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

Dr Naveed ur Rehman Siddiqui
Aga Khan University Hospital
PAKISTAN
Intravenous potassium replacement (IVPR)

• preferred route in most intensive care settings

• Associated with its known safety risks and can lead to arrhythmias, cardiac arrest and death

• Need for a central line that can lead to central line-related infection due to frequent access of the line

• Additionally, a larger volume of fluid is required for delivery of the desired dose of potassium

• Also ECG and hemodynamic monitoring during replacement

Enteral potassium replacement (EPR)

• Equal or superior safety profile, may be a better alternative to IV potassium replacement

• A retrospective review showed that efficacy of Oral potassium replacement was comparable to IV potassium replacement in Post Cardiac Surgery pediatric patients

Primary objective

• Compare efficacy of Oral versus IV Potassium replacement for treatment of hypokalemia.
  • change in serum potassium levels in mmol/L
  • percentage change in level after potassium replacement
Secondary objectives

- Compare the adverse effects (hyperkalemia, diarrhea, GI bleeds, nausea, vomiting, arrhythmia) after oral and IV Potassium Replacement

- Compare number of dose/s (events) required in achieving resolution of hypokalemia (as described per protocol) for each episode of hypokalemia
Methods

• Open-label, Randomized, non-blinded, trial with two arms (IV and Oral Potassium Replacement)

• Pediatric Post Cardiac Surgery patients, from 1 month to 15 years, admitted in CICU of Aga Khan University Hospital

• Data collected through a structured proforma and informed consent
Block randomization scheme

Patients recruited for the study based on inclusion and exclusion criteria

IVPR week
Block randomisation to IVPR for the duration of stay in PCICU

Alternate weeks

EPR week
Block randomisation to EPR for the duration of stay in PCICU

In case patient develops vomiting, GI upset (as described in the adverse event section) and unable to tolerate PO supplementation or developed critically low potassium
Inclusion Criteria

All patients undergoing surgical/palliative repair of CHD at Aga Khan University Hospital and admitted to PCICU for postoperative management

Serum potassium levels (<4.4 mmol/L) immediately postoperatively

Patients/parents willing to participate in this study

Have a central venous line for IV potassium replacement and an arterial line for monitoring and blood draws
Exclusion Criteria

Patients with acute renal failure (estimated clearance creatinine—ecCr <50)

Patients with paralytic ileus, necrotizing enterocolitis or GI bleeding

Patients with nausea, vomiting or diarrhea prior to randomization.

Patients was not excluded if these symptoms develop during the trial after initial recruitment.
Sample Size

Using a power of 90%, p value of <0.05 (95% for one sided CI and 90% for two-sided CI)

Total of 310 (sample) events of hypokalemia were required with 155 in each arm
Definitions

• **HYPOKALEMIA**: potassium < 4.4 mmol/L

• **EVENT**: Each potassium replacement irrespective of whether hypokalemia was completely resolved or not

• **EPISODE**: End of Hypokalemia when potassium level comes back to the normal range
## Dosing for Potassium replacement

<table>
<thead>
<tr>
<th>Serum Potassium level (mmol/L)</th>
<th>Potassium replacement (I/V and Enteral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 – 4.4</td>
<td>0.1 mmol/kg/dose</td>
</tr>
<tr>
<td>3.5 -3.9</td>
<td>0.3 mmol/kg/dose</td>
</tr>
<tr>
<td>3.0 -3.4</td>
<td>0.5 mmol/kg/dose</td>
</tr>
<tr>
<td>2.5 – 2.9</td>
<td>0.7 mmol/kg/dose</td>
</tr>
<tr>
<td>2.1- 2.4</td>
<td>1 mmol/kg/dose and call physician</td>
</tr>
</tbody>
</table>

**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
This EIPS trial is registered at Clinicaltrials.gov. Registration number: NCT02015962.
Statistical Analysis

• Data was analyzed using two approaches; Intention to treat (ITT) and actual treatment (AT) received analysis.

• **Mean (+/-SD)** was calculated for continuous 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**
RESULTS
Patients who developed vomiting and GI upset and could not tolerate enteral feeding or developed critically low potassium levels
Age of Patients

IV Potassium Replacements

- < 1 Year: 28%
- 1-5 Year: 28%
- > 5 year: 44%

Oral Potassium replacements

- < 1 Year: 39%
- 1-5 Year: 17%
- > 5 year: 44%
<table>
<thead>
<tr>
<th>Age at randomization (count,%)</th>
<th>Intention to treat (ITT)</th>
<th>Actual treatment received (AT)</th>
<th>p-value</th>
<th>Intention to treat (ITT)</th>
<th>Actual treatment received (AT)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV K (n=18)</td>
<td>Oral K (n=23)</td>
<td></td>
<td>IV K (n=23)</td>
<td>Oral K (n=18)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>5(27.8%)</td>
<td>4(17.4%)</td>
<td>0.54</td>
<td>6(26.1%)</td>
<td>3(16.7%)</td>
<td>0.61</td>
</tr>
<tr>
<td>1-5 years</td>
<td>5(27.8%)</td>
<td>10(43.5%)</td>
<td></td>
<td>7(30.4%)</td>
<td>8(44.4%)</td>
<td></td>
</tr>
<tr>
<td>5-15 years</td>
<td>8(44.4%)</td>
<td>9(39.1%)</td>
<td></td>
<td>10(43.5%)</td>
<td>7(38.9%)</td>
<td></td>
</tr>
<tr>
<td>Mean Age(years) *</td>
<td>4.8 ± 4.0</td>
<td>4.6 ± 4.0</td>
<td>0.91</td>
<td>4.8 ± 4.2</td>
<td>4.6 ± 3.8</td>
<td>0.87</td>
</tr>
</tbody>
</table>

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

- VSD
- TOF
- ASD
- AVSD
- Complex CHD

**DORV**: Double outlet right ventricle; **TGA**: Transposition of Great Arteries; **ccTGA**: congenitally corrected Transposition of Great Arteries; **PS**: Pulmonary Stenosis; **COA**: Coarctation of Aorta; **MV**: Mitral Valve; **TA**: Tricuspid Atresia; **TAPVR**: Total Anomalous Pulmonary Venous Return.

Oral Potassium

IV Potassium

9/15/2015
## Indicators at beginning of episode

<table>
<thead>
<tr>
<th></th>
<th>Intention to treat (ITT)</th>
<th>Actual treatment received (AT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV K (n=18)</td>
<td>Oral K (n=23)</td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Potassium level (count,%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>33(71.7%)</td>
<td>31(63.3%)</td>
</tr>
<tr>
<td>Mod</td>
<td>13(28.3%)</td>
<td>17(34.7%)</td>
</tr>
<tr>
<td>Severe</td>
<td>--</td>
<td>1(2.0%)</td>
</tr>
<tr>
<td>Mean potassium*</td>
<td>3.7 ± 0.5 (3.5-3.8)</td>
<td>3.6 ± 0.5 (3.5-3.8)</td>
</tr>
<tr>
<td>Average Urine output*</td>
<td>3.9 ± 2.1 (3.4-4.6)</td>
<td>4.3 ± 2.5 (3.6-5.0)</td>
</tr>
<tr>
<td>Diuretic average dose (mg/kg)**†</td>
<td>0.4 ± 0.5 (0.3-0.6)</td>
<td>0.4 ± 0.6 (0.2-0.5)</td>
</tr>
<tr>
<td>Inotrope Score*</td>
<td>8.5 ± 9.1 (5.5-10.7)</td>
<td>4.6 ± 4.1 (3.4-5.8)</td>
</tr>
</tbody>
</table>

* 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
Episodes, events and mean % change in potassium concentration in IVPR and EPR arms

<table>
<thead>
<tr>
<th></th>
<th>Intention to treat (ITT)</th>
<th>Actual treatment received (AT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV K</td>
<td>Oral K</td>
</tr>
<tr>
<td>Change in Potassium(N)</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.82±0.7</td>
<td>0.86±0.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.62-1.01)</td>
<td>(0.62-1.10)</td>
</tr>
<tr>
<td>Relative percentage change in Potassium(N)</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>24±20</td>
<td>26±30</td>
</tr>
<tr>
<td>95% CI</td>
<td>(18-30)</td>
<td>(18-35)</td>
</tr>
<tr>
<td>Episode per child(N)</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2.7 ± 2.1</td>
<td>2.1 ± 1.3</td>
</tr>
<tr>
<td>Event per episode(N)</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>5.0 ± 4.9</td>
<td>4.6 ± 4.2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
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<th></th>
<th>Adjusted*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Coef.</td>
<td>SE</td>
<td>95% CI</td>
<td>p-value</td>
<td>Coef.</td>
<td>SE</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Change in Potassium Concentration</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Intervention</td>
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<tr>
<td>Oral K</td>
<td>0.02</td>
<td>0.05</td>
<td>-0.08 to 0.13</td>
<td>0.66</td>
<td>0.01</td>
<td>0.05</td>
<td>-0.08 to 0.10</td>
<td>0.86</td>
</tr>
<tr>
<td>IV K</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent Change in Potassium Concentration*</td>
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<tr>
<td>Intervention</td>
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<td></td>
</tr>
<tr>
<td>Oral K</td>
<td>0.10</td>
<td>1.89</td>
<td>-3.60 to 3.80</td>
<td>0.95</td>
<td>0.30</td>
<td>1.90</td>
<td>-3.42 to 4.03</td>
<td>0.87</td>
</tr>
<tr>
<td>IV K</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
<td>Ref</td>
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</tbody>
</table>

*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

• IV Potassium replacements
  • None

• Oral potassium replacements
  • Vomiting (4)
  • Arrhythmias (1)
Conclusion:

There is no difference in Oral or IV potassium replacement in treating hypokalemia in critically ill post surgical congenital heart disease pediatric patients.

Oral replacement may be an equally efficacious alternative to treat hypokalemia in these patients.
Strength

• First prospective randomized trial comparing the routes (Oral versus IV) for potassium replacement

• Findings from this trial will lead the way to further validation studies ➔ more inclination towards use of enteral route for potassium
Weaknesses

• EIPS is not a blinded study owing to different routes of administration of K supplementation (Oral versus IV) and may create an observer bias

• Confounding factors, such as concomitant use of diuretics and inotropic agents may have affected the response to K supplementation

• Patients with K < 2 mmol/L were excluded and thus the results of this study are not generalizable for such severe hypokalemia
Acknowledgement

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Questions ??