Hypoglycaemia in Under-five Children with Diarrhoea

by S. Huq, M. I. Hossain, M. A. Malek, A. S. G. Faruque, and M. A. Salam

Clinical Sciences Division, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR), GPO Box 128, Dhaka 1000, Bangladesh

Summary

The present study aimed to observe the clinical features of hypoglycaemia, and identify predictors of hypoglycaemia in under-five diarrhoeal children requiring hospitalization for close observation and support. Such information could be useful to the clinicians and policy makers in developing appropriate management protocols both for identification of such children and optimizing their management. We performed a prospective study in 782 under-five children who presented with diarrhoeal illnesses. Blood glucose was determined when hypoglycaemia was suspected in 598 (62%), and 65 (11%) of them were hypoglycaemic (study group). From the other 533 non-hypoglycaemic children, 195 were randomly selected as comparison group. Bacteraemia was significantly (P = 0.026) often detected in 17 out of 260 (7%) children as opposed to 3 out of 184 (2%) children who did not have a rapid glucose test performed. Among hypoglycaemic children, 7 (11%) were bacteraemic and among non-hypoglycaemic children 10 (5%) had bacteraemia. In univariate analysis, history of shorter (<72 h) pre-admission duration of diarrhoea (75 vs. 58%, P = 0.01), documented convulsion (28 vs. 11%, P < 0.001), shorter (<72 h) hospitalization (52 vs. 33%, P = 0.01), higher case fatality rate (28 vs. 14%, P = 0.02) were associated with hypoglycaemia. In logistic regression, bacteraemic children (with clinical sepsis) were 4 times more likely to develop hypoglycaemia (OR = 4.2, 95% CI = 1.4–12.9, P = 0.012). Therefore, in a diarrhoeal disease health care service with limited resources, a rapid bedside glucose test may be considered as an inexpensive alternative in the management decisions of diagnosing bacteraemia and initiating empiric antibiotic treatment.

Introduction

Hypoglycaemia is associated with chronic metabolic disorders [1], severe malnutrition [2–6] and persistent diarrhoea [7]. Decreased stores of glycogen, impaired gluconeogenesis, increased peripheral utilization of glucose, and intestinal malabsorption have all been associated with hypoglycaemia [8]. Defective homeostatic mechanisms in association with hyper-insulinism, adrenal insufficiency, growth hormone deficiency, glucose-6-phosphate deficiency, glycogen synthetase deficiency, and defects in fatty acid oxidation have also been implicated to play a role in pathogenesis of hypoglycaemia [1, 5, 9, 10]. In children, hypoglycaemia resulting from impaired glucogenesis is associated with deaths from infectious diarrhoea regardless of their nutritional status [11]. Based on autopsy findings of adrenal necrosis and haemorrhage, epinephrine and cortisol deficiency have also been implicated as possible causes of hypoglycaemia in infectious diarrhoea [3–5]. The association between hypoglycaemia and severe infection was first described in three children with severe meningococcaemia and adrenal haemorrhage [9]; however, hypoglycaemia as a feature or complication of gram-negative or gram-positive bacteraemia or overwhelming sepsis is not adequately mentioned in the textbooks. In one descriptive study, prevalence of and clinical features associated with hypoglycaemia reported that of 49 children receiving resuscitative care, 9 were found to be hypoglycaemic. Four of these nine had septic...
shock [12]. The detailed mechanisms involved in hypoglycaemia in bacteraemia or sepsis are also not well-studied. In humans, endotoxin plays a crucial role in the pathogenesis of gram-negative septic shock, which leads to impairment of glucose homeostasis and lethal septic shock [13]. Endotoxin also decreases the activity of phosphoenolpyruvate carboxykinase (PEPCK), and inhibits gluconeogenesis from lactate and pyruvate in the livers of mice by antagonizing its induction by glucocorticoids [14–16]. Although features of hypoglycaemia (tremulousness, lethargy, poor feeding, irritability, hypotonia, hypothermia, respiratory distress, cyanosis, apnoea, bradycardia, seizures and coma) and its predictors are well-described [8, 17], its association with bacteraemia among severely ill under-five children with diarrhoea hasn’t been well-demonstrated. The purpose of our study was to observe the clinical features of hypoglycaemia, and identify predictors of hypoglycaemia in under-five diarrhoeal children who are requiring hospitalization for diarrhoeal illnesses in ICDDR,B’s facility for close observation and support.

Materials and Methods

Study design
This prospective study was conducted in a diarrhoeal disease facility of ICDDR,B, located in Dhaka, Bangladesh. Each year around 110 000 patients attend the hospital seeking treatment for diarrhoea, with or without complications and associated health problems. In the triage area, an experienced nurse assesses status of the patients and decides either of the followings: (i) referral of non-diarrhoeal patients to other city hospitals; (ii) referral of milder, uncomplicated diarrhoeal patients to a collaborating primary health care clinic located within the hospital premises, and operated by a local health NGO; (iii) admission of patients with dehydrating diarrhoea to a short stay unit (SSU) for rehydration and maintenance of hydration; (iv) admission of patients with complications of diarrhoea and/or other associated illness to a longer stay unit (LSU); and (v) admission of severely ill patients (presenting with electrolyte imbalance, severe pneumonia, respiratory distress, cyanosis, apnoea, tachypnoea, tachycardia, bradycardia, thermoinstability, clinical sepsis, marked lethargy, hypotonia, impaired mental state, convulsion, low pulse volume not attributable to severe dehydration, coma, etc.) to a Special Care Unit (SCU). Patients admitted to the LSU and SCU are subjected to laboratory investigations, as appropriate, and they often need administration of antimicrobials, other supportive measures, closer observation, and frequent assessments. Immediately upon admission into the SCU, patients are assessed by a clinician of the hospital, who obtains medical history, performs thorough physical examination, and collects biological specimens e.g. blood or cerebro-spinal fluid for appropriate laboratory work-ups. When clinically indicated, oxygen saturation of the patients is measured using portable pulse-oximeter, and blood glucose level is measured using a bedside glucocheck machine.

During the study period, 10 187 severely ill patients were admitted to the SCU, and a systematic 10% of them (n=967), aged 3 days to 80 years, were prospectively enrolled into this study, and 782 (81%) under-five children were identified. The admission blood glucose levels were determined for 598 suspected hypoglycaemic children (and clinical sepsis), of whom 65 (11%) were hypoglycaemic (blood glucose <3 mmol/L). These children constituted the study group. For this comparative analysis, 195 of the 533 (1:3 ratio) non-hypoglycaemic children were randomly identified as the comparison group (Fig. 1).

Laboratory diagnosis
Stool or rectal swab cultures were done for the identification of *Vibrio cholerae*, *Salmonella*, and
Shigella using standard method [21]. Blood cultures were performed for all patients. Blood glucose was determined for those with abnormal mentation, lethargy, convulsion, or low pulse volume (just countable or thready pulse) not attributable to severe dehydration (suspected sepsis; at least two of the following: thermoinstability, tachypnoea, tachycardia, or poor peripheral perfusion) using a bedside instrument (Reflolux, Mannheim Boehringer, Germany). Arterial oxygen saturation was determined for children with pneumonia or difficult breathing using a portable ‘pulse oximeter’. (Nellcor N-20/N-20P Portable Pulse Oximeter).

**Definitions**

We defined bacteraemia as the presence of bacteria in the blood stream among children presented with diarrhoea; watery diarrhoea as three or more watery/abnormally loose stools in the previous 24 h; hypoglycaemia as blood glucose concentration of <3 mmol/l; hypokalaemia as serum potassium concentration of <3.5 mmol/l; and severe acidosis as serum total bicarbonate concentration of <10 mmol/l [10].

**Statistical methods**

Data were analysed using SPSS for windows. The data on weight and height of the children were converted into z-scores according to National Center for Health Statistics (NCHS) reference medians. Differences in the proportions between the groups were compared by the Chi-square test or Fisher’s exact test. Both univariate and multivariate (backward, stepwise logistic regression) analyses were performed to examine the independent relationship of different clinical (age, diarrhoea duration at home, dehydration, hospitalization duration, convulsion and death) and laboratory findings (acidosis, hypokalaemia and bacteraemia) with hypoglycaemia (dependent variable; coded as hypoglycaemic = 1, non-hypoglycaemic = 0). For this, in addition to variables that were significantly associated with hypoglycaemia in univariate analyses, those of theoretical importance were also included in the regression models for simultaneous adjustments. A level of significance of <0.05 was used for all interpretations.

**Results**

Of 782 study children <5 years old, all had diarrhoeal illnesses, half (52%) of them gave a history of stool frequency more than 10 in any 24 h period, 82% had vomiting, 90% presented with watery diarrhoea, and 74% had clinical dehydration. Moreover, 51% were lethargic, 2% unconscious, 16% restless, 40% had low pulse volume, 46% presented with pneumonia, and 21% were admitted in gasping state.

Seventy-five percent among all under-five children were infants (<1 year), 20% were 12–35 months old, and 5% were 36–59 months old with equal sex distribution. Blood glucose was determined for 598 out of 782 (62%) children at their admission to SCU, and 65 (11%) of them had hypoglycaemia (study group). Randomly selected (assisted by SPSS for windows software) 195 out of 533 (1 : 3 ratio) non-hypoglycaemic children were identified as comparison group. Half to three quarters of the hypoglycaemic children were malnourished, as indicated by wasting or stunting or underweight. In univariate analysis (Table 1), hypoglycaemic children more frequently had shorter (<72 h) history of...
Results of backward stepwise logistic regression analysis: characteristics significantly associated with hypoglycaemia in severely ill study children

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteraemia</td>
<td>4.2</td>
<td>1.4–12.9</td>
<td>0.012</td>
</tr>
<tr>
<td>Hospitalization (&lt;72 h)</td>
<td>2.2</td>
<td>1.1–4.4</td>
<td>0.027</td>
</tr>
<tr>
<td>Age &gt;1 year</td>
<td>2.9</td>
<td>1.3–6.5</td>
<td>0.011</td>
</tr>
<tr>
<td>Hypokalaemia (K⁺ &lt;3.5 mmol/l)</td>
<td>0.4</td>
<td>0.2–0.8</td>
<td>0.016</td>
</tr>
<tr>
<td>Convulsion</td>
<td>2.3</td>
<td>0.9–5.9</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Note: The significant association between bacteraemia and hypoglycaemia was estimated after adjusting for age, diarrhoea duration at home, clinical dehydration, hospitalization, convulsion, death, acidosis and hypokalaemia.

diarrhoea before admission (75 vs. 58%, P = 0.01), documented convulsion (28 vs. 11%, P < 0.001), shorter (<72 h) hospitalization (52 vs. 33%, P = 0.01), and higher case fatality rate (28 vs. 14%, P = 0.02) than the non-hypoglycaemic children. Hypoglycaemia was not related to malnutrition. Of these malnourished children with hypoglycaemia (n = 27), 83% had vomiting, 82% were lethargic, 4% unconscious, 4% restless, 15% had low pulse volume, 35% presented with pneumonia, and 48% reported in gasping state.

The results of logistic regression analysis to identify characteristics associated with hypoglycaemia in severely ill hospitalized children are shown in Table 2. After controlling for age, pre-admission duration of diarrhoea, clinical dehydration, hospitalization duration, convulsion, death, acidosis, and hypokalaemia in final backward stepwise logistic regression model, bacteraemia was 4 times as common in hypoglycaemic children (OR = 4.2, 95% CI = 1.4–12.9, P = 0.012). Bacteraemia was significantly (P = 0.026) often presented in 17 out of 260 (7%) children as opposed to 3 out of 184 (2%) children who did not have a rapid glucose test performed. Among hypoglycaemic children, 7 (11%) were bacteraemic and among non-hypoglycaemic children 10 (5%) had bacteraemia.

Discussion

In this study, blood glucose level was determined for children with suspected hypoglycaemia upon their admission to the Special Care Unit. Eleven percent of these children had documented hypoglycaemia, and we examined features that could be used in predicting hypoglycaemia in our severely ill, under-five children with diarrhoea.

There are few studies that examined hypoglycaemia in children with diarrhoeal diseases. Daral and colleagues [23] reported a 14% prevalence of hypoglycaemia (blood glucose <45 mg/dl) among Indian male children (n = 81), younger than 3 months, with dehydrating diarrhoea; however, the clinical features of the hypoglycaemia were not described. A 8% prevalence of hypoglycaemia (blood glucose <50 mg/dl) in 868 children, aged 2 to 35 months, with dehydrating gastroenteritis has been reported in two South African hospitals [4], they reported a higher prevalence among malnourished and hypothermic patients. The reason for hypothermia, which is also a feature of sepsis, was not described. In our study, the prevalence among severely ill children was similar to this study but the rate was not higher among malnourished children. In an earlier study at our hospital, Bennish and associates [11] observed hypoglycaemia (blood glucose <40 mg or 2.2 mmol/l) in 91 out of 2003 (5%) patients younger than 15 years, and observed hypoglycaemia more frequently in patients with shigellosis than those with diarrhoea due to other/unidentified aetiology. In that study, 39% of the hypoglycaemics were severely malnourished—a finding similar to ours, perhaps due to expected similarities among the population studied at the same health facility. The prevalence of hypoglycaemia in the reference study was lower than that we observed, and the higher rate in our study is most likely due to the fact that we enrolled younger children with severe illnesses and clinically suspected hypoglycaemia and sepsis, while the previous study included more of the general population. The earlier study observed hypoglycaemic children to report to the hospital with shorter history of diarrhoea, a finding similar to ours. The earlier study also observed longer (>12 h) fasting as a risk factor for hypoglycaemia, and reported seizures in 16 out of 46 (35%) and unconsciousness in 52% of the hypoglycaemic patients. The study reported a case-fatality of 35% among hypoglycaemic patients compared with 12% in normoglycaemics. In an even earlier study conducted at our hospital, Hirschhorn and coworkers [3] observed hypoglycaemia in 2% of 693 children with dehydrating gastroenteritis, aged 1 to 6 years. Most of those children had documented bacterial pathogens in stool and all had an altered mental status, however, none were apparently malnourished. We observed higher rate of documented convulsion (28 vs. 11%, P < 0.001, hypoglycaemic vs. non-hypoglycaemic), a finding that was expected since altered mentation and convulsion are recognized features of hypoglycaemia. The case fatality (28 vs. 14%, P = 0.02) (Table 1) was also higher among our hypoglycaemic children, a finding similar to that observed by Bennish and his colleagues [12].
hypoglycaemic than in non-hypoglycaemic (5%) children, suggesting a strong relationship between these two. The case fatality was proportionately higher in children who had both bacteraemia and hypoglycaemia (43%) compared to those who had bacteraemia, but not hypoglycaemia (30%). The prevalence of hypoglycaemia has been found to be 9% in children <5 years of age with gastroenteritis and the duration of vomiting was the only clinical variable significantly associated with hypoglycaemia [6]. Thus, other clinical criteria besides lethargy, altered mentation, convulsions and sepsis have been shown to be associated with hypoglycaemia in young children with gastroenteritis.

In multivariate analysis, bacteraemic children with clinical sepsis were 4 times more likely to be hypoglycaemic (OR = 4.2, 95% CI = 1.4–12.9, \( P = 0.012 \)). Higher deaths and higher rate of referral of hypoglycaemic children explains their shorter duration of hospitalization. In bacteraemia due to Gram-negative organisms the liberation of endotoxin reduces gluconeogenesis, perhaps due to inhibition of synthesis of gluconeogenic enzymes [14–16], leading to hypoglycaemia.

The management of bacteraemic patients requires immediate institution of an effective antimicrobial therapy, and other supportive measures according to their clinical condition. However, a definitive diagnosis requiring isolation and identification of pathogens using standard cultural techniques require time, moreover a single culture using smaller volume of blood, usually practiced in resources-constraint facilities, may give rise to false-negative results. Thus, there is a need to apply other, indirect means to identify possible cases of bacteraemia. In a diarrhoeal disease health care facility with limited resources, a rapid bedside glucose test should be considered as an inexpensive alternative in the management decisions of diagnosing bacteraemia and initiating empiric antibiotic treatment.

**References**