Effect on mortality of increasing the cutoff blood glucose concentration for initiating hypoglycaemia treatment in severely sick children aged 1 month to 5 years in Malawi (SugarFACT): a pragmatic, randomised controlled trial

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Summary

Background Low blood glucose concentrations are common in sick children who present to hospital in low-resource settings and are associated with increased mortality. The cutoff blood glucose concentration for the diagnosis and treatment of hypoglycaemia currently recommended by WHO (2.5 mmol/L) is not evidence-based. We aimed to assess whether increasing the cutoff blood glucose concentration for hypoglycaemia treatment in severely ill children at presentation to hospital improves mortality outcomes.

Methods We did a pragmatic, randomised controlled trial at two referral hospitals in Malawi. Severely ill children aged 1 month to 5 years presenting to the emergency department with a capillary blood glucose concentration of between 2.5 mmol/L (3.0 mmol/L in severely malnourished children) and 5.0 mmol/L were randomly assigned (1:1) by a computer-generated randomisation sequence, stratified by study site and severe malnutrition, to receive either an immediate intravenous bolus of 10% dextrose at 5 mL/kg followed by a 24-h maintenance infusion of 10% dextrose at 100 mL/kg for the first 10 kg of bodyweight, 50 mL/kg for the next 10 kg, and 20 mL/kg for each subsequent kg of bodyweight (intervention group) or observation for a minimum of 60 min and standard care (control group). Participants and study personnel were not masked to treatment allocation. The primary outcome was all-cause in-hospital mortality, assessed on an intention-to-treat basis. Safety was also assessed in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT02989675.

Findings Between Dec 5, 2016, and Jan 22, 2019, 10 947 children were screened, of whom 332 were randomly assigned and 322 were included in the final analysis (n=162 in the control group and n=160 in the intervention group). The study was terminated after an interim analysis at 24% enrolment indicated futility. The median age of participants was 2.3 years (IQR 1.4–3.2), 65 (45%) were female, and the baseline characteristics of participants were similar between the two groups. The number of in-hospital deaths from any cause was 26 (16%) in the control group and 24 (15%) in the intervention group, with an absolute mortality difference of 1.0% (95% CI –6.9 to 9.0). Serious adverse events, including hypoglycaemia, hyperglycaemia, convulsions, reduced consciousness, and death, were reported in 47 (29%) children in the control group and 39 (24%) children in the intervention group.

Interpretation Increasing the cutoff blood glucose concentration for hypoglycaemia treatment in severely sick children in Malawi from 2.5 mmol/L to 5.0 mmol/L did not reduce all-cause in-hospital mortality. Our findings do not support changing the cutoff for dextrose administration, and further research on the optimal management of severely ill children who present to the emergency department with low blood glucose concentrations is warranted.

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Introduction

Hypoglycaemia is a medical emergency that affects 3–7% of children admitted to hospital in low-income settings, with a reported case fatality rate of 20–61% and an increased risk of neurological sequelae. WHO recommends treating hypoglycaemia with a prompt bolus of intravenous dextrose, followed by re-evaluation of blood glucose concentrations and initiation of a dextrose maintenance infusion. The cutoff blood glucose concentration for a diagnosis of hypoglycaemia is a topic of debate and is not uniform throughout the world. Based on observational data and expert opinion, WHO uses a cutoff of less than 2.5 mmol/L in a well nourished child and a cutoff of less than 3.0 mmol/L in a malnourished child. Several studies have found that mortality in children admitted to hospital with low blood glucose concentrations, defined as those with a concentration of greater than 2.5 mmol/L but less than the cutoff for normoglycaemia, which has a variable definition of around 5.0 mmol/L, is higher than in children with normoglycaemia. Low blood glucose concentrations are a common finding in...
Research in context

Evidence before this study
We searched PubMed on Dec 15, 2019, using the search terms “blood glucose” OR “hypoglycaemia” OR “dysglycemia” AND any combination of “mortality” AND “child” AND “paediatric” AND NOT “diabetes”. To these search terms, we also added “developing country” OR “low or middle-income country” OR “Africa”. We searched for primary research articles, with no language restrictions. We found no trials evaluating improved outcomes associated with treatment of low blood glucose concentrations in severely sick children. Six studies assessed the association between blood glucose concentrations at admission to hospital and mortality in children in low-income settings. We identified five studies done in Africa. One large retrospective analysis of glucose measurements in 23,805 non-malnourished children aged 1-59 months who were admitted to a hospital in Kenya over an 11-year period found that a blood glucose concentration of less than 4 mmol/L at admission to hospital was associated with an odds ratio for death of greater than 2. In a prospective Tanzanian study of 3319 children aged 2-59 months who were admitted to hospital with a fever, 54 (7%) of 773 children with a blood glucose concentration of 2.5-5.0 mmol/L at admission died compared with 72 (2.9%) of 2441 children with a blood glucose concentration of more than 5.0 mmol/L. Receiver operating characteristic (ROC) curve analysis suggested an optimal mortality prediction at a hospital admission cutoff blood glucose concentration of less than 5 mmol/L. In a retrospective analysis of all paediatric admissions aged 0-15 years over a 13-year period in Mozambique, an increased case fatality rate was observed in those with blood glucose concentrations of 3.0-4.0 mmol/L compared with those who had a concentration of 4.0-7.0 mmol/L. Compared with overall admissions, mortality figures were higher in severely ill children with low blood glucose concentrations. For instance, in 437 Malian children with severe malaria, 24 (46.2%) of 52 with a blood glucose concentration of 2.2-4.4 mmol/L on admission died compared with 28 (13.4%) of 209 with a blood glucose concentration of 4.5-8.3 mmol/L, and ROC analysis suggested a cutoff for treatment with intravenous dextrose in children aged 1 month to 10 years with a blood glucose concentration of less than 3.6 mmol/L. In Nigeria, critically ill children aged 1 month to 10 years with a blood glucose concentration of less than 3.6 mmol/L had a case fatality rate of 33.9% compared with 9.9% in those with a blood glucose concentration of 3.6-6.2 mmol/L. However, another study of 420 children aged 1 month to 15 years admitted to hospital in Madagascar showed no increased mortality among those with a blood glucose concentration of 2.2-4.4 mmol/L on admission compared with those who had blood glucose concentrations of 4.4-8.3 mmol/L. Outside of Africa, mortality in children admitted to hospital in Laos with a blood glucose concentration of 2.2-4.4 mmol/L was higher (6.0%) than those with a concentration of 4.4-8.3 mmol/L (1.4%).

Added value of this study
This study is the first randomised controlled trial to assess the effect on mortality of increasing the cutoff blood glucose concentration for initiating hypoglycaemia treatment from 2.5 mmol/L to 5.0 mmol/L in severely sick children admitted to a hospital in a low-income country. The study was stopped when the interim analysis at 24% recruitment indicated futility. Our results suggest that mortality cannot be reduced by increasing the cutoff blood glucose concentration for treating hypoglycaemia in severely ill children at admission to hospital from 2.5 mmol/L to 5.0 mmol/L.

Implications of all the available evidence
Low blood glucose concentration at hospital admission is associated with an increased risk of death in sick children in low-income countries. Changing the cutoff blood glucose concentration for treatment with intravenous dextrose in children from 2.5 mmol/L to 5.0 mmol/L does not appear to improve outcomes. Further research is needed to understand why some sick children present with low blood glucose concentrations, why they have worse outcomes, and how they should best be managed.

Methods

Study design
SugarFACT was a pragmatic, randomised controlled trial done at two referral hospitals in Malawi. The study started as a single-centre study at Queen Elizabeth Central Hospital (QECH) in Blantyre, and was extended to a second site at Zomba Central Hospital (ZCH) on Oct 17, 2017, to increase the rate of enrolment. The trial design has been published in detail previously.15 QECH is a large tertiary hospital that serves a mixed urban and rural population and admits 23,000 children annually. ZCH is a tertiary hospital in Zomba located 70 km northeast of Blantyre, with 2500 paediatric admissions annually. The WHO Emergency Triage Assessment and Treatment (ETAT) protocol16 was developed at QECH and is used at both sites for the standard management of sick children.

The trial was run by the College of Medicine, University of Malawi (Blantyre, Malawi) in collaboration with the Karolinska Institutet (Stockholm, Sweden). The study received ethics approval from the Research and Ethics Committee at the College of Medicine, University of
Malawi (COMREC P.01/16/1852), and from the Central Ethical Research Board in Sweden (EPN 2017/33–31/4). An independent Data and Safety Monitoring Board (DSMB), consisting of two epidemiologists, a paediatrician, and a biostatistician, oversaw the safety of the study, and the trial was monitored by an independent clinical trial monitoring team. An interim analysis was planned at 50% enrolment, with predefined stopping criteria, using a design determined by 10000 trial simulations, including futility if the conditional power was less than 5% (ie, if the probability of the trial producing a positive result given the interim data was <5%).

**Participants**

Children aged 1 month to 5 years were included if they presented to the emergency department of QECH or ZCH with a capillary blood glucose concentration of between 2·5 mmol/L (3·0 mmol/L in severely malnourished children) and less than 5·0 mmol/L, and if there was either a WHO-defined emergency sign (ie, obstructed or absent breathing, central cyanosis, severe respiratory distress, shock or impaired perfusion, coma or reduced consciousness, convulsions, or severe dehydration) or a clinical concern that the child’s condition was an emergency. Exclusion criteria were a known diagnosis of diabetes mellitus, enrolment in the trial in a previous hospital admission, and refusal of consent. Written consent for participation in the trial was obtained before emergency treatment or was deferred until after emergency treatment if the child’s clinical condition was so severe that any treatment delay was adjudged to be detrimental.

**Randomisation and masking**

Children were randomly assigned (1:1) to receive dextrose (intervention group) or standard care (control group). Randomisation was stratified by study site and by severe malnutrition (defined as clinical severe acute malnutrition or a mid-upper arm circumference of <11·5 cm in children aged ≥6 months and <11·0 cm in children aged <6 months). An independent statistician prepared the computer-generated randomisation schedule with variable block sizes of six and eight. Study staff revealed the group allocation by opening sealed opaque envelopes in strict sequential order once a child had presented to the emergency department of QECH or ZCH, and the trial was monitored by an independent clinical trial monitoring team. An interim analysis was planned at 50% enrolment, with predefined stopping criteria, using a design determined by 10000 trial simulations, including futility if the conditional power was less than 5% (ie, if the probability of the trial producing a positive result given the interim data was <5%).

**Procedures**

We used a pragmatic approach for the study design, in which study procedures were designed to optimise feasibility and the direct implementation of findings into real-world clinical practice. Exclusion criteria were minimal; participants were managed in the same setting as other children and they received standard triaging and clinical care. Participants were recruited between 0700 h and 2100 h Monday to Friday, and between 0800 h and 1630 h on Saturdays and Sundays. Study staff based in the hospital emergency departments were available during the recruitment period, and included clinical officers (non-physician clinicians) and nurses. Capillary blood glucose concentrations were measured on arrival to the hospital by use of the HemoCue Glucose 201 RT (HemoCue AB, Angelholm, Sweden) point-of-care glucometers, which have previously shown reliable performance. Quality control checks of the glucometers were done once per week with GlucoTrol-NG control fluids (Eurotrol, Ede, Netherlands). We report the results from the glucometer tests as blood glucose concentrations, as per standard practice, even though the glucometers test whole blood glucose concentrations and convert the measured concentration to plasma glucose concentrations by use of an inbuilt algorithm.

Children in the intervention group were immediately given an intravenous bolus of 10% dextrose at 5 mL/kg, prepared using one part 50% dextrose and four parts 0·9% sodium chloride (or Ringer’s lactate in severely malnourished children). A maintenance infusion of 10% dextrose was started and prescribed for the first 24 h at standard maintenance rates of 100 mL/kg for the first 10 kg of bodyweight, 50 mL/kg for the next 10 kg, and 20 mL/kg for each subsequent kg of bodyweight. If the clinical condition allowed, the child was also permitted oral nutrition in accordance with local procedures. Capillary blood glucose concentrations were re-checked at 30-min intervals and, if required, repeat boluses of dextrose were given until blood glucose concentrations measured 5·0 mmol/L or higher. The children were observed in the emergency department for a minimum of 60 min. Because of their susceptibility to fluid overload from intravenous fluids, severely malnourished children received sugar-containing maintenance fluids via a nasogastric tube, as per WHO standards.

Children in the control group received no dextrose boluses or routine dextrose infusions, consistent with usual standard care. These children were observed in the emergency department for a minimum of 60 min. Re-checking of blood glucose was not done routinely, but was acceptable when the child was reassessed, if clinically warranted. If the child was able to feed orally, they were allowed to receive oral nutrition.

All other investigations and treatments for children in the intervention and control groups were done according to standard care procedures at the two hospitals. Once a participant was admitted to the ward from the emergency department, the usual clinical teams managed their care, and the study team did not have any further involvement in decisions about blood glucose monitoring, treatment with dextrose, or clinical care.
Children were followed up for 24 h after enrolment, and data on repeat blood glucose measurements done in the wards, the total quantity of dextrose received intravenously and by nasogastric tube, any food or sweet drinks received, and the occurrence of serious adverse events were collected. Subsequently, participants were followed up daily until discharge from hospital, and data on outcomes, discharge diagnoses, and investigation results were collected.

All study staff were trained on ETAT and International Conference on Harmonisation Good Clinical Practice procedures. To optimise protocol adherence, study staff received regular refresher training sessions on the study procedures. One of the study investigators was available for a telephone consultation throughout the study period. The study provided all glucose monitoring and treatment equipment, including glucometers, cuvettes, dextrose, and intravenous fluids. The electronic clinical record forms were developed and used to collect data on Android tablets with Open Data Kit. Data were uploaded daily to a database overseen by a data manager, and data queries were raised and resolved with regular meetings between the investigators and data manager.

Outcomes

The primary outcome was all-cause in-hospital mortality. The secondary outcome was in-hospital mortality at 24 h after enrolment.

As the study population was severely sick, only serious adverse events were reported, including reduced coma score, convulsion, hypoglycaemia, hyperglycaemia, or death. Serious adverse events were identified by the study team and reported to an independent clinical monitor within 48 h for blind assessment of a potential association with the study intervention. Serious adverse event reports were subsequently sent to the DSMB and ethics review board. Grading of serious adverse events was not done, as all events were considered potentially life-threatening.

Statistical analysis

A sample size of 633 participants in each study group was required, assuming an in-hospital mortality of 15.4% in the control group and 10.0% in the intervention group (mortality estimates based on an analysis of previous Tanzanian data), to provide 80% power at a two-sided \( \alpha \)-level of 0.05 and using Fleiss continuity correction. Independent statisticians developed the interim and final statistical analysis plans, and did the analyses in collaboration with the trial investigators and trial statistician. Data were exported to STATA version 15 for analysis. The principal analysis was done on an intention-to-treat basis, and a per-protocol analysis involving children who received treatment in the emergency department according to the protocol for their allocated group was also done. We summarised parametric data with means and SDs, non-parametric data by medians and range or IQR, and categorical data as proportions. We tested hypotheses using rank-sum tests, \( \chi^2 \) tests, generalised linear models, and negative binomial regression models, as appropriate. Mortality outcomes were analysed by use of logistic regression and a Kaplan-Meier chart was constructed. Participants were divided into several subgroups (listed in the appendix p 1), which were predefined in the study protocol.

This trial is registered with ClinicalTrials.gov, NCT02989675.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The principal investigator (HH) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were recruited between Dec 5, 2016, and Jan 22, 2019. Due to the slow rate of recruitment, an earlier than originally planned interim analysis was done at 24% enrolment. As the calculated conditional power in the interim analysis was 2.84%, the stopping criterion for futility had been met and the trial was terminated.

When the study was stopped (Jan 22, 2019), 10 947 children had presented to the emergency department, 6706 of whom were aged between 1 month and 5 years and had either a WHO-defined emergency sign or there was clinical concern that the child’s condition was an emergency. Of these children, 451 (7%) had low blood sugar concentrations (113 [2%] had hypoglycaemia). 332 (5%) children were eligible for the study and randomly assigned to the control group (n=166) or the intervention...
Implementation of the assigned intervention led to the administration of different treatments for low blood glucose concentrations in the two study groups. In the emergency department, where the study team were involved in the care of the children, all those in the intervention group and seven (4·2%) children in the control group received a dextrose bolus, and children in the intervention group were given a greater amount of dextrose than those in the control group. Participants in the intervention group had their blood glucose re-checked after 30 min, and eight (5%) participants had a blood glucose concentration of less than 5·0 mmol/L or whether oral nutrition was received between the two groups (table 2).

In the wards at 24 h after enrolment, participants involved in the care of the children, all those in the intervention group and seven (4·2%) children in the control group received at QECH and 146 (45%) were recruited at ZCH. The baseline characteristics of the participants were similar between the two groups (table 1). The median age of participants was 2·3 years (IQR 1·4–3·2) and 65 (45%) were female. The median blood glucose concentration on arrival to hospital was 4·1 mmol/L (IQR 3·4–4·6) in the control group and 4·2 mmol/L (3·4–4·6) in the intervention group.

| Recruitment site* | Control group (n=162) | Intervention group (n=160) | Total (n=322) |
|-------------------|----------------------|---------------------------|--------------|
| Queen Elizabeth Central Hospital | 90 (56%) | 86 (54%) | 182 (56%) |
| Zomba Central Hospital | 72 (44%) | 74 (46%) | 146 (45%) |
| Malnutrition† | 14 (9%) | 14 (9%) | 28 (9%) |
| Age, years | 2·2 (1·4–3·2) | 2·3 (1·5–3·3) | 2·3 (1·4–3·2) |
| Sex | | | |
| Female | 65 (40%) | 80 (50%) | 145 (45%) |
| Male | 97 (60%) | 80 (50%) | 177 (55%) |
| Weight, kg | 10·6 (8·6–12·6) | 10·4 (8·8–12·5) | 10·5 (8·7–12·5) |
| Emergency signs | | | |
| Obstructed or absent breathing | 0 | 1 (1%) | 1 (1%) |
| Cyanosis | 7 (4%) | 8 (5%) | 15 (5%) |
| Severe respiratory distress | 49 (30%) | 54 (34%) | 103 (32%) |
| Shock | 2 (1%) | 3 (2%) | 7 (2%) |
| Convolutions | 49 (30%) | 43 (27%) | 92 (29%) |
| Dehydration | 5 (3%) | 7 (4%) | 12 (4%) |
| Clinical concern | 46 (28%) | 41 (26%) | 87 (27%) |
| Vital signs | | | |
| Blantyre Coma Score‡ | 4 (1·4) | 4 (1·3) | 4 (1·3) |
| Temperature, °C | 37·5 (1·4) | 37·5 (1·3) | 37·5 (1·4) |
| Respiratory rate, breaths per min | 47 (16) | 46 (15) | 47 (16) |
| Oxygen saturation | 94% (8) | 94% (8) | 94% (8) |
| Heart rate, beats per min | 135 (33) | 141 (32) | 138 (32) |
| Clinical diagnoses at admission§ | | | |
| Malaria | 88 (54%) | 104 (65%) | 192 (60%) |
| Pneumonia | 26 (16%) | 16 (10%) | 42 (13%) |
| Gastroenteritis | 19 (12%) | 16 (10%) | 35 (11%) |
| Meningitis | 25 (15%) | 15 (9%) | 40 (12%) |
| Sepsis | 29 (18%) | 29 (18%) | 58 (18%) |
| Bronchiolitis | 7 (4%) | 7 (4%) | 14 (4%) |
| Anaemia | 41 (25%) | 42 (27%) | 83 (26%) |

| Discharge diagnoses§ | | | |
| Malaria | 90 (56%) | 101 (63%) | 191 (59%) |
| Pneumonia | 26 (16%) | 12 (8%) | 38 (12%) |
| Gastroenteritis | 17 (11%) | 18 (11%) | 35 (11%) |
| Meningitis | 16 (10%) | 10 (6%) | 26 (8%) |
| Sepsis | 41 (25%) | 44 (28%) | 85 (26%) |
| Bronchiolitis | 6 (4%) | 5 (3%) | 11 (3%) |
| Anaemia | 30 (19%) | 32 (20%) | 62 (19%) |

| HIV status | | | |
| Negative | 71 (44%) | 69 (43%) | 140 (44%) |
| Positive | 10 (6%) | 10 (6%) | 20 (6%) |
| Exposed | 8 (6%) | 9 (6%) | 17 (5%) |
| Unknown | 72 (44%) | 73 (46%) | 145 (45%) |

| Blood glucose at arrival, mmol/L | 4·1 (3·4–4·6) | 4·2 (3·4–4·6) | 4·1 (3·4–4·6) |

Data are n (%), median (IQR), or mean (SD). *Stratification variable. †Defined as clinical severe acute malnutrition or a mid-upper arm circumference of less than 11·5 cm in children aged 6 months or older, and less than 11 cm in children aged younger than 6 months. ‡A commonly used method in Malawi that provides a measure of a child’s level of consciousness. The score ranges from 0 (lowest level of consciousness) to 5 (highest level of consciousness). §Total could equal more than 100%, as participants could have more than one diagnosis.

Table 1: Baseline characteristics

Group (n=166; figure 1). Ten (3%) children were excluded from the analyses (four in the control group and six in the intervention group), and no children were lost to follow-up. The primary analysis included a total of 322 children (162 in the control group and 160 in the intervention group). 176 (55%) of 332 children were recruited at QECH and 146 (45%) were recruited at ZCH.
Articles

For the primary outcome of all-cause in-hospital mortality, 26 (16%) of 162 children in the control group and 24 (15%) of 160 children in the intervention group died (absolute mortality difference 1-0% [95% CI −6-8 to 9-0]). The odds ratio (OR) for death in children in the intervention group was 0-91 (95% CI 0-50–1-69, p=0-795; table 4). The Kaplan-Meier survival curves did not show a significant difference in time to mortality between the two groups (p=0-397; figure 2).

At 24 h after enrolment, 12 (7%) of 162 children in the control group and 14 (9%) of 160 children in the intervention group had died (absolute mortality increase of 1-3% [95% CI −7-2 to 4-6]). The OR for death in children in the intervention group was 1-20 (95% CI 0-53 to 2-68, p=0-659; table 4).

The predefined subgroups contained few participants, and no significant differences between the two groups were identified (appendix p I).

Per-protocol analyses included 313 participants (n=154 in the control group and n=159 in the intervention group). 25 (16%) children in the control group and 24 (15%) children in the intervention group died in hospital. The OR for in-hospital death in children in the intervention group was 0-91 (95% CI 0-50–1-69, p=0-782).

86 (27%) of 322 children had one or more serious adverse events, including death (table 5). This result was not unexpected in this severely unwell patient population. The clinical monitors and DSMB, who were masked to the study groups, did not adjudicate any serious adverse event to be definitely related to the intervention. Three children with a serious adverse event of hypoglycaemia were assessed as probably related to the intervention, all of whom were in the control group. The remaining 83 serious adverse events were adjudged to be not related (n=14), unlikely to be related (n=46), or possibly related (n=23) to the intervention. 13 (8%) children in the control group had an episode of hypoglycaemia in the emergency department or in the wards 24 h after enrolment compared with four (3%) children in the intervention group (p=0-027). The number of other reported serious adverse events were distributed evenly between the two groups (table 5).

### Discussion

In this randomised controlled trial done in Malawi, we found no evidence of a reduction in mortality from increasing the cutoff blood glucose concentration for hypoglycaemia treatment in severely sick children from 2-5 mmol/L to 5-0 mmol/L. The study was stopped following an interim analysis at 24% planned enrolment, as the similar mortality estimates between the intervention and control groups suggested futility.

The pragmatic design of the trial succeeded, as children in the intervention group were successfully given an intravenous bolus of dextrose and a repeated blood sugar test after 30 min, and an intravenous dextrose infusion was initiated in the emergency department. Children in the intervention group received significantly more dextrose than those in the control group within the first 24 h of enrolment, both in the emergency department and in the wards, even though care in the wards was not directed by the trial. The absence of benefit of increasing the cutoff blood glucose concentration observed in the primary outcome of all-cause in-hospital mortality was also observed in the secondary outcome of mortality at 24 h after enrolment. There was no evidence that the intervention led to an increase in the number of adverse events; however, significantly fewer children in the intervention group had recorded episodes of hypoglycaemia in the wards within the first 24 h of hospital admission than in the control group.

A 2019 study by our research group supports previous findings showing that mortality in severely ill children with low blood glucose concentrations is higher than in those with normoglycaemia. The absence of a treatment effect from providing dextrose to children with low blood glucose concentrations in our study might therefore seem
surprising, but there could be several possible explanations. One plausible explanation is that children with low blood glucose concentrations might not require additional dextrose. The low blood glucose concentrations in these children could be a marker of illness severity, possibly caused by poor feeding, an exhausted cortisol response, cortisol resistance, other endocrinological disturbances related to the severity of illness,20,21 depleted glucose stores,22 chronic illness, or malnutrition.23 This possibility could imply that identifying low blood glucose concentrations in a severely ill child might warrant an increased degree of triage, but that the risk of death cannot be lowered through provision of dextrose alone. Another possible explanation is that the pragmatic design of the trial masked biological complexity. Dextrose boluses can sometimes cause hyperglycaemia or rebound hypoglycaemia, both of which are known to be harmful.24,25,26 Due to the risk of rebound hypoglycaemia, some guidelines now recommend a 10% dextrose bolus at 2 mL/kg for hypoglycaemia, rather than 5 mL/kg.24 Alternatively, some children could have become dangerously hypoglycaemic on the ward despite receiving dextrose, as hypoglycaemic episodes can be common and go clinically undetected.25 In chronically unwell or malnourished children, increased nutrition in the form of dextrose could have led to refeeding syndrome, which could have had a negative effect on outcomes among participants in the intervention group.26 Increasing the frequency of observations, continuous dextrose monitoring, or electrolyte evaluations could have identified indicators of hypoglycaemia or electrolyte imbalances and enabled prevention or treatment of their occurrence.21,27

The predefined subgroups contained few participants, but the results of subgroup analyses indicated that the trial might have included a population that was too heterogeneous. Some children with low blood glucose concentrations could have benefited from dextrose administration, such as those who were the most severely ill (ie, those presenting with a true WHO-defined emergency sign or those who were unable to feed at arrival to hospital), those who were older than 2 years of age, or those without malnutrition. An additional possibility is that treatment of low blood glucose concentrations could have been beneficial only in children with particular diseases, such as malaria or infection with specific species of bacteria or other pathogens.28

This study is the first to evaluate the effect of dextrose administration in severely ill children with low blood glucose concentrations in a low-income country. The strengths of the study are the randomised controlled design, and the pragmatic and inclusive approach, which was designed to facilitate implementation of the findings in real-world hospital care. Limitations include the lower incidence of low blood glucose concentration in screened children than expected, leading to slow participant recruitment. There was also a large proportion of children recruited without a WHO-defined emergency sign. The inclusion of these children was considered to be important because of the non-specific nature of severe illness that could occur in the absence of specific signs in a severely sick child. However, this specification led to the inclusion of a subgroup of children who could be considered as less severely unwell than those who had a WHO-defined emergency sign. The study was terminated after the interim analysis, in accordance with the predefined stopping criteria. The similar mortality observed between the two groups led to a low conditional power, implying that the probability of a type II error was small and that further recruitment would be futile.

| Table 4: Study endpoints |
|--------------------------|
| **Study endpoints**      | **Control group** | **Intervention group** | **Odds ratio** (95% CI) | **p value** |
| In-hospital deaths       | 26 (16%)          | 24 (15%)               | 0·92 (0·50–1·69)         | 0·795       |
| Deaths at 24 h after enrolment | 12 (7%)          | 14 (9%)                | 1·20 (0·54–2·68)         | 0·659       |

Mortality outcomes analysed by logistic regression.

| Table 5: Serious adverse events |
|-------------------------------|
| **Total number of serious adverse events** | **Control group** (n=162)* | **Intervention group** (n=160)* | **Total** (n=322) |
| Death                         | 26 (16%)               | 24 (15%)               | 50 (16%)          |
| Convulsion                    | 14 (9%)                | 13 (8%)                | 27 (8%)           |
| Reduced consciousness         | 16 (10%)               | 8 (5%)                 | 24 (8%)           |
| Hypoglycaemia                 | 13 (8%)                | 4 (3%)                 | 17 (5%)           |
| Hyperglycaemia                | 1 (1%)                 | 0                      | 1 (<1%)           |

Data are n (%). *The sum of serious adverse events is greater than the total number, as a registered serious adverse event could include more than one event.

Figure 2: Kaplan-Meier curve showing in-hospital survival to 30 days after admission to hospital
Even though efforts were made to mask group allocation whenever possible, true blinding was not possible because of the nature of the dextrose boluses, repeat blood glucose testing, and intravenous infusions received by the participants in the intervention group. We do not believe that the absence of blinding had a substantial effect on the results, and indeed, the importance of blinding in randomised controlled trials has recently been questioned. A methodological consideration was the use of point-of-care glucometers. This strategy was considered to be a pragmatic necessity, as point-of-care glucometers are the most common instrument used for testing blood glucose in emergency care, and results from laboratory testing could not have been delivered rapidly enough to inform urgent treatment in this study. However, point-of-care whole blood glucose testing, with conversion to plasma glucose concentrations by use of an inbuilt algorithm, is not as accurate as laboratory testing, and some children with blood glucose concentrations near to the cutoff values for hypoglycaemia, low blood glucose concentrations, or normoglycaemia could have been misclassified.

Children in the control group could have also received more care aimed at normalising blood glucose concentrations than was intended by the study protocol definition of standard care. The trial could have raised awareness about the clinical issue of dysglycaemia, and there might have been contamination leading to clinical staff treating children in the control group with more dextrose, especially if they were not receiving dextrose infusions. Indeed, a greater proportion of children in the control group received oral feeds in the emergency department and a dextrose bolus in the wards than in the intervention group.

Mortality in the study was high, but was expected due to the severe condition of the children at enrolment. Although we did not find a benefit of administering dextrose to severely ill children with low blood glucose concentrations, we also did not find evidence that this intervention increased mortality compared with standard care. Hypoglycaemia is a potentially life-threatening condition, and is associated with long-term neurological complications. Compared with children in the control group, the lower occurrence of hypoglycaemia as a serious adverse event in those in the intervention group suggests that additional dextrose could have prevented some episodes of hypoglycaemia. Further research could focus on increased monitoring of blood glucose and clinical parameters in children with low blood glucose concentrations, the long-term follow-up of these children, or the treatment of low blood glucose concentrations in particular subgroups of children, such as those who are older (ie, those aged >5 years), those with more severe illness, or those without malnutrition. Explanatory studies are needed to understand the determinants of low blood glucose concentrations and hypoglycaemia, and the reasons for increased mortality in children with low blood glucose concentrations.

In conclusion, the results of our study show that increasing the cutoff blood glucose concentration for hypoglycaemia treatment in severely sick children in Malawi from 2·5 mmol/L to 5·0 mmol/L did not reduce all-cause in-hospital mortality.

Contributors
TB, QD, JL, GM, HH conceptualised and designed the study. TB and HH acquired funding. TB, FN, HM, JL, and HH collected the data; TB, FN, GM, and HH analysed the data; and all authors interpreted the data. TB, FN, and HH wrote the original draft of the manuscript, and all authors contributed to the writing, review, and editing of the manuscript. All authors approved the final version of the manuscript.

Declaration of interests
We declare no competing interests.

Data sharing
Anonymised data collected for the study and a data dictionary will be made available to other researchers following approval of a study proposal by HH (helena.hildenwall@ki.se) for 5 years from publication. The study protocol, statistical analysis plan, and informed consent forms are also available from HH.

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