Perspective Piece

Improving the Management of Dysglycemia in Children in the Developing World

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Abstract. Improving the availability of point-of-care (POC) diagnostics for glucose is crucial in resource-constrained settings (RCS). Both hypo and hyperglycemia have an appreciable frequency in the tropics and have been associated with increased risk of deaths in pediatrics units. However, causes of dysglycemia, including hyperglycemia, are numerous and insufficiently documented in RCS. Effective glycemic control with glucose infusion and/or intensive insulin therapy can improve clinical outcomes in western settings. A non-invasive way for insulin administration is not yet available for hyperglycemia. We documented a few causes and developed simple POC treatment of hypoglycemia in RCS. We showed the efficacy of sublingual sugar in two clinical trials. Dextrose gel has been recently tested for neonate mortality. This represents an interesting alternative that should be compared with sublingual sugar in RCS. New studies had to be done to document dysglycemia mechanism, frequency and morbid-mortality, and safe POC treatment in the tropics.

Recently, Michael Hawkes and colleagues¹ reported the performance of point-of-care (POC) tests to guide the management of 179 children with severe malaria in a resource-limited Ugandan hospital. They paired measurements of glucose using i-STAT and OneTouch Ultra glucometer and other measurements for lactate and hemoglobin. Despite the small sample size of children with hypoglycemia and the lack of gold standard methods, they concluded that diagnostic tools, although imperfect, may expedite clinical decision-making in the management of critically ill children in resource-constrained settings (RCS). We completely agree with the crucial need for improving the availability of point-of-care diagnostics for glucose, particularly in RCS where hypoglycemia is a common and underdiagnosed cause of death.^{2–4} However, the sole diagnosis of dysglycemia is not sufficient if an access to effective therapy is not feasible, especially in the field for comatose children.

For this purpose, we assessed the frequency of dysglycemia in sick children in non-malaria areas.² In the pediatric ward of a referral hospital in Madagascar, an appreciable frequency (10.9%) (95% confidence interval [CI], 8.1–14.3) of hyperglycemic children at admission carried an increased risk of death (risk ratio [RR]: 2.2, 95% CI: 1–4.7).² This association of hyperglycemia and increased mortality was described in rural Kenya and in a tertiary care hospital in India.^{5,6} However, data on hyperglycemia frequency, causes, and mortality remains scarce in the tropics.^{7,8} In the same study, we also found a 3.0% (95% CI, 1.6–5.2) prevalence of hypoglycemia among 420 consecutive children.² Hypoglycemia was associated with increased risk of deaths (RR: 19.4, 95% CI: 5.0–74.7) after multivariate analyses. The rate of hypoglycemia was consistent with reports from Tanzania⁹ but lower than rates reported in malaria areas.^{5–7,10,11}

Hypoglycemia is a common and serious complication in children with severe malaria, and it also is indicative of mortality caused by this disease.^{10,12} Depletion of glucose stores caused by starvation, parasite use of glucose, and cytokine-induced impairment of gluconeogenesis have been impli-

cated.¹³ Hyperinsulinemia, secondary to parenteral quinine therapy, has been advanced as an iatrogenic cause and is well established in adults.^{14,15} Hypoglycemia related to intoxication is probably another highly underestimated cause of death in the tropics. As an example, we investigated the seasonal epidemic of fatal encephalopathy in preschool children in Burkina Faso and related the deaths to the consumption of unripe ackee (*Blighia sapida*) fruit and hypoglycin, a potent lethal hypoglycemic agent present in unripe ackee.^{16,17} There are numerous other causes that often remain undiagnosed. Moreover, hypoglycemia may be aggravated by several generally accepted risk factors such as the altered nutritional status, the severity of the infectious diseases, the young age, the delay in admittance to the hospital, the use of potentially toxic herbal preparations, and the lack of diagnostic facilities.^{2,13}

Younger children and neonates are particularly susceptible to hypoglycemia, both in tropical and western countries.¹⁸ Undernourished children are prone to hypoglycemia any time their fragile nutritional balance is compromised. Delay in admittance to the hospital may impair glucose production and contribute to the worsening of hypoglycemia. We showed that the time of the last meal enhanced the depth of hypoglycemia.² In the tropics, prolonged delay of referral before both diagnosis and glucose administration increased the fasting period. Therefore, a period of prolonged fasting is considered as a risk factor because glycogen stores in the young child are limited, which can result in decreased hepatic glucose production.^{3,19} Healthy adults are able to maintain normal plasma glucose levels up to 86 hours of fasting,⁹ although healthy children are not able to maintain a normal plasma glucose concentration during a fasting period of 24 hours and show a significant steeper decrease in plasma glucose concentration than adults. Therefore, the availability of POC tests must be extended to the primary health care settings for hypoglycemia detection at the consultation level. Moreover, repeated measurements should be advisable to detect late or recurrent hypoglycemia.

Untreated hypoglycemia is a major cause of deaths in the tropics. Newborn hypoglycemia is probably underestimated completely as a result of the lack of safe and reliable POC diagnostic tests in maternity wards in resource-limited countries.¹ Despite considerable interest recently in neonate mortality in

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the new world, neonate hypoglycemia has been rarely documented in the tropics.^{7,20–22} A rapid search in Medline using the terms “hypoglycemia,” “neonatal or neonates,” and “developing countries or low income” yields no more than 23 papers, although the same search found over 177,334 papers when dropping the terms “developing countries or low income.”

Having an available POC test for hypoglycemia diagnostics resolves only one part of the problem, particularly in remote settings where dextrose infusion for young children is currently non-available or feasible. We proposed the use of the ordinary sugar powder administered by the sublingual route (SL), which benefits from an abundant absorption network for glucose.^{23–25} This simple treatment is now recommended for the rapid on-site treatment of unripe *Blighia sapida* consumption.¹⁷ We also showed its efficacy in two clinical trials in resource-constrained settings in Mali and Burkina Faso. The SL absorption of glucose was faster than by the oral route (Figure 1).²⁴ An increase of 36 mg/dL (17.6–54.5) of blood glucose concentrations was obtained within 10 minutes and 64% of children reached blood glucose concentration higher than 3.3 mmol/L in 20 minutes. Indeed, the sublingual surface has a restricted absorption capacity that allows limited amounts of 0.2 g/kg to be absorbed in young infants. The saturation of the SL glucose carriers prevents the use of high doses and required repeated SL administration to by-pass this drawback.^{23–25} Recently, evidence was given that 40% dextrose gel rubbed into the inside of the cheek is effective and well tolerated and could also be considered for first-line treatment to manage hypoglycemia in late preterm and term babies in the first 48 hours after birth.²⁶ The benefit of dextrose, the physiological D-isomer of glucose over the disaccharide sucrose, which required a split into glucose and fructose, is to be more rapidly and fully absorbed.²⁷ Dextrose gel reduces the admission rate to the intensive care unit (ICU), but its cost (US\$2 per baby) and availability might be a limitation for resource-poor settings.²³ Sublingual administration of sugar should be proposed to health workers for the management of unconscious children hypoglycemic in out-of-hospital or when a dextrose infusion is not available. Further work is needed to increase the availability of this dextrose gel in the tropics and further trials to compare it with SL sugar.²³

FIGURE 1. Mean delta of initial blood glucose concentration (g/L) after sublingual and oral sugar, and placebo (water) in young children in the tropics. Sixty-nine children (3–13 years of age) with blood glucose concentration < 3.9 mmol/L after overnight fasting randomly received 2.5 g of moistened sugar either orally or sublingually, oral water as placebo. Adapted from Barennes and others.²⁴

In well-equipped intensive care, patients with or without diabetes have frequent dysglycemia, and hyperglycemia is associated with poor outcomes.²⁸ Several studies in western countries showed that a strict glycemic control is a safe and effective method for reducing the incidence of nosocomial infections in a predominantly non-diabetic, general surgical ICU patient population.^{29,30} Effective glycemic control with glucose infusion and/or intensive insulin therapy showed improved clinical outcomes in critically ill term neonates.^{31,32} Nevertheless, a recent multicenter trial has questioned the efficacy of a tight glucose control of hyperglycemia in critically ill children.³³ In RCS, the risk involved in hyperglycemia is probably underestimated and is rarely assessed outside of ICU.³⁰ Studies are needed for a better understanding of hyperglycemic outcomes and the necessity to initiate an early insulin therapy in severely ill hyperglycemic children admitted to pediatric emergency wards in the tropics. Therefore, recommendations of an intensive insulin therapy for hyperglycemia seem premature in primary health centers. Moreover, it requires a health system able to provide not only insulin and syringe but also ensure effective monitoring. A non-invasive way for insulin administration such as sublingual or nasal routes should be considered in the future.^{34–36}

Finally, we conclude that increasing the availability of POC diagnostic tests is crucial but should be accompanied by increasing information on non-invasive treatment of dysglycemia. Sublingual sugar or ready to use dextrose gel being a good example of POC treatment of hypoglycemia, that will benefit all children.²⁶ New studies have to be done for hyperglycemia in children regarding diagnosis, understanding, and POC treatment in the tropics.

Received April 8, 2014. Accepted for publication July 17, 2014.

Published online October 13, 2014.

Acknowledgments: We thank Percy Aaron for kind editing.

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