Nebulized salbutamol diminish the blood glucose fluctuation in the treatment of non-oliguric hyperkalemia of premature infants

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Abstract

Background: Hyperkalemia is a risky and potentially life-threatening condition in pre-term infants. Glucose-insulin infusion has been considered a major therapeutic way for non-oliguric hyperkalemia but affects the stability of blood sugar level. We aimed to evaluate the effectiveness of salbutamol nebulization compared to glucose-insulin infusion for the treatment of non-oliguric hyperkalemia in premature infants.

Methods: Forty premature infants (gestation age ≤36 weeks) with non-oliguric hyperkalemia (central serum potassium level greater than 6.0 mmol/L) within 72 h of birth were enrolled in this study. These infants were randomly assigned into two groups. One group received a regular insulin bolus with glucose infusion (Group A; n = 20), and the other received salbutamol (Ventolin\textsuperscript{®}) by nebulization (Group B; n = 20). Potassium level, blood sugar, heart rate, and blood pressure were recorded for each group before treatment and at 3, 12, 24, 48, and 72 h posttreatment.

Results: The serum potassium levels were reduced after treatment in both groups. No significant changes in heart rate or blood pressure were observed in either group. The fluctuation in glucose levels was gentler in the salbutamol-treated group than in the glucose-insulin infusion group.

Conclusion: Salbutamol nebulization is not only as effective as glucose-insulin infusion for treating non-oliguric hyperkalemia in premature infants but can avoid potential side effects such as vigorous blood glucose fluctuations.

Keywords: Blood sugar; Hyperkalemia; Nebulizers usage; Premature infant; Salbutamol

1. INTRODUCTION

Hyperkalemia is a risky and potentially life-threatening condition, especially when it occurs in infants born prematurely. In premature infants, serum potassium usually reaches a peak at 24 h of age and returns to normal by 72 h.\textsuperscript{1,2} Non-oliguric hyperkalemia in neonates is defined as a serum potassium level greater than 6.0 mmol/L and is more commonly observed in extremely low birthweight (ELBW) infants\textsuperscript{3,4} or in pre-term infants even with normal renal function for their age. Although the pathophysiology is not completely understood, it seems to be related to immaturity in regulating the internal distribution of potassium.\textsuperscript{5} Hyperkalemia in the neonate may occur as a result of increased potassium intake, decreased renal excretion, a shift of potassium from the intracellular to extracellular space, or medications. For instance, a digoxin overdose and β2 adrenergic blockers can induce hyperkalemia by inhibiting Na\textsuperscript{+}-K\textsuperscript{+} adenosine triphosphatase (Na\textsuperscript{+}-K\textsuperscript{+} ATPase).\textsuperscript{6} A recent study reported that non-oliguric hyperkalemia in premature infants can be caused by severe birth asphyxia and thereby contribute to extensive periventricular white matter injury.\textsuperscript{7} Furthermore, persistent hyperkalemia in infants is a medical emergency that may also lead to complications such as cardiac arrhythmia, intraventricular hemorrhage, periventricular leukomalacia, and death.\textsuperscript{4,8,9} Therefore, infants at risk of hyperkalemia must be identified and treated as early as possible.

In the past, glucose-insulin infusion has usually been considered the first therapeutic choice for treating hyperkalemia in premature infants. Insulin can regulate the Na\textsuperscript{+}-K\textsuperscript{+} ATPase in the cell membranes by increasing the rate of ATP hydrolysis that occurs in order to maintain intracellular and extracellular potassium concentrations. However, in spite of the fact that some previous studies have recommended specific dosages of insulin in order to reduce the possible side effects of hypoglycemia, such side effects still occur frequently.\textsuperscript{7} As such, in order to prevent the possibility of hypoglycemia resulting from insulin, glucose is usually included with the insulin in order to counteract the insulin’s potential side effects. On the other hand, given the difficulty of prescribing precise dosages of insulin and glucose, iatrogenic hyperglycemia it is not uncommon. Either hypoglycemia or hyperglycemia in premature infants can result
in acute or chronic life-threatening conditions such as seizure, cerebral damage, and intraventricular hemorrhage. As the infant liver is still underdeveloped and has limited capacity for glycogen production and storage, the prevention of vigorous blood sugar fluctuations in infants is essential.

Salbutamol is a kind of β2 adrenergic agonist that can activate adenylate cyclase via the binding of β2 adrenoreceptors. This mechanism will stimulate the production of cyclic adenosine monophosphate with the help of ATPase and, in turn, facilitate the transfer of potassium into cells. Though many studies have demonstrated that salbutamol is effective in treating hyperkalemia, prospective clinical comparison studies have been rare. In previous studies, intravenous salbutamol injections have been used as a means of treating hyperkalemia in neonates, with those studies reporting that such injections successfully reduce serum potassium levels without marked side effects. Nebulized salbutamol also had been reported to yield significantly better results than intravenously administered forms of the drug. In the present study, we sought to compare the value, effectiveness, and potential side effects of nebulized salbutamol and glucose-insulin infusion in order to assess whether nebulized salbutamol is a safer alternative treatment for hyperkalemia in premature infants.

2. METHODS

2.1. Patients

All the premature infants included in this study were cared for according to the clinical guidelines of the newborn intensive care unit of Cheng Ching General Hospital, Taichung, Taiwan. We excluded premature infants born with any major congenital malformations (including chromosomal abnormalities), infants with confirmed or suspected sepsis or pneumonia, infants in a terminal state on admission, infants with umbilical anomalies, and infants with skin infections.

2.2. Ethics statement

This study was approved by the Institutional Review Board of Cheng Ching General Hospital (IRB No: HP110006). Written informed consent was obtained from the parents or guardians of each of the minors before any study related procedures were performed.

2.3. Study design

Prospectively double-blind, randomized clinical study was set up under the IRB approval and went through as followings: Forty premature infants (gestation age <36 weeks) with non-oliguric hyperkalemia (central serum potassium level greater than 6.0 mmol/L) within 72 h of birth were enrolled in this study. They were randomly assigned into two groups (according to their chart number is singular or plural): each Group A infant (n = 20, chart number is singular) received a glucose-insulin infusion and each Group B infant (n = 20, chart number is plural) received a Ventolin® (salbutamol) respirator solution (Glaxo Canada Inc; Montreal, Canada) via nebulizer. The glucose-insulin infusion consisted of 10–15 mg of glucose and 1 unit of regular insulin bolus (RI), maintained at a rate of 6 mg/kg/min. Salbutamol (400 μg in 2 ml saline solution) was administered as an aerosol using an endotracheal tube. The central serum potassium, blood glucose, heart rate, and blood pressure of each infant were measured before treatment and at 3, 6, 12, 24, and 72 h posttreatment.

2.4. Analytic procedures

For each infant, the central serum potassium level and blood glucose level were monitored throughout the study by intermittent arterial line sampling. Potassium was measured using the Ion-Selective Electrode (indirect ISE) method (Hitachi 008AS), and glucose was measured using automated biochemical methods (Hitachi 008AS). The glucose fluctuation was obtained by subtracting the value of the lowest blood glucose concentration from that of the peak concentration. The heart rate (HR) and mean arterial blood pressure (MAP) were also monitored, while the electrocardiograms were continuously monitored. We paid greater attention to such monitoring when abnormally high potassium levels (central serum potassium greater than 7.5 mmol/L) occurred. When this happened, aggressive medical interventions and management were applied without any delay. Furthermore, due to safety concerns, any infant facing such a situation would be excluded from the present study.

2.5. Statistical analysis

Statistical analysis was done using Student’s t-test for paired values. Between-groups differences were tested using analysis of variance (ANOVA) and Fisher’s post hoc tests. The results were expressed as mean value ± SEM at a significance level of p < 0.05. In both tables, we used nonparametric statistics (Wilcoxon rank sum test) to test data differences between two groups if the data distribution is not corresponding Gaussian/normal distribution. Relatively, data in tables with normal distribution will be present as mean value ± SD.

3. RESULTS

3.1. Comparison of the effects of nebulized salbutamol and glucose-insulin infusion on potassium level, heart rate, and mean arterial pressure

There was no significant difference in the distributions of neonatal birth weights between the nebulized salbutamol and glucose-insulin infusion management groups (Table 1, Student’s t-test: p > 0.05). The mean blood glucose, HR, and MAP levels before treatment of the two groups also showed no significant difference (Table 2, Student’s t-test: p > 0.05). Both interventions were found to significantly reduce the serum potassium levels (Fig. 1 & Table 2; Student’s t-test: Pre-treat vs. 3-h & 72-h, RI + glucose, p < 0.01; Pre-treat vs. 3-h & 72-h, salbutamol, p < 0.01) but not HR or MAP (Table 2, Student’s t-test: Pre-treat vs. 72-h, p > 0.05). However, the effects of these two treatments on serum potassium level, HR, and MAP did not show any significant difference (Figs. 1–3, ANOVA: p > 0.05).

3.2. Nebulized salbutamol alleviates blood glucose fluctuation

Because glucose-insulin infusions can cause either hypoglycemia or hyperglycemia, we measured the blood glucose fluctuations of both therapeutic groups. There were no significant statistical differences in blood glucose levels over the observation period of each study time points (Table 2, ANOVA: p > 0.05). However, the blood glucose fluctuations (indicated by the difference resulting from subtracting the lowest blood glucose concentration from the peak concentration during study period) showed significant differences. The degree of the mean blood glucose fluctuation in the nebulized salbutamol group was significantly lower than that in the glucose-insulin
infusion group (42.3 ± 3.70 mg/dL and 105.35 ± 14.05 mg/dL, respectively, \( p < 0.001 \), Fig. 4B).

### 4. DISCUSSION

Glucose-insulin infusion has been considered a classic treatment for non-oliguric hyperkalemia in premature infants. However, the potential risks of blood glucose fluctuations are not uncommon in these infants, and such fluctuations will sometimes result in severe sequelae.\(^4,24\) The results of the present study indicate that salbutamol is as effective as typical glucose-insulin infusion therapy in lowering the blood potassium level of an infant. No known side effects such as tachycardia or hypertension were observed in either group. In addition, the blood glucose levels, heart rates, and blood pressures of these patients were all within normal limits throughout the study. We also demonstrated that the nebulized salbutamol therapy resulted in less vigorous fluctuations of blood glucose in comparison with the typical glucose-insulin infusion treatment.

Hyperkalemia in premature neonates results from abnormal potassium reabsorption or shifting between the intracellular and extracellular space.\(^4,24\) Therapies for hyperkalemia in neonates include lowering blood potassium levels through the intravenous administration of calcium gluconate, sodium bicarbonate, bolus glucose-insulin infusion, or the administration of sodium polystyrene sulfonate (Kayexalate\(^6\)) enema.\(^9,25-27\) However, the effectiveness of these treatments in terms of lowering serum potassium has been doubted in several reports due to their coinciding with various unwanted side effects. For example, the extravasation of intravenous calcium gluconate can lead to regional soft tissue calcification, necrosis, cellulitis, and osteomyelitis, and may even cause compartment syndrome.\(^25,28,29\); glucose-insulin infusion can cause either hypoglycemia or hyperglycemia;\(^2,23\); and Kayexalate\(^6\) enema can lead to stool impaction, rectal perforation, and even necrotizing enterocolitis.\(^30-32\)

Preterm infants are in danger of abnormal glucose homeostasis. Hyperglycemia is a remarkable risk factor for mortality and morbidity in preterm infants and occurs in 40–80% of ELBW newborns due to the inability of these newborns to inhibit gluconeogenesis in response to a glucose infusion, which leads to insulin resistance.\(^33,34\) Moreover, these infants may also develop hypoglycemia due to the limitation of glycogen and fat storage, especially during an exogenous insulin infusion.\(^13\) These sequelae will lead to adverse neurodevelopmental outcomes.\(^35\)

To sum up, glucose-insulin infusions are accompanied by both side effects and potential risk factors. Relatedly, in this study, we detected more severe glucose fluctuations in the glucose-insulin infusion group, in spite of the infusions being administered according to accurate medical guidance. Based on these results of the present study and a recent review article, it can be concluded that nebulized salbutamol should be given higher priority in treating hyperkalemia in premature neonates.\(^36\)

In 1992, Dilmen et al. conducted the first study in which salbutamol was used as an alternative for treating hyperkalemia in LBW neonates. They also reported that side effects such as tremor and a slight increase in heart rate occurred when glucose-insulin infusion was used as a treatment.\(^20\) However, to the best of our knowledge, no study prior to the present one has investigated the differences between nebulized salbutamol and glucose-insulin infusion for the treatment of hyperkalemia in premature infants. Our data demonstrated that the therapeutic effectiveness of both treatments in terms of lowering serum

### Table 1

**Birthweight (BW) of hyperkalemic neonates enrolled in each group.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group A</th>
<th>Group B</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF + glucose</td>
<td>1515 (1039–1625)</td>
<td>1100 (1042–1792.5)</td>
<td>( p &gt; 0.05 )</td>
</tr>
<tr>
<td>Total n(^i)</td>
<td>20</td>
<td>20</td>
<td>( p &gt; 0.05 )</td>
</tr>
<tr>
<td>n ≤ 1000 g</td>
<td>3 (15.0%)</td>
<td>3 (15.0%)</td>
<td></td>
</tr>
<tr>
<td>1000 g &lt; n &lt; 1500 g</td>
<td>5 (25.0%)</td>
<td>8 (40.0%)</td>
<td></td>
</tr>
<tr>
<td>1500 g ≤ n</td>
<td>12 (60.0%)</td>
<td>9 (45.0%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^i\)Regular insulin.

\( ^i \)Birthweight.

\( ^i \)Median (lower quadrant-upper quadrant).

\( ^i \)Number of infants.

### Table 2

**Serum potassium, blood sugar, heart rate, and blood pressure pre- and 72 h post-treatment in two groups of hyperkalemic infants.**

<table>
<thead>
<tr>
<th>Group</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-treat</strong></td>
<td><strong>72 h</strong></td>
</tr>
<tr>
<td><strong>Group A</strong> (RF + glucose)</td>
<td><strong>Group B</strong> (Ventolin(^b))</td>
</tr>
<tr>
<td>n(^b)</td>
<td>20</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>6.50 (6.25–7.05)</td>
</tr>
<tr>
<td>Blood sugar (mg/dL)</td>
<td>80.5 (61.5–105.5)</td>
</tr>
<tr>
<td>Heart rate (count/min)</td>
<td>150.0 ± 17.4</td>
</tr>
<tr>
<td>BP(^c) (mmHg/min)</td>
<td>43.1 ± 11.2</td>
</tr>
</tbody>
</table>

\(^b\)Regular insulin.

\( ^b \)Number of infants.

\( ^c \)Blood Pressure.
potassium in premature infants was similar. Though no known side effect of salbutamol was observed in our study, some previous studies have claimed that rebound hyperkalemia can occur after dialysis in end-stage renal disease patients.\textsuperscript{37} However, there are some $\beta_2$ adrenergic agonistic medications such as procaterol or salmeterol possess higher selectivity react to $\beta_2$ adrenergic receptor than salbutamol, which may reduce some unwanted side effects resulting from $\beta_1$ adrenergic receptors.\textsuperscript{38} In present study we still choose salbutamol as study target owing to the first: it is the earliest $\beta_2$ adrenergic agonist that being applied in lowering serum potassium.\textsuperscript{20} Second, the applications of other highly selective $\beta_2$ adrenergic agonists are few being reported.\textsuperscript{39} Third, most documented side effects of salbutamol were little and acceptable.\textsuperscript{40} Fourth, present study focused on the difference comparison of $\beta_2$ adrenergic agonist and glucoseinsulin therapy but not benefi ts of $\beta_2$ adrenergic agonists between. Maybe we can raise another clinical study to compare the effi ciency and effi cacy of these $\beta_2$ adrenergic agonists in the future.

Though the present study had a number of potential limitations, including a small sample of participants and some possible biases such as the correlations of the fluid statuses, feeding protocols, and body weights of the infants, it nonetheless provides a prospective, case–control, comparison study of the two treatment groups. Further, more extensive studies are essential in order to gather more evidence to support the effectiveness of salbutamol as an alternative treatment for life-threatening hyperkalemia in premature infants. In addition, the use of more intensive and continuous in-time monitors is also needed to avoid the risk of inconsistent responses.

In conclusion, in comparison with glucose-insulin infusions, the treatment of hyperkalemia in premature infants with nebulized salbutamol can provide a safe and eff ective clinical option. It can achieve the goals of being less invasive and causing less severe blood glucose fiuctuations.

![Fig. 1](image1.png) Changes in serum potassium (K) level in hyperkalemic infants three days after treatment with a glucose and insulin infusion (RI + glucose, Group A) or nebulized salbutamol (Ventolin®, Group B). Data are presented as the mean ± SEM. **, Pre-treat vs. 3-h, RI + glucose, p < 0.01; ##, Pre-treat vs. 3-h, Ventolin®, p < 0.01.

![Fig. 2](image2.png) Changes in heart rate (HR) of hyperkalemic infants three days after treatment with a glucose and insulin infusion (RI + glucose, Group A) or nebulized salbutamol (Ventolin®, Group B). Data are presented as the mean ± SEM.

![Fig. 3](image3.png) Changes in mean arterial blood pressure (MAP) of hyperkalemic infants three days after treatment with a glucose and insulin infusion (RI + glucose, Group A) or nebulized salbutamol (Ventolin®, Group B). Data are presented as the mean ± SEM.

![Fig. 4](image4.png) A. Changes in blood glucose level (Glu) in hyperkalemic infants three days after treatment with a glucose and insulin infusion (RI + glucose, Group A) or nebulized salbutamol (Ventolin®, Group B). B. The fiuctuations of glucose level. Data are presented as the mean ± SEM.
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APPENDIX A. SUPPLEMENTARY DATA

The gender, gestational age and apgar score of individual infant was provided in supplementary information.

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jcma.2018.04.002.

REFERENCES


