) with standard deviation of 4%. Equivalence limit assumed to be +/- (15%), using a power of 90% and level of significance 5%, a total of 155 events were required in each arm to reject the null hypothesis which states that there is no difference in the efficacy (change in Serum Potassium levels) of IVPR and EPR. Sample size was calculated using PASS software.

Statistical Analysis:

The primary objective of study was to compare the efficacy of EPR and IVPR for treatment of hypokalemia. End points (primary outcome) used were change in serum potassium levels in mmol/L and percentage change in serum potassium levels after each

event of potassium replacement by both methods

Data were analyzed using two approaches; Intention to treat (ITT) and actual treatment (AT) received analysis. Intention to treat (ITT) was considered the primary analysis. Mean (+/-SD) was calculated for continuous parametric variables while median was used to describe continuous non-parametric variables. Categorical variables are presented as frequencies. To explore bivariate associations, independent student-t and Mann-Whitney U-tests were used for parametric and non-parametric continuous variables respectively, while Chi Square was used for categorical variables. Change in potassium concentration over time, was assessed by mixed effects regression modeling. It incorporated a random intercept trend. This analytic approach included all participants that have data available on at-least one time point. A hierarchical model developed that nests event within episode and patients through random intercept model to adjust inter-individual and episode related variation in change in potassium concentration. The analysis included linear time effect with main effect of treatment to examine whether the experimental condition (EPR) resulted in greater changes in potassium than the control (IVPR) over time. Age of participants, potassium concentration at beginning of episode, average urine output, diuretic dose and inotrope score were incorporated in model as confounding factors and results were reported as coefficients with 95% CI's. Data were analyzed using STATA version 12 through xtmixed command. The model building command includes three steps. As a first step an unconditional model was tested with episode and event levels random intercepts to examine the variation in outcomes at these levels. In the next step, time variable was added with outcome as a fixed effect and random slope. Likelihood ratio (LR) test was used to confirm whether the variance of the slope is significantly

different from zero. Time was treated as a fixed effect where LR test failed to provide evidence for this null hypothesis. Finally outcome adjusted for all potential covariates significant at a liberal $p<0.2$ in bivariate analysis and retained if significant at $p<0.05$. Fit of the models assessed through Akaike information criteria (AIC) and Bayesian information criteria (BIC). Generally the smallest the statistical value the better the model fits the data

An interim analysis was performed after 155 events (cumulative in both arms) to ensure protocol compliance and monitor adverse effects. Analysis did not reveal any major adverse effects and validated comparable efficacy between two arms. Thus, no major changes were made to protocol and trial was continued to achieve final sample size.

Data collection, storage and record keeping:

The data abstraction form was used to abstract patient data for study.

Data were collected by investigators (NR, QM, AR) throughout the duration of study and was kept safe under lock and password protected e-files at all times.

Ethics committee and regulatory approval:

This study was approved by ERC and Clinical Trials Unit at Aga Khan University Hospital.

Results:

Patients were recruited from December 2013 to May 2014. Initially 55 patients were approached. The first 10 patients were consented and recruited for the pre-trial period and were not included in the trial analysis. During the pre-trial period, the EPR and IVPR

potassium protocol was introduced for training of the staff. The next 45 patients were approached with the intention of trial recruitment. Out of these, 4 were excluded as they did not meet the inclusion criteria (2 participants were excluded as they developed critically low levels of potassium while the other 2 participants never developed an episode of hypokalemia during their PICU stay). Thus 41 patients eventually fulfilled the inclusion criteria for the trial. There were no attrition from the patients recruited.

The most common cardiac lesion in both groups was found to be ventricular Septal Defect (VSD) and most common surgical procedure was VSD closure. No patients received continuous or modified ultrafiltration during or after surgery. After randomization, 18 patients were recruited in IVPR arm while 23 patients in EPR arm. The mean age of the patients was 4.8 (SD+/- 4) in IVPR group and 4.6 (SD+/-4.0) in EPR group (table 2A).

Table 2a: Baseline characteristics of enrolled children in IVPR and EPR arms

	Intention to treat(ITT)			Actual treatment received(AT)		
	IV K (n=18)	Oral K (n=23)	p-value	IV K (n=23)	Oral K (n=18)	p-value
Age at randomization (count,%)						
<1 year	5(27.8%)	4(17.4%)	0.54	6(26.1%)	3(16.7%)	0.61
1-5 year	5(27.8%)	10(43.5%)		7(30.4%)	8(44.4%)	
5-15 year	8(44.4%)	9(39.1%)		10(43.5%)	7(38.9%)	
Mean Age(years) *	4.8 ± 4.0	4.6 ± 4.0	0.91	4.8±4.2	4.6±3.8	0.87
Indicators at beginning of episode						
Potassium level (count,%) ‡						
Mild	33(71.7%)	31(63.3%)	0.47	41(74.5%)	23(57.5%)	0.14
Mod	13(28.3%)	17(34.7%)		14(25.5%)	16(40.0%)	
Severe	--	1(2.0%)		--	1(2.5%)	
Mean potassium*	3.7 ± 0.5 (3.5-3.8)	3.6 ± 0.5 (3.5-3.8)	0.71	3.7 ± 0.5 (3.6-3.8)	3.6 ± 0.5 (3.4-3.7)	0.23
Average Urine output*	3.9 ± 2.1 (3.4-4.6)	4.3 ± 2.5 (3.6-5.0)	0.44	4.1 ± 2.2 (3.5-4.7)	4.2 ± 2.5 (3.4-5.0)	0.81

Diuretic average dose (mg/kg)*†	0.4 ± 0.5 (0.3-0.6)	0.4 ± 0.6 (0.2-0.5)	0.57	0.5±0.6 (0.3-0.6)	0.3±0.4 (0.2-0.4)	0.15
Inotrope Score*	8.5 ± 9.1 (5.5-10.7)	4.6 ± 4.1 (3.4-5.8)	0.01	8.4±8.8 (5.6-10.5)	4.1±3.3 (3.0-5.1)	0.004
Total episodes	48	49		57	40	

* Values reported as Mean ±SD (95% CI)

† Diuretics were given either at bolus every 6 hrs or as a continuous infusion. Average dose was calculated as total diuretic (mg) received in 6hrs/ weight (kg) of the patient/6 to get mg/kg/hour.

‡ Severity of hypokalemia defined as potassium level of Mild: 3.5 -4.4 mEq/L, Moderate: 2.5 -3.4 mEq/L, Severe: 2.1- 2.4 mEq/L

Five patients from EPR arm crossed over to IVPR arm (figure 1) due to development of adverse events i.e. 4 vomiting and one arrhythmia. The median length of CICU stay was 2 (0.63-14) days and 1.95 (0.58-8) days (p= 0.26) in IVPR and EPR respectively. The median length of hospital stay in IVPR was 7 (3-19) days while in EPR was 6 (4-18) days (p=0.83). A total of 97 episodes of hypokalemia were recorded (48 and 49 in IVPR and EPR arm respectively). From these episodes a total of 460 events of hypokalemia were recorded (234 and 226 in IVPR arm and EPR arm respectively). There was no difference in episode (IVPR 2.7 SD +/- 2.1; EPR 2.1 SD +/- 1.3) and events (number of doses) (IVPR 5.0 SD+/-4.9; EPR 4.6 SD+/- 4.2) per child between the two arms (table 2B).

Table 2b: Episodes, events and mean percent change in potassium concentration in IVPR and EPR arms

	Intention to treat(ITT)			Actual treatment received(AT)		
	IV K	Oral K	p-value[3]	IV K	Oral K	p-value[3]
Events	234	226		279	181	
Episode per child(N)	18	23		23	18	
Mean±SD	2.7 ± 2.1	2.1 ± 1.3	0.32	2.5±1.9	2.2±1.4	0.63
Event per episode(N)	48	49		57	40	
Mean±SD	5.0 ± 4.9	4.6 ± 4.2	0.70	5.0±4.8	4.5±4.2	0.64
Change in Potassium(N) [1]	48	49		57	40	

Mean±SD	0.82±0.7	0.86±0.8	0.80	0.78±0.6	0.93±0.8	0.34
95% CI	(0.62-1.01)	(0.62-1.10)		(0.65-0.95)	(0.64-1.21)	
Relative percentage change in Potassium(N) [2]	48	49		57	40	
Mean±SD	24±20	27±29	0.59	22±20	29±30	0.22
95% CI	(18-30)	(19-35)		(17-27)	(19-39)	
Mean difference (95% CI)	-2.7% (-12.8% to 7.3%)			-5.5% (-17% to 4.2%)		
Relative percentage change in Potassium first episode(N) [2]	18	23		23	18	
Mean±SD	25±20	30±20	0.51	24±20	33±30	0.18
95% CI	(16-34)	(19-41)		(16-31)	(20-46)	

All values reported as Mean ±SD (95% CI)
1- Change in potassium concentration calculated as 'last event K-first event K' of an episode
2- Relative percent change calculated as (first K value of the episode –Last K value of the episode)/first K value of the episode * 100.
3- Mann-Whitney U test was used for comparison of episodes and events due to skewed distribution while change in potassium concentration and relative percent change were compared using independent sample t-test

Baseline characteristics of patients in both arms are presented in table 2A. Both groups had similar baseline characteristics; however, the IVPR arm had a higher inotropic score when compared to EPR arm at both ITT (8.5 ± 9.1 vs 4.6 ± 4.1, p= 0.01, respectively) and AT (8.4 ± 8.8 vs 4.1 ± 3.3, p= 0.004, respectively) analysis.

Mode of supplementation and response to therapy:

There was no difference between IVPR and EPR arm in mean serum potassium levels at the beginning (3.67 ± 0.42 vs 3.62± 0.48, p=0.45, respectively) and at the end of episode of hypokalemia (4.47 ± 0.62 vs 4.48 ± 0.60, p=0.94, respectively) (figure 2).

Univariate analysis showed no difference in response to therapy (number of doses required, dosage of potassium replaced, absolute change (IV 0.82±0.7; 95% CI:0.62-1.01 vs. Oral 0.86±0.8 ;95% CI: 0.62-1.10 p=0.8) and percentage change (IV 24±20 ;95% CI: 18-30 vs. Oral 26±30; 95% CI: 18-35 p=0.59) in potassium levels in both arms at initial

episode (table S1). The overall difference of relative change in potassium concentration was -2.7% (95% CI: -12.8% to 7.3%) with intention to treat analysis which was within the predetermined equivalence limit (+/- 15%).

Actual treatment received analysis was also performed and findings were not significantly different from intention to treat analysis.

Using repeated measure analysis, after adjusting for age of patient, potassium concentration at beginning of episode, average urine output, inotropic score and diuretic dose, change in absolute potassium level for each event of hypokalemia, after EPR and IVPR was equal with no statistically significant difference between two arms at ITT (β=0.01; 95% CI: -0.08 to 0.10, p=0.86) and AT analysis (table S2). Similar results were seen when analysis was performed for using percentage change in potassium levels after supplementation at ITT (β=0.30; 95% CI: -3.42 to 4.03, p =0.87) (table 3) and AT (Table S3).

Table 3: Repeated measure analysis of change in serum potassium concentration in IVPR and EPR arms(ITT)

	Unadjusted				Adjusted*			
	Coef.	SE	95% CI	p-value	Coef.	SE	95% CI	p-value

Potassium Concentration								
Intervention								
Oral K	0.02	0.05	-0.08 to 0.13	0.66	0.01	0.05	-0.08 to 0.10	0.86
IV K	Ref				Ref			
Percent Change in Potassium Concentration*								
Intervention								
Oral K	0.10	1.89	-3.60 to 3.80	0.95	0.30	1.90	-3.42 to 4.03	0.87
IV K	Ref				Ref			
Percent Change (per hour) in Potassium Concentration*								
Intervention								
Oral K	-3.01	1.55	-6.11 to -0.003	0.05	1.16	1.50	-1.76 to 4.08	0.44
IV K	Ref							

* Percent change calculate as (previous K –current K)/previous K * 100
Linear mixed effect regression analysis, adjusted for episode level variations and controlled for covariates of age, potassium levels at the beginning of episode, inotropic score, average urine output and average diuretic dose. The β co-efficient is the standardized coefficient' showing the degree of impact of intervention on the outcome.

Adverse events:

No mortality occurred in either of the arms. Total of 5 adverse events in EPR and none in IVPR arm were recorded. Out of these 5 cases, 4 were episodes of vomiting within two hours of enteral potassium replacement. A single atrial arrhythmia occurred in a 4.5 month old patient who underwent complete repair for tetralogy of Fallot. Abnormal rhythm was noticed an hour after enteral supplementation for treating mild hypokalemia. Rhythm was evaluated to be a run of ectopic atrial tachycardia. This patient was also noted to have such episodes of tachycardia immediately post-operatively before the enteral supplementation was started. Rhythm improved after patient was placed on oral amiodarone. No episodes of hyperkalemia were appreciated.

Discussion:

Our trial portrays comparable efficacy between both the modes of supplementation, intravenous and enteral, for correction of hypokalemia in post-cardiac surgery pediatric patients in PCICU setting. Through this trial we were able to establish that enteral potassium supplementation is an equally efficacious and safe mode of potassium replacement during hypokalemia in selected patient with congenital heart disease in the immediate post-operative period.

Pediatric patients after congenital heart disease repair are particularly susceptible to hypokalemia in post-operative period due to administration of high doses of loop diuretics and inotropes [1, 7]. In immediate postoperative period, body does not conserve potassium efficiently thus making potassium supplementation a requirement for many such pediatric cardiac patients [1]. Potassium supplementation has a narrow therapeutic range and thus a guarded safety profile. Although serious adverse effects with either mode of supplementation are quite rare, inappropriate administration of potassium in these patients may lead to worsening of heart failure, cardiac arrest, hyperkalemia, arrhythmias and death [2, 8, 9]. Given all the above-mentioned factors, efficient potassium replacement through a safe route holds pivotal importance in post cardiac surgery pediatric patients.

A comparable efficacy between enteral versus intravenous potassium supplementation was initially demonstrated in a recent retrospective study [9]. This retrospective study conducted by Moffet BS et al. included 66 post congenital heart surgery pediatric patients, who received 399 blouses of potassium (266 intravenous and 233 enteral). As a change of practice was advocated to encourage the use of enteral potassium

supplementation before data collection for this retrospective study, authors believe that physician's clinical experience and judgment may have skewed administration of enteral potassium to less critically ill patients. Also, limitations associated with a retrospective review reduced the generalizability of the findings of this study. Keeping above mentioned limitations in consideration; a prospective study with pre-defined protocol practices in place to reduce the clinician to clinician variability was warranted.

Although equally efficacious in improving potassium levels, IVPR requires stringent monitoring by PCICU staff and presence of a central line [9]. Correcting potassium levels back to normal usually requires multiple replacements, making repeated access to central line, a necessity. This may lead to central line related infections [9, 14]. Also, transition to enteral supplementation from IVPR poses a challenge in some patients and central lines have to be kept in place longer than required otherwise, for intravenous potassium supplementation [14]. Another downside of using IVPR is that a large volume of fluid is required for delivery of the desired dose of potassium with peripheral lines which is not preferable in post-operative cardiac patients in whom clinicians aim to achieve a negative fluid balance. On other hand, enteral supplementation, with comparable efficacy offers many advantages. It is easier to transition post-operative pediatric congenital heart disease patients directly to enteral supplementation and if required they can be discharged home on these supplementation. Moreover, use of enteral potassium supplementation can lead to significant reduction in fluid administration, which is of great advantage as hypokalemia is frequently a consequence of administration of loop diuretics to treat fluid overload in this patient population. Although, pediatric data regarding pharmacokinetics of enteral potassium supplementation is lacking, safety and efficacy of enteral

supplementation of potassium in adult population has been well established previously. One more potential advantage of administrating enteral potassium supplementation for treatment of hypokalemia is its cost effectiveness [9]. Along with being ten times more costly at our institution, IVPR also require central line utilization, increased nursing time and syringe pump utilization that further adds to overall cost of potassium supplementation. Adverse events seen in enteral arm mainly comprised of episodes of vomiting seen in some participants in the beginning of the trial. This can be attributed to sour taste of formulation or inappropriately fast administration through NG tube. The former can be taken care of by feeding through NG tube or mixing enteral potassium formulation with fruit juices. Other than these few episodes of vomiting, participants in this trial tolerated enteral supplementation of potassium. Given its equal efficacy, low adverse event profile and a potential benefit, EPR was shown to be an excellent alternative to IVPR in our patient cohort.

Generalizability:

EIPS included cardiac surgery patients after being received in PCICU post-operatively. Mean age of participants was 4.7 years with the youngest child being 1 month and the oldest child being 14 years, while predominant surgical procedure was VSD repair surgery. We believe that results of our study can be generalized to this patient population. However, there were only two patients with severely low potassium levels (see definition) and patients with critically low potassium i.e. <2.0 mmol/L were excluded from trial thus results from this trial should be generalized with caution in patients with severely and critically low potassium levels. Further investigation is warranted to determine safety profile of enteral potassium in these patients. Also, EIPS is a single-

center randomized study, with alternate week patient randomization, leading to potential significant selection and allocation bias and limiting generalizability of the findings.

We used a more aggressive potassium replacement strategy i.e. levels between 3.5-4.4 mmol/L based on observations of higher potassium levels required in cardiac patients (7). Though no episode of hyperkalemia was noticed in our cohort, our study is not powered to comment on the safety of this strategy.

Limitations:

EIPS is a single-center, non-blinded, equivalence study that may lead to observer bias. Blinding was not feasible in this trial owing to different routes of administration of same supplementation (enteral versus intravenous) and different time interval for checking serum levels in each arm (1 hour after intravenous replacement and 2 hours after enteral replacement). Confounding factors, such as concomitant use of diuretics and inotropic agents during the episode may have affected potassium metabolism. These factors were identified and were adjusted in analysis.

Auto-analyzer, located in PCICU, was used to measure point of care potassium levels in this trial. This might have been a potential limiting factor in our study. Central lab values, although being gold standard, could not be used, as turnover time for each sample at our institution is about 4 hours. Central lab values were obtained only when a critically low or high value was seen on the auto analyzer testing. Strong correlation between two values had previously been established during daily practice at our PCICU.

Difference in severity of the patient condition (as depicted by difference in inotropic scores in the 2 arms) may also have confounded our results. This was accounted for at a

statistical level by adjusting for inotropic scores in the multivariate modeling in which the score did not seem to affect the results.

Some participants got shifted out of PCICU before completion of episode of hypokalemia. Patients could not be followed once they moved out of PCICU to step-down unit or ward as stringent monitoring for trial and point of care potassium levels was not available in ward settings. This does affect generalizability of study. Routinely, patients who had been moved to step down units or wards in our institutions receive oral potassium supplementation.

It is imperative to know that enteral potassium replacement may not be possible in some patients due to gastrointestinal intolerance.

Lastly, our trial was also underpowered to detect difference in frequency of adverse effects between both arms. This limits inference of equivalence between the 2 modes when it comes to their safety/adverse events profile.

Conclusion: We had found similar effectiveness of EPR or IVPR in treating hypokalemia in post-operative congenital heart disease pediatric patients. EPR may be an equally efficacious alternative to treat hypokalemia in these patients.

Trial Registration:

This trial is registered at Clinical Trials.Gov. Registration number: NCT02015962.

Protocol:

Merchant Q, Rehman Siddiqui NU, Rehmat A, Amanullah M, Haq AU, Hasan B. Comparison of Enteral versus Intravenous Potassium Supplementation in hypokalemia in

post-cardiac surgery paediatric cardiac intensive care patients: prospective open label randomized control trial (EIPS). British Medical Journal Open. 2014 Sep; 4(9): -. Cited in PubMed; PMID: 25190615.

Abbreviations:

PCICU: Pediatric cardiac intensive care unit. ERC: Ethical Review Committee. CTU: Clinical Trials Unit. IVPR: intravenous potassium replacement. EPR: enteral potassium replacement.

Conflict of Interest:

All authors declare no support from any organization for submitted work, no financial relationships with any organizations that might have an interest in submitted work in previous three years and no other relationships or activities that could appear to have influenced submitted work.

Author's contributions:

NR, QM, MA, AH and BH: contributed equally to the research idea, study design, protocol writing, initiation, data acquisition, analysis and manuscript writing. AR and AR contributed in data acquiring, analysis of data and manuscript writing. BH was the senior author on this project involved in study idea genesis, design, data analysis and interpretation and manuscript writing. All authors have read and approved final manuscript.

Data sharing statement: No additional data available.

Source of Funding:

None

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Figure Legends:

Figure 1: Recruitment flow chart EIPS

Figure 2: Change in potassium concentration at the beginning and end of episode

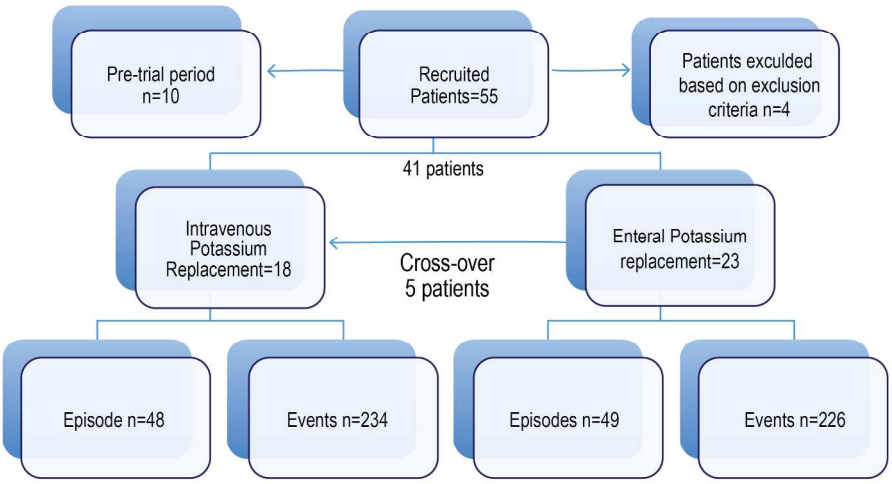

Figure 1: Recruiment flow chart EIPS

Figure 1: Recruitment flowchart EIPS

210x151mm (300 x 300 DPI)

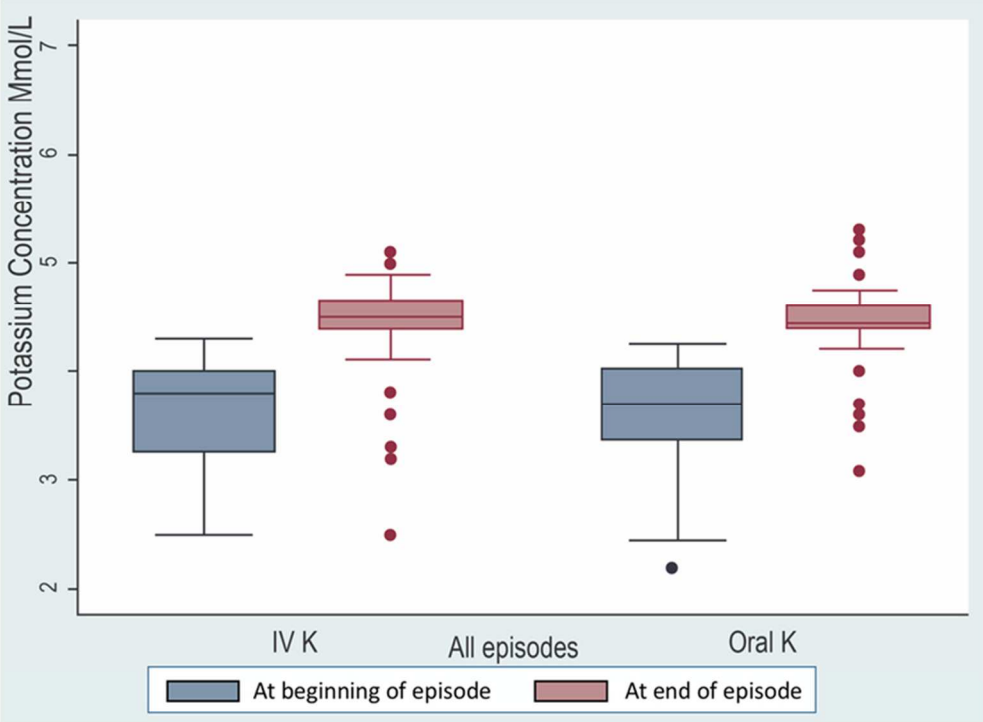

Figure 2: Boxplots representing all episodes. The extension lines represent the interquartile ranges. Midlines represent the median. Top and bottom represent the first and third quartiles, respectively.

73x59mm (300 x 300 DPI)

Supplementary tables are as under:

Table SI : Unadjusted repeated measure analysis of change in serum potassium concentration and percent change in potassium concentration.

	change in serum potassium concentration				percent change in potassium concentration			
	Coef.	**SE**	**95% CI**	**p-value**	**Coef.**	**SE**	**95% CI**	**p-value**
Time	0.01	0.001	0.008 to 0.01	<0.0001	0.25	0.02	0.21-0.29	<0.0001
Intervention(ITT)								
IV K	0.02	0.05	-0.08 to 0.13	0.66	0.10	1.89	-3.60 to 3.80	0.95
Oral K	Ref				Ref			
Intervention(ATT)*								
IV K	0.05	0.05	-0.06 to 0.16	0.37	0.68	1.93	-0.31 to 4.50	0.72
Oral K								
Average Urine output	-0.04	0.01	-0.06 to -0.02	<0.0001	-0.47	0.36	-1.21 to 0.26	0.20
inotrope score	0.13	0.05	0.03 to 0.22	0.007	-0.39	1.77	-0.38 to 3.08	0.83
Diuretic average dose	-0.07	0.04	-0.14 to 0.01	0.08	-1.13	1.40	-3.86 to 1.59	0.41
Age groups								
<1 yrs	-0.21	0.06	-0.33 to -0.08	0.01	0.82	2.40	-0.38 to 5.45	0.72
1-5 yrs	-0.13	0.07	-0.27 to 0.005	0.06	0.83	2.68	-4.43 to 6.10	0.75
5-15 yrs	Ref				Ref			
Potassium level at beginning of episode								
mild	0.41	0.29	-0.18 to 0.97	0.17	-24.1	11.7	-46.9 to -1.20	0.04
mod	0.26	0.29	-0.32 to 0.83	0.38	-20.3	11.7	-43.2 to 2.69	0.08
sever	Ref							

*Hierarchical effect of patient and episode incorporate in the model as random intercept

Table S2: Multivariate repeated measure analysis of change in serum potassium concentration by ITT and AT in IVPR and EPR arms.

	Intention to treat(ITT)				Actual treatment received(AT)			
	Coef.	SE	95% CI	p-value	Coef.	SE	95% CI	p-value
Intervention								
IV K	0.01	0.05	-0.08 to 0.10	0.86	0.04	0.05	-0.05 to 0.13	0.39
Oral K	Ref				Ref			
Average Urine output	-0.02	0.01	-0.04 to -0.01	0.01	-0.02	0.01	-0.04 to -0.00	0.01
inotrope score	0.15	0.04	0.06 to 0.23	0.00	0.14	0.04	0.06 to 0.23	0.00
Age groups								
<1 yrs	-0.14	0.06	-0.25 to -0.02	0.02	-0.14	0.06	-0.25 to -0.02	0.02
1-5 yrs	-0.12	0.06	-0.24 to 0.00	0.06	-0.13	0.06	-0.25 to -0.01	0.04
5-15 yrs	Ref				Ref			
Potassium level at beginning of episode								
mild	0.55	0.25	0.07 to 1.03	0.03	0.58	0.25	0.09 to 1.06	0.02
mod	0.40	0.25	-0.08 to 0.88	0.11	0.42	0.25	-0.06 to 0.90	0.09
sever	Ref				Ref			

*Analysis performed to examine effect of oral and IV on potassium concentration adjusting for age, potassium levels at the beginning of episode, inotropic score, average urine output and average diuretic dose. All of the variables treated as fixed effect. Hierarchical effect of patient and episode incorporate in the model as random interc

Table S3: Multivariate Repeated measure analysis of percentage change in serum potassium concentration by ITT and AT. Percent change calculate as (previous K –current K)/previous K * 100

	Intention to treat(ITT)				Actual treatment received(AT)			
	Coef.	SE	95% CI	p-value	Coef.	SE	95% CI	p-value
Time	0.24	0.02	0.21-0.29	<0.0001	0.24	0.02	0.21-0.29	<0.0001
Intervention								
IV K	0.30	1.90	-3.42 to 4.03	0.87	0.50	1.90	-3.27 to 4.30	0.79
Oral K	Ref							
Potassium level at beginning of episode								
Mild	-23.94	11.71	-46.88 to -1.00	0.04	-23.8	11.7	-46.76 to -0.79	0.04
Mod	-20.09	11.77	-43.17 to 2.98	0.09	-19.9	11.8	-43.04 to 3.15	0.09
Sever	Ref							

* Hierarchical effect of patient and episode incorporate in the model as random intercept.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	-
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	12
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	-

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
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Recruitment	14a	Dates defining the periods of recruitment and follow-up	Clinicaltrials.gov
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*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Comparison of Enteral versus Intravenous Potassium Supplementation in hypokalemia in post cardiac surgery Pediatric Cardiac Intensive Care patients – Open label Randomized equivalence trial (EIPS)

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Comparison of **E**nteral versus **I**ntravenous **P**otassium **S**upplementation in hypokalemia in post cardiac surgery Pediatric Cardiac Intensive Care patients – Open label Randomized equivalence trial **(EIPS)**

Authors: Naveed ur Rehman Siddiqui*, Quratulain Merchant*, Babar S. Hasan, Arjumand Rizvi, Muneer Amanullah, Amina Rehmat, Anwar ul Haq.

Institution: Aga Khan University Hospital, Stadium Road P.O Box 3500, Karachi, Pakistan.

*These authors contributed equally and will share first authorship. **EIPS is a non-funded trial. Reprints will not be ordered. No extra data is available.**

Corresponding author: Babar Hasan MD FAAP, Associate Professor, Head of Section, Pediatric Cardiology

Email address: babar.hasan@aku.edu

Address: Department of Pediatrics and Child Health, Aga Khan University Hospital, Stadium Road 75500, Karachi

Quratulain Merchant MD

Email address: annie.merchant@hotmail.com

Naveed ur Rehman Siddiqui, FCPS MBBS Fellow, Pediatric Critical Care Medicine

Email address: drnrsvd@hotmail.com

Arjumand Rizvi, MSc, Statistician, Department of Pediatrics and Child Health

Email address: arjumand.rizvi@aku.edu

Muneer Amanullah, FRCS MBBS Associate Professor, Department of Surgery

Email address: muneer.amanullah@aku.edu

Amina Rehmat, BscN Head nurse, PCICU

Email address: amina.rehmat@aku.edu

Anwar ul Haq, MD, Diplomat Amercican Board of Pediatric Critical Care, Associate Professor, PICU

Email address: anwar.haq@aku.edu

Abstract:

Objectives: Primary Objective was to compare the efficacy of enteral potassium replacement (EPR) and intravenous potassium replacement (IVPR), as first-line therapy. Secondary objectives included comparison of adverse effects and number of doses required to resolve the episode of hypokalemia.

Trial design: EIPS trial is designed as a randomized, equivalence trial between two treatment arms.

Study Setting: Study was conducted at the Pediatric Cardiac Intensive care Unit (PCICU) of Aga Khan University Hospital, Karachi.

Participants: 41 post-cardiac surgery patients (1 month- 15 year) admitted to PCICU were recruited (23 IVPR arm and 18 EPR arm).

Intervention: Intervention arms were block randomized as alternate week for IVPR and EPR.

Outcome measure: Change in serum potassium levels in (mmol/L) and % change after each event of potassium replacement by Intravenous or Enteral route.

Results: Both groups (41 patients) had similar baseline characteristics. Mean age was 4.7 (SD +/-4) years while the most common surgical procedure was ventricular septal defect repair (12 patients 29.3%). No mortality was observed in either arm. 4 episodes of vomiting and one arrhythmia were seen in the EPR group. After adjusting for age, potassium level at beginning of episode, average urine output, inotropic score and diuretic dose, it was found that there was no statistically significant difference in change in potassium levels after EPR and IVPR 0.86 mmol/L(+/-0.8) and 0.82 mmol/L(+/-0.7)

respectively (p=0.86, 95% CI, -0.08 -1.10), as well as percentage change in potassium level after enteral and intravenous replacement 26%(+/-30) and 24%(+/-20) (95% CI: -3.42 to 4.03, p =0.87).

Conclusion: EPR may be an equally efficacious alternative first line therapy in treating hypokalemia in selective post-operative congenital heart disease patients.

Ethics and Dissemination: This study has been approved by Ethics Review Committee at AKU.

Trial Registration: Clinical Trials.Gov. Registration number: NCT02015962.

Funding: None

Key words: Hypokalemia, potassium replacement, pediatric post-surgical patients, intravenous potassium replacement, enteral potassium replacement.

Article Summary

1) EIPS is the first prospective randomized equivalence trial comparing the routes (enteral versus intravenous) for potassium replacement in the post cardiac-surgery pediatric patients in the PCICU.
2) A retrospective review has previously shown comparable efficacy between the two routes.
3) Research from this trial will lead the way for further research in this field, possibly bringing about a change in the management of hypokalemia in post-op patients and subsequently lower complications and morbidity associated with intravenous potassium replacement.
4) EIPS is not a blinded study, which may lead to a procedure bias. Blinding could not be carried out in this trial owing to different routes of administration of the same supplementation (enteral versus intravenous) and different time interval for checking serum levels in each arm (1 h after intravenous replacement and 2 h after enteral replacement).
5) Confounding factors, such as concomitant use of diuretics and inotropic agents during the episode, were identified and adjusted in the analysis.

Introduction:

Hypokalemia is a frequently encountered electrolyte abnormality in daily clinical practices of pediatric cardiac intensive care unit (PCICU). In the post-operative period, activation of renin-angiotensin-aldosterone system enhanced sympathetic tone and use of potassium-wasting diuretics for positive fluid balance leads to increased occurrence and consequences of severe hypokalemia [1]. Hypokalemia is a strong independent predictor of mortality in heart failure patients [2-4]. Potassium replacement remains the cornerstone therapy for hypokalemia. There is mounting evidence that the serum potassium level should be maintained between 3.5 - 4.5 mmol/L[5] or even higher in the setting of acute cardiac injury [6-7]. Thus it is highly desirable to avoid hypokalemia by close monitoring and subsequent potassium replacement.

Although intravenous potassium replacement (IVPR) in hypokalemia is preferred route in most of the intensive care settings, it is associated with known safety risks. IVPR can lead to arrhythmias, cardiac arrest and death if administered inappropriately [2,8,9]. Given these risks, IVPR is considered a "high-alert medication" by Institute of Safe Medication practice [10,11]. The need to maintain and frequently access a central line for administration of higher concentrations of potassium can lead to serious central line infections. Inability to use high concentration potassium through peripheral lines may lead to administration of larger volume of fluid for the delivery of desired dose of potassium, thus disturbing the fluid balance in these patients. This may be detrimental in post-surgical cardiac patients in whom a negative fluid balance is optimal. Given all the above mentioned issues with IVPR, enteral potassium replacement (EPR), with its equal or superior safety profile may be a better alternative to IVPR. A retrospective review

showed that the efficacy of EPR was comparable to IVPR in pediatric patients after surgery for congenital heart disease [9].

We sought to explore this comparison between EPR and IVPR in a randomized equivalence trial to determine if EPR can be used as an alternative to IVPR.

This trial was registered at the Clinicaltrials.gov. Registration number: NCT02015962. Details of the trial protocol and design have been previously published [12].

Objectives:

Primary objective was to compare the equivalence of efficacy (measured as change in serum potassium levels in mmol/L and percentage change in level after potassium replacement) between EPR versus IVPR as first line therapy for treatment of hypokalemia. The secondary objectives were: i) to compare the adverse effects (hyperkalemia, diarrhea, GI bleeds, nausea and vomiting) after EPR and IVPR, ii) to compare number of dose/s required in achieving resolution of hypokalemia (as described per protocol) for each episode of hypokalemia, and iii) to determine the efficacy of EPR versus IVPR for various degrees of severity of hypokalemia i.e. mild, moderate or severe hypokalemia.

We hypothesize that EPR will be equally efficacious in treatment of hypokalemia as IVPR, as first line therapy.

Trial design:

Trial protocol and design had been published previously [12]. Briefly, the EIPS trial was designed as a randomized, non-blinded, equivalence trial with two arms. Arm A (IVPR) received intravenous potassium replacement while Arm B (EPR) received enteral potassium replacement as a treatment of hypokalemia. Intervention arms were block randomized as alternate week for IVPR and EPR for the sake of convenience and to minimize error in drug delivery.

Methods

Definitions used for the study:

Hypokalemia: Hypokalemia was defined as serum Potassium <4.4mmol/L

Event and episode of hypokalemia: Serum potassium <4.4 mmol/L was considered as hypokalemia. This marked beginning of EPISODE of hypokalemia. Each potassium replacement was considered an EVENT of hypokalemia irrespective of whether hypokalemia was completely resolved or not. The EPISODE of hypokalemia ended when the potassium level returned to the normal range as described above.

Study setting:

The study was conducted at PCICU of Aga Khan University Hospital, Karachi, Pakistan.

Eligibility Criteria:

Inclusion criteria:

This trial included patients, 1 month to 15 years of age, undergoing surgical repair/palliation of congenital heart lesion at Aga Khan University Hospital and admitted to PCICU for post-operative management. Patients/Parents willingness to participate in this study, serum potassium levels <4.4 mmol/l in the post-operative period, ability to tolerate oral or nasogastric administration of medication for EPR and presence of a central line for IVPR were also included in eligibility criteria.

Exclusion Criteria:

We excluded patients with acute renal failure (clearance creatinine - ecCr <75%, urine output <0.3 ml/kg/h × 16 hrs.)[13]. Patients with paralytic ileus, necrotizing enterocolitis, gastrointestinal bleeding, nausea, vomiting or diarrhea were excluded as well, as they could not be given EPR. However, patients were not excluded if vomiting or diarrhea developed after initial recruitment. Patients with critically low serum potassium <2.0 mmol and patients with symptomatic hypokalemia were also not recruited.

Consent Procedure:

Informed consent and assent was taken by investigators, from each patient (or parents) before going for cardiac surgery.

Study Recruitment, procedure and Monitoring:

Detailed description about recruitment, study procedure, and monitoring has been previously published in the protocol [12]. Patients were enrolled and potassium levels were checked routinely, once they were moved to PCICU post-operatively. When the patients developed hypokalemia, they received treatment according to the intervention arm and were followed till they had reached optimal potassium levels or moved from PCICU to step down unit. Repeat serum potassium levels were checked 1 hour after replacement in IVPR group and 2 hours after replacement in EPR group. Further monitoring of the serum electrolytes was determined by patient's clinical status.

In cases, where patient stayed in PCICU beyond one week and block changed, patients continued to follow the route, they were originally assigned to. EPR patients who developed side effects (e.g. vomiting GI upset) or critically low levels of potassium <2mmol (exclusion criteria) were allowed to cross over and receive IVPR subsequently. An intention to treat analysis was performed to account for cross over patients.

During pre-recruitment trial period, it was recognized that patients, who were given enteral potassium supplementation couldn't tolerate enteral formulation and ended up vomiting due to sour taste of formulation. Thus it was decided to administer enteral potassium through nasogastric (NG) tube, placed intra-operatively, in mechanically ventilated patients. Once patients were extubated and started tolerating oral feeds, enteral potassium supplementation was administered with apple juice to improve the taste and palatability of medicine. These measures were adopted throughout the trial to improve tolerance and compliance to EPR.

Study Drugs, Drug management:

Drug dosing protocol for potassium replacement was shown in table 1, details about maximum concentration, dose in each arm, and drug management can be reviewed in previously published protocol [12].

Table 1 Potassium replacement dosing.

Serum Potassium level (mmol/L)	Potassium replacement (I/V and Enteral)
4.0 – 4.4	0. 1 mmol/kg/dose
3.5 -3.9	0.3 mmol/kg/dose
3.0 -3.4	0.5 mmol/kg/dose
2.5 – 2.9	0.7 mmol/kg/dose
2.1- 2.4	1 mmol/kg/dose and call physician

Intravenous Potassium Chloride
Maximum dose: 3mmol/kg/day;
Dilution and infusion rate: 8mmol/100ml, 10mmol/hour for peripheral line, 15mmol/100ml, 15mmol/hour for central line.

Oral Potassium Chloride
Maximum dose 240mmol/24 hours . Maximum per dose 60mmol.
Concentration 13.33mmol/5ml

Adverse Events:

Adverse effects of potassium supplementation that were monitored included hyperkalemia (potassium levels > 5 mmol/L), arrhythmias, diarrhea, gastrointestinal bleeds and nausea and vomiting, during or within 2 hours of potassium replacement.

The adverse events were monitored and documented on hourly bases by PCICU nursing staff and notified to on-call physician and PI.

Sample size calculation:

Sample size was calculated using equivalence test of mean procedure, considering equal efficacy of both interventions (EPR and IVPR) with standard deviation of 4%. Equivalence limit assumed to be +/- (15%), using a power of 90% and level of significance 5%, a total of 155 events were required in each arm to reject the null hypothesis which states that there is no difference in efficacy (change in Serum Potassium levels) of IVPR and EPR. Sample size was calculated using PASS software.

Statistical Analysis:

The primary objective of study was to compare the efficacy of EPR and IVPR as a first line therapy for treatment of hypokalemia. End points (primary outcome) used were change in serum potassium levels in mmol/L and percentage change in serum potassium levels after each event of potassium replacement by both methods.

Data was analyzed using two approaches; Intention to treat (ITT) and actual treatment (AT) received analysis. Intention to treat (ITT) was considered the primary analysis. Mean (+/-SD) was calculated for continuous parametric variables while median was used to describe continuous non-parametric variables. Categorical variables are presented as frequencies. To explore bivariate associations, independent student-t and Mann-Whitney U-tests were used for parametric and non-parametric continuous variables respectively, while Chi Square was used for categorical variables. Change in potassium concentration over time, was assessed by mixed effects regression modeling. It incorporated a random intercept trend. This analytic approach included all participants that had data available on at-least one time point. A hierarchical model was developed that nests event within

episode and patients through random intercept model to adjust inter-individual and episode related variation in change in potassium concentration. The analysis included linear time effect with main effect of treatment to examine whether the experimental condition (EPR) resulted in greater changes in potassium than the control (IVPR) over time. Age of participants, potassium concentration at beginning of episode, average urine output, diuretic dose and inotrope score were incorporated in model as confounding factors and results were reported as coefficients with 95% CI's. Data were analyzed using STATA version 12 through xtmixed command. The model building command includes three steps. As a first step an unconditional model was tested with episode and event levels random intercepts to examine the variation in outcomes at these levels. In the next step, time variable was added with outcome as a fixed effect and random slope. Likelihood ratio (LR) test was used to confirm whether the variance of the slope is significantly different from zero. Time was treated as a fixed effect where LR test failed to provide evidence for this null hypothesis. Finally outcome adjusted for all potential covariates significant at a liberal $p < 0.2$ in bivariate analysis and retained if significant at $p < 0.05$. Fit of the models assessed through Akaike information criteria (AIC) and Bayesian information criteria (BIC). Generally the smallest the statistical value the better the model fits the data.

An interim analysis was performed after 155 events (cumulative in both arms) to ensure protocol compliance and monitor adverse effects. Analysis did not reveal any major adverse effects and validated comparable efficacy between two arms. Thus, no major changes were made to protocol and trial was continued to achieve final sample size.

Data collection, storage and record keeping:

The data abstraction form was used to abstract patient data for study.

Data were collected by investigators (NR, QM, AR) throughout the duration of study and was kept safe under lock and password protected e-files at all times.

Ethics committee and regulatory approval:

This study was approved by ERC and Clinical Trials Unit at Aga Khan University Hospital.

Results:

Patients were recruited from December 2013 to May 2014. Initially 55 patients were approached. The first 10 patients were consented and recruited for the pre-trial period and were not included in the trial analysis. During the pre-trial period, EPR and IVPR potassium protocol was introduced for the training of staff nurses. The next 45 patients were recruited for the trial. Out of these, 4 were excluded as they did not meet the inclusion criteria (2 participants were excluded as they developed critically low levels of potassium while the other 2 participants never developed an episode of hypokalemia during their PCICU stay). Thus 41 patients fulfilled the inclusion criteria for the trial. There was no attrition from the patients recruited. The most common cardiac lesion in both the groups was found to be Ventricular Septal Defect (VSD) and the most common surgical procedure was VSD closure. None of the patients received continuous or modified ultrafiltration during or after surgery. After randomization, 18 patients were

recruited in IVPR arm while 23 patients in EPR arm. The mean age of patients were 4.8 (SD+/- 4) in IVPR group and 4.6 (SD+/-4.0) in EPR group (table 2A).

Table 2a: Baseline characteristics of enrolled children in IVPR and EPR arms

	Intention to treat(ITT)			Actual treatment received(AT)		
	IV K (n=18)	Oral K (n=23)	p-value	IV K (n=23)	Oral K (n=18)	p-value
Age at randomization (count,%)						
<1 year	5(27.8%)	4(17.4%)	0.54	6(26.1%)	3(16.7%)	0.61
1-5 year	5(27.8%)	10(43.5%)		7(30.4%)	8(44.4%)	
5-15 year	8(44.4%)	9(39.1%)		10(43.5%)	7(38.9%)	
Mean Age(years) *	4.8 ± 4.0	4.6 ± 4.0	0.91	4.8±4.2	4.6±3.8	0.87
Indicators at beginning of episode						
Potassium level (count,%) ‡						
Mild	33(71.7%)	31(63.3%)	0.47	41(74.5%)	23(57.5%)	0.14
Mod	13(28.3%)	17(34.7%)		14(25.5%)	16(40.0%)	
Severe	--	1(2.0%)		--	1(2.5%)	
Mean potassium*	3.7 ± 0.5 (3.5-3.8)	3.6 ± 0.5 (3.5-3.8)	0.71	3.7 ± 0.5 (3.6-3.8)	3.6 ± 0.5 (3.4-3.7)	0.23
Average Urine output(ml/kg/hr)*	3.9 ± 2.1 (3.4-4.6)	4.3 ± 2.5 (3.6-5.0)	0.44	4.1 ± 2.2 (3.5-4.7)	4.2 ± 2.5 (3.4-5.0)	0.81
Diuretic average dose (mg/kg)*†	0.4 ± 0.5 (0.3-0.6)	0.4 ± 0.6 (0.2-0.5)	0.57	0.5±0.6 (0.3-0.6)	0.3±0.4 (0.2-0.4)	0.15
Inotrope Score*	8.5 ± 9.1 (5.5-10.7)	4.6 ± 4.1 (3.4-5.8)	0.01	8.4±8.8 (5.6-10.5)	4.1±3.3 (3.0-5.1)	0.004
Total episodes	48	49		57	40	

* Values reported as Mean ±SD (95% CI)

† Diuretics were given either at bolus every 6 hrs or as a continuous infusion. Average dose was calculated as total diuretic (mg) received in 6hrs/ weight (kg) of the patient/6 to get mg/kg/hour.

‡ Severity of hypokalemia defined as potassium level of Mild: 3.5 -4.4 mEq/L, Moderate: 2.5 -3.4 mEq/L, Severe: 2.1- 2.4 mEq/L

Five patients from EPR arm crossed over to IVPR arm (figure 1) due to development of adverse events i.e. 4 vomiting and one arrhythmia. The median length of PCICU stay was 2 (0.63-14) days and 1.95 (0.58-8) days (p= 0.26) in IVPR and EPR respectively. The median length of hospital stay in IVPR was 7 (3-19) days while in EPR was 6 (4-18) days (p=0.83). A total of 97 episodes of hypokalemia were recorded (48 and 49 in IVPR and

EPR arm respectively). From these episodes, a total of 460 events of hypokalemia were recorded (234 and 226 in IVPR arm and EPR arm respectively). There was no difference in episode (IVPR 2.7 SD +/- 2.1; EPR 2.1 SD +/- 1.3) and events (number of doses) (IVPR 5.0 SD+/-4.9; EPR 4.6 SD+/- 4.2) per child between the two arms (table 2B).

Table 2b: Episodes, events and mean percent change in potassium concentration in IVPR and EPR arms

	Intention to treat(ITT)			Actual treatment received(AT)		
	IV K	Oral K	p-value[3]	IV K	Oral K	p-value[3]
Events	234	226		279	181	
Episode per child(N)	18	23		23	18	
Mean±SD	2.7 ± 2.1	2.1 ± 1.3	0.32	2.5±1.9	2.2±1.4	0.63
Event per episode(N)	48	49		57	40	
Mean±SD	5.0 ± 4.9	4.6 ± 4.2	0.70	5.0±4.8	4.5±4.2	0.64
Change in Potassium(N) [1]	48	49		57	40	
Mean±SD **95% CI**	0.82±0.7 (0.62-1.01)	0.86±0.8 (0.62-1.10)	0.80	0.78±0.6 (0.65-0.95)	0.93±0.8 (0.64-1.21)	0.34
Relative percentage change in Potassium(N) [2]	48	49		57	40	
Mean±SD **95% CI**	24±20 (18-30)	26±30 (18-35)	0.59	22±20 (17-27)	29±30 (19-39)	0.20
Mean difference (95%CI)	-2.7% (-12.8% to 7.3%)			-5.5% (-17% to 4.2%)		
Relative percentage change in Potassium first episode(N) [2]	18	23		23	18	
Mean±SD **95% CI**	25±20 (16-34)	30±20 (19-41)	0.51	24±20 (16-31)	33±30 (20-46)	0.18

All values reported as Mean ±SD (95% CI)
1- Change in potassium concentration calculated as 'last event K-first event K' of an episode
2- Relative percent change calculated as (first K value of the episode –Last K value of the episode)/first K value of the episode * 100.
3- Mann-Whitney U test was used for comparison of episodes and events due to skewed distribution while change in potassium concentration and relative percent change were compared using independent sample t-test

Baseline characteristics of patients in both arms are presented in table 2A. Both groups had similar baseline characteristics; however, the IVPR arm had a higher inotropic score

when compared to EPR arm at both ITT (8.5 ± 9.1 Vs 4.6 ± 4.1, p= 0.01, respectively) and AT (8.4 ± 8.8 Vs 4.1 ± 3.3, p= 0.004, respectively) analysis.

Mode of supplementation and response to therapy:

There was no difference between IVPR and EPR arms in the mean serum potassium levels at the beginning (3.67 ± 0.42 Vs 3.62± 0.48, p=0.45, respectively) and at the end of episode of hypokalemia (4.47 ± 0.62 Vs 4.48 ± 0.60, p=0.94, respectively) (figure 2).

Univariate analysis showed no difference in response to therapy (number of doses required, absolute change (IV 0.82±0.7; 95% CI: 0.62-1.01 vs. Oral 0.86±0.8; 95% CI: 0.62-1.10 p=0.8) and percentage change (IV 24±20; 95% CI: 18-30 vs. Oral 26±30; 95% CI: 18-35 p=0.59) in potassium levels in both arms at initial episode (table 2b). The overall difference of relative change in potassium concentration was -2.7% (95% CI: -12.8% to 7.3%) with intention to treat analysis which was within the predetermined equivalence limit (+/- 15%).

Actual treatment received analysis was also performed and findings were not significantly different from intention to treat analysis.

Using repeated measure analysis, after adjusting for the age of the patient, potassium concentration at the beginning of the episode, average urine output, inotropic score and diuretic dose, the change in absolute potassium level for each event of hypokalemia was equal with no statistically significant difference between the two arms at ITT (β=0.01; 95% CI: -0.08 to 0.10, p=0.86) and AT analysis. Similar results were seen when analysis was performed for using percentage change in potassium levels after supplementation at ITT (β=0.30; 95% CI: -3.42 to 4.03, p =0.87) and AT (table 3, S2, S3).

Table 3: Repeated measure analysis of change in serum potassium concentration in IVPR and EPR arms(ITT)

	Unadjusted				Adjusted*			
	Coef.	SE	95% CI	p-value	Coef.	SE	95% CI	p-value
Potassium Concentration								
Intervention								
Oral K	0.02	0.05	-0.08 to 0.13	0.66	0.01	0.05	-0.08 to 0.10	0.86
IV K	Ref				Ref			
Percent Change in Potassium Concentration*								
Intervention								
Oral K	0.10	1.89	-3.60 to 3.80	0.95	0.30	1.90	-3.42 to 4.03	0.87
IV K	Ref				Ref			
Percent Change (per hour) in Potassium Concentration*								
Intervention								
Oral K	-3.01	1.55	-6.11 to -0.003	0.05	1.16	1.50	-1.76 to 4.08	0.44
IV K	Ref							

* Percent change calculate as (previous K –current K)/previous K * 100

Linear mixed effect regression analysis, adjusted for episode level variations and controlled for covariates of age, potassium levels at the beginning of episode, inotropic score, average urine output and average diuretic dose. The β co-efficient is the standardized coefficient' showing the degree of impact of intervention on the outcome.

Adverse events:

No mortality occurred in either of the arms. Total of 5 adverse events were observed in the EPR arm while none were recorded in the IVPR arm. Out of these 5 cases, 4 were episodes of vomiting within two hours of enteral potassium replacement. A single atrial arrhythmia occurred in a 4.5 month old patient who underwent complete repair for tetralogy of Fallot. Abnormal rhythm was noticed an hour after enteral supplementation for treating mild hypokalemia. Rhythm was evaluated to be a run of ectopic atrial tachycardia. This patient was also noted to have such episodes of tachycardia in the

immediate post-operative period before the enteral supplementation was started. Rhythm improved after patient was placed on oral amiodarone. No episodes of hyperkalemia were appreciated.

Discussion:

Our trial portrays comparable efficacy of both the modes of supplementation, intravenous and enteral as first line therapy, for correction of hypokalemia in post-cardiac surgery pediatric patients in PCICU setting. Through this trial we were able to establish that enteral potassium supplementation is an equally efficacious and safe mode of potassium replacement as first line therapy, during hypokalemia in selected patient with congenital heart disease in immediate post-operative period.

Pediatric patients, after congenital heart disease repair, are particularly susceptible to hypokalemia in post-operative period due to administration of high doses of loop diuretics and inotropes [1, 7]. In immediate postoperative period, body does not conserve potassium efficiently thus making potassium supplementation a requirement for many such pediatric patients after cardiac surgery [1]. Potassium supplementation has a narrow therapeutic range and thus a guarded safety profile. Although serious adverse effects with either mode of supplementation are quite rare, inappropriate administration of potassium in these patients may lead to worsening of heart failure, cardiac arrest, hyperkalemia, arrhythmias and death [2, 8, 9]. Given all the above mentioned factors, efficient potassium replacement through a safe route holds pivotal importance in post cardiac surgery pediatric patients.

A comparable efficacy between enteral versus intravenous potassium supplementation

was initially demonstrated in a recent retrospective study [9]. This retrospective study conducted by Moffet BS et al. included 66 post congenital heart surgery pediatric patients, who received 399 blouses of potassium (266 intravenous and 233 enteral). As a change of practice was advocated to encourage the use of enteral potassium supplementation before data collection for this retrospective study, authors believe that physician's clinical experience and judgment may have skewed administration of enteral potassium to less critically ill patients. Also, limitations associated with a retrospective review reduced the generalizability of findings of this study. Keeping the above mentioned limitations in consideration; a prospective study, with pre-defined protocol and practices in place to reduce clinician to clinician variability, was warranted.

Although equally efficacious in improving potassium levels, IVPR requires stringent monitoring by PCICU staff and presence of a central line [9]. Correcting potassium levels back to normal usually requires multiple replacements, making repeated access to central line, a necessity. This may lead to central line related infections [9, 14]. Also, transition to enteral supplementation from IVPR poses a challenge in some patients and central lines have to be kept in place longer than required otherwise, for intravenous potassium supplementation [14]. Another downside of using IVPR is that a large volume of fluid is required for the delivery of desired dose of potassium with peripheral lines which is not preferable in post-operative cardiac patients in whom clinicians aim to achieve negative fluid balance. On the other hand, enteral supplementation, with comparable efficacy offers many advantages. It is easier to transition post-operative pediatric congenital heart disease patients directly to enteral supplementation and if required they can be discharged home on these supplementation. Moreover, use of enteral potassium supplementation can

lead to significant reduction in fluid administration, which is of great advantage as hypokalemia is frequently a consequence of administration of loop diuretics to treat fluid overload in these patients. Although, pediatric data regarding pharmacokinetics of enteral potassium supplementation is lacking, safety and efficacy of enteral supplementation of potassium in adult population has been well established previously. One more potential advantage of administrating enteral potassium supplementation for treatment of hypokalemia is its cost effectiveness [9]. Along with being ten times more costly than EPR at our institution, IVPR also require central line utilization, increased nursing time and syringe pump utilization that further adds to overall cost of potassium supplementation. Adverse events seen in enteral arm mainly comprised of episodes of vomiting seen in some participants in the beginning of the trial. This can be attributed to sour taste of formulation or inappropriately fast administration through NG tube. The former can be taken care of by feeding through NG tube or mixing enteral potassium formulation with fruit juices. Other than these few episodes of vomiting, participants in this trial tolerated enteral supplementation of potassium well. Given its equal efficacy, low adverse event profile and a potential benefit, EPR was shown to be an excellent alternative to IVPR as first line therapy in our patient cohort.

Generalizability:

EIPS included cardiac surgery patients after being received in PCICU post-operatively. Mean age of participants was 4.7 years with the youngest child being 1 month and the oldest child being 14 years, while the predominant surgical procedure was VSD repair surgery. We believe that the results of our study can be generalized to these patient populations. However, there were only two patients with severely low potassium levels

(see definition) and patients with critically low potassium i.e. <2.0 mmol/L who were excluded from trial thus results from this trial should be generalized with caution in patients with severely and critically low potassium levels. Further investigation is warranted to determine safety profile of enteral potassium in these patients. Also, EIPS is a single-center randomized study, with alternate week patient randomization, leading to potential significant selection and allocation bias and limiting generalizability of the findings.

We used a more aggressive potassium replacement strategy i.e. levels between 3.5-4.4 mmol/L based on observations that higher potassium levels are required in cardiac patients (7). Though no episode of hyperkalemia was noticed in our cohort, our study is not powered to comment on the safety of this strategy.

Limitations:

EIPS is a single-center, non-blinded, equivalence study that may lead to observer bias. Blinding was not feasible in this trial owing to different routes of administration of the same supplementation (enteral versus intravenous) and different time interval for checking serum levels in each arm (1 hour after intravenous replacement and 2 hours after enteral replacement). Confounding factors, such as concomitant use of diuretics and inotropic agents during the episode may have affected potassium metabolism. These factors were identified and were adjusted in analysis.

Auto-analyzer, located in PCICU, was used to measure point of care potassium levels in this trial. This might have been a potential limiting factor in our study. Central lab values, although being gold standard, could not be used, as turnover time for each sample at our

institution is about 4 hours. Central lab values were obtained only when a critically low or high value was seen on the auto analyzer testing. Strong correlation between two values had previously been established during daily practice at our PCICU.

Difference in severity of the patient's condition (as depicted by difference in inotropic scores in the 2 arms) may also have confounded our results. This was accounted for at a statistical level by adjusting for inotropic scores in the multivariate modeling and did not seem to affect the results.

Some participants got moved out of PCICU before completion of episode of hypokalemia. Patients could not be followed once they moved out of PCICU to step-down unit or floor as stringent monitoring for trial and point of care potassium levels was not available in floor settings. This does affect generalizability of study. Routinely, patients who get moved to step down units or floor receive oral potassium supplementation in our institution.

It is imperative to know that enteral potassium replacement may not be possible in some patients due to gastrointestinal intolerance.

Lastly, our trial was also underpowered to detect difference in frequency of adverse effects between both arms. This limits inference of equivalence between the 2 modes when it comes to their safety/adverse events profile.

Conclusion:. We found similar effectiveness of EPR or IVPR, as first-line therapy, in treating hypokalemia in post-operative congenital heart disease pediatric patients. EPR may be an equally efficacious alternative to treat hypokalemia, as first-line therapy, in these patients.

Trial Registration:

This trial is registered at Clinical Trials.Gov. Registration number: NCT02015962.

Protocol:

Merchant Q, Rehman Siddiqui NU, Rehmat A, Amanullah M, Haq AU, Hasan B. Comparison of Enteral versus Intravenous Potassium Supplementation in hypokalemia in post-cardiac surgery paediatric cardiac intensive care patients: prospective open label randomized control trial (EIPS). British Medical Journal Open. 2014 Sep; 4(9): -. Cited in PubMed; PMID: 25190615.

Abbreviations:

PCICU: Pediatric cardiac intensive care unit. ERC: Ethical Review Committee. CTU: Clinical Trials Unit. IVPR: intravenous potassium replacement. EPR: enteral potassium replacement.

Conflict of Interest:

All authors declare no support from any organization for submitted work, no financial relationships with any organizations that might have an interest in submitted work in previous three years and no other relationships or activities that could appear to have influenced submitted work.

Author's contributions:

NR, QM, MA, AH and BH: contributed equally to the research idea, study design, protocol writing, initiation, data acquisition, analysis and manuscript writing. AR

contributed in data acquiring, analysis of data and manuscript writing. BH was the senior author on this project involved in study idea genesis, design, data analysis and interpretation and manuscript writing. All authors have read and approved final manuscript.

Data sharing statement: No additional data available.

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None

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Figure Legends:

Figure 1: Recruitment flow chart EIPS

Figure 2: Change in potassium concentration at the beginning and end of episode

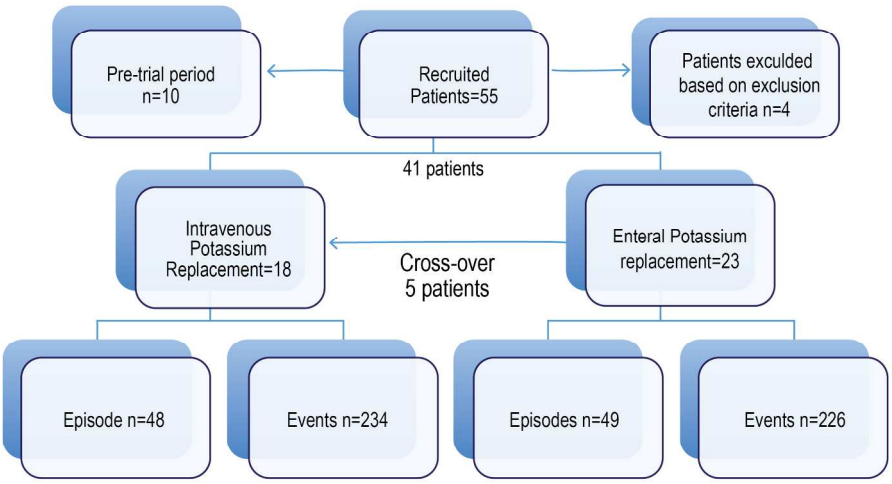

Figure 1: Recruiment flow chart EIPS

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210x151mm (300 x 300 DPI)

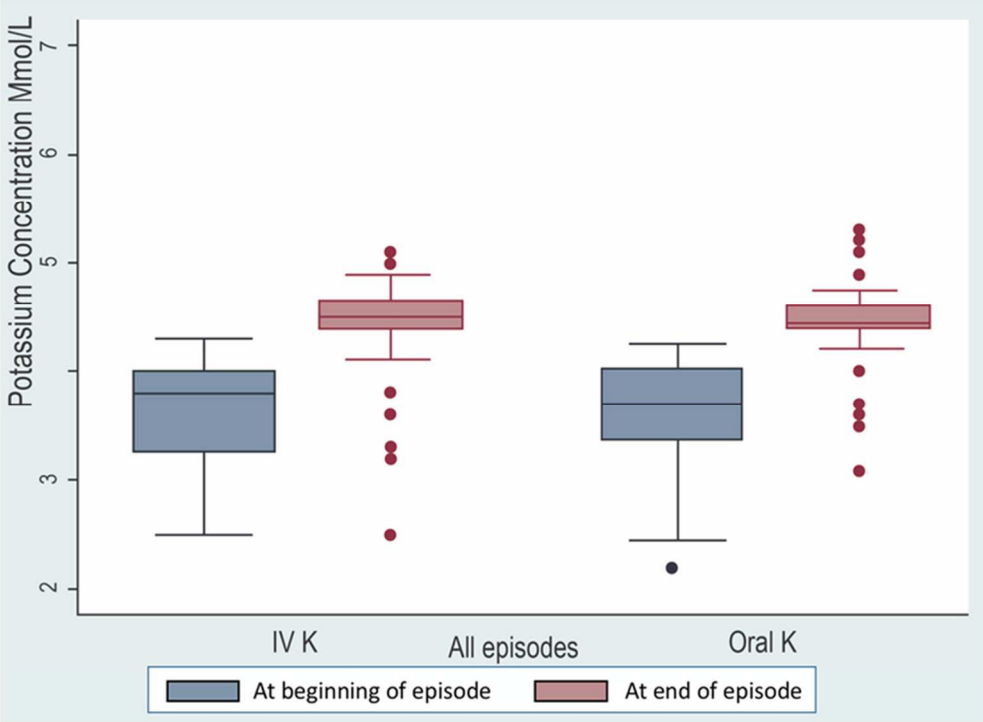

Figure 2: Boxplots representing all episodes. The extension lines represent the interquartile ranges. Midlines represent the median. Top and bottom represent the first and third quartiles, respectively.

73x59mm (300 x 300 DPI)

Table SI : **Unadjusted repeated measure analysis of change in serum potassium concentration and percent change in potassium concentration**.

	change in serum potassium concentration				percent change in potassium concentration			
	Coef.	**SE**	**95% CI**	**p-value**	**Coef.**	**SE**	**95% CI**	**p-value**
Time	0.01	0.001	0.008 to 0.01	<0.0001				
Intervention(ITT)*								
IV K	0.02	0.05	-0.08 to 0.13	0.66	0.10	1.89	-3.60 to 3.80	0.95
Oral K	Ref				Ref			
Intervention(ATT)*								
IV K	0.05	0.05	-0.06 to 0.16	0.37	0.68	1.93	-0.31 to 4.50	0.72
Oral K								
Average Urine output	-0.04	0.01	-0.06 to -0.02	<0.0001	-0.47	0.36	-1.21 to 0.26	0.20
inotrope score	0.13	0.05	0.03 to 0.22	0.007	-0.39	1.77	-0.38 to 3.08	0.83
Diuretic average dose	-0.07	0.04	-0.14 to 0.01	0.08	-1.13	1.40	-3.86 to 1.59	0.41
Age groups								
<1 yrs	-0.21	0.06	-0.33 to -0.08	0.01	0.82	2.40	-0.38 to 5.45	0.72
1-5 yrs	-0.13	0.07	-0.27 to 0.005	0.06	0.83	2.68	-4.43 to 6.10	0.75
5-15 yrs	Ref				Ref			
Potassium level at beginning of episode								
mild	0.41	0.29	-0.18 to 0.97	0.17	-24.1	11.7	-46.9 to -1.20	0.04
mod	0.26	0.29	-0.32 to 0.83	0.38	-20.3	11.7	-43.2 to 2.69	0.08
sever	Ref							

*Hierarchical effect of patient and episode incorporate in the model as random intercept

Table S2: Multivariate repeated measure analysis of change in serum potassium concentration by ITT and AT in IVPR and EPR arms.

	Intention to treat(ITT)				Actual treatment received(AT)			
	Coef.	SE	95% CI	p-value	Coef.	SE	95% CI	p-value
Intervention*								
IV K	0.01	0.05	-0.08 to 0.10	0.86	0.04	0.05	-0.05 to 0.13	0.39
Oral K	Ref				Ref			
Average Urine output	-0.02	0.01	-0.04 to -0.01	0.01	-0.02	0.01	-0.04 to -0.00	0.01
inotrope score	0.15	0.04	0.06 to 0.23	0.00	0.14	0.04	0.06 to 0.23	0.00
Age groups								
<1 yrs	-0.14	0.06	-0.25 to -0.02	0.02	-0.14	0.06	-0.25 to -0.02	0.02
1-5 yrs	-0.12	0.06	-0.24 to 0.00	0.06	-0.13	0.06	-0.25 to -0.01	0.04
5-15 yrs	Ref				Ref			
Potassium level at beginning of episode								
mild	0.55	0.25	0.07 to 1.03	0.03	0.58	0.25	0.09 to 1.06	0.02
mod	0.40	0.25	-0.08 to 0.88	0.11	0.42	0.25	-0.06 to 0.90	0.09
sever	Ref				Ref			
Intercept	3.14	0.25	2.64-3.64	<0.0001	3.10	0.25	2.60-3.60	<0.0001

*Analysis performed to examine effect of oral and IV on potassium concentration adjusting for age, potassium levels at the beginning of episode, inotropic score, average urine output and average diuretic dose. All of the variables treated as fixed effect. Hierarchical effect of patient and episode incorporate in the model as random intercept .

Table S3: Multivariate Repeated measure analysis of percentage change in serum potassium concentration by ITT and AT. Percent change calculate as (previous K –current K)/previous K * 100

	Intention to treat(ITT)				Actual treatment received(AT)			
	Coef.	**SE**	**95% CI**	**p-value**	**Coef.**	**SE**	**95% CI**	**p-value**
Time	0.24	0.02	0.21-0.29	<0.0001	0.24	0.02	0.21-0.29	<0.0001
Intervention								
IV K	0.30	1.90	-3.42 to 4.03	0.87	0.50	1.90	-3.27 to 4.30	0.79
Oral K	Ref							
Potassium level at beginning of episode								
Mild	-23.94	11.71	-46.88 to -1.00	0.04	-23.8	11.7	-46.76 to -0.79	0.04
Mod	-20.09	11.77	-43.17 to 2.98	0.09	-19.9	11.8	-43.04 to 3.15	0.09
Sever	Ref							
Intercept	19.84	10.39	-0.53 to 40.21	0.06	19.81	10.4	-0.57 to 40.19	0.06

* Hierarchical effect of patient and episode incorporate in the model as random intercept.

CONSORT Statement 2006 - Checklist for Non-inferiority and Equivalence Trials

Items to include when reporting a non-inferiority or equivalence randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned"), *specifying that the trial is a non-inferiority or equivalence trial.*	1,3-4
INTRODUCTION Background	2	Scientific background and explanation of rationale, *including the rationale for using a non-inferiority or equivalence design.*	5-6
METHODS Participants	3	Eligibility criteria for participants *(detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment)* and the settings and locations where the data were collected.	7-8
Interventions	4	Precise details of the interventions intended for each group *detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy,* and how and when they were actually administered.	6-7,8-9
Objectives	5	Specific objectives and hypotheses, *including the hypothesis concerning non-inferiority or equivalence.*	6
Outcomes	6	Clearly defined primary and secondary outcome measures *detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	6,7
Sample size	7	How sample size was determined *detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.* When applicable, explanation of any interim analyses and stopping rules (*and whether related to a non-inferiority or equivalence hypothesis*).	10,11
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	8,9
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	8
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	8
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	-
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s), *specifying whether a one or two-sided confidence interval approach was used.* Methods for additional analyses, such as subgroup analyses and adjusted analyses.	10,11
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	12
Recruitment	14	Dates defining the periods of recruitment and follow-up.	12
Baseline data	15	Baseline demographic and clinical characteristics of each group.	12,13 Table 2a
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was *"intention-to-treat" and/or alternative analyses were conducted.* State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	10,13-14

Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval). *For the outcome(s) for which non-inferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful*.	13-14 Table 2b
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	Table 3
Adverse events	19	All important adverse events or side effects in each intervention group.	14
DISCUSSION Interpretation	20	Interpretation of the results, taking into account the *non-inferiority or equivalence hypothesis and any other* study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	14
Generalizability	21	Generalizability (external validity) of the trial findings.	17
Overall evidence	22	General interpretation of the results in the context of current evidence.	19

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