Blood glucose and prognosis in children with presumed severe malaria: what is the threshold for “hypoglycaemia”? 

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5. Department of Public Health and Primary Care, Oxford University, UK

Context
• Severe malaria kills 0.8-1 million a year, mainly African children
• Hypoglycaemia (HG):
  – a defining feature of severe malaria (SM) (WHO 2000b)
  – Observed in 10 to 20% in SM children
  – Poor prognosis when associated with severe malaria
  – 3-10-fold fatality
• HG frequent in tropical/others context:
  – Malnutrition, intoxication, neonates

What is hypoglycaemia?
• WHO guidelines:
  - <2.2mmol/l (<40mg/dl)
    “If blood glucose is <2.2mmol/l then hypoglycaemia should be treated immediately (0.3 – 0.5g/kg bw of glucose).”
  • Of concern
    – Is hypoglycaemia detected in comatose children?
    – How can you detect it?
    – Is IV dextrose available,
    – Feasible at the health centre?

Different definitions of hypoglycaemia

<table>
<thead>
<tr>
<th>mmol/l</th>
<th>mg/dl</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2</td>
<td>40</td>
<td>WHO</td>
</tr>
<tr>
<td>3.0</td>
<td>54</td>
<td>Willcox et al, 2008</td>
</tr>
<tr>
<td>4.4</td>
<td>80</td>
<td>Barennes, 2005</td>
</tr>
</tbody>
</table>

When asked, pediatricians provided different thresholds age/disease etc.

Why define a threshold?
• Case definitions of severe malaria 
• Inclusion criterion for clinical trials 
• Indication of prognosis 
• Protocols for treatment 

• Are we sure that 2.2mmol/l (<40mg/dl) is accurate?
• Is this not too late to treat children and prevent deaths/further brain damage?
• What is the prognosis of 40-80 mg?
Material and method

Study site: Sikasso hospital, SW Mali
Mortality rate 24.3%,
42.4% of Deaths attributed to malaria.
Inclusion: All children clinical severe malaria /+ B smears
Lab: Blood glucose measured (bedside glucometer)
Treatment: 1st line antimalarial = Artemether i-m, then AQ
+ Ceftriaxone, 100mg/kg i-v for all comatose children
+ Treatment of Convulsions/severe anemia Hb<5
+ IV Glucose (10%) when blood glucose <4.4 mmol/l.
Ethics: Parents consent/Ethics Committee Mali
Context: 6 year Malaria project

Definitions
• Hypoglycaemia: glucose <2.2 mmol/l (<40 mg/dl)
• Low glycaemia: glucose 2.2–4.4 mmol/l (40–79 mg/dl)
• Normal glycaemia: glucose 4.4–8.3 mmol/l (80–149 mg/dl)
• Hyperglycaemia: glucose > 8.3 mmol/l (>150 mg/dl)

Main outcome
• Case fatality

Defining threshold
• Relative frequency and OR
• Models of mortality /baseline glycaemia/ Uni-Multivariate
• Receiver operator curve (ROC) approach

Analysis

Results. Study Flow chart

417 children with presumed severe malaria*
19 excluded/ no Blood G or left
418 enrolled 95.7%

71 died (17%) 338 Complete Recovery (81%)
9 Sequelae (2%)

11 (15%) before any treatment
12 (17%) 1 hour after admission
62 (87%) within 24 hours

* 20% of interpretable Blood films negative
Blood glucose on admission

- Hypoglycaemia (34.4%)
- Low glycaemia (12.4%)
- Normal glycaemia (52.3%)

Case fatality according to BG

<table>
<thead>
<tr>
<th>Deaths rate</th>
<th>45% of children &lt;4.4 mmol/l died versus 9.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemia</td>
<td>61.5% of the hypoG</td>
</tr>
<tr>
<td>Low glycaemia</td>
<td>46.2% of normal G</td>
</tr>
<tr>
<td>Normal glycaemia</td>
<td>13.4% of normal G</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>7.6% of hyperglycaemia</td>
</tr>
</tbody>
</table>

D significantly related to:
- Girls,
- Hypo, Low glycemia
- Coma+3, Resp Distress

Risk of deaths according to G level (OR)

<table>
<thead>
<tr>
<th>Glycaemia (mg/dl) [mmol/l]</th>
<th>number</th>
<th>Fatal (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-199 [4.4 – 11.0]</td>
<td>209</td>
<td>(13.4%)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>&lt; 40 (&lt;2.2)</td>
<td>3</td>
<td>(61.5%)</td>
<td>11.8 (2.1-67.0)</td>
</tr>
<tr>
<td>40-80 [2.2 – 4.4]</td>
<td>12</td>
<td>(46.2%)</td>
<td>5.2 (1.8-14.6)</td>
</tr>
<tr>
<td>&gt; 200 (&gt;11.0)</td>
<td>144</td>
<td>(7.6%)</td>
<td>0.3 (0.1-0.9)</td>
</tr>
</tbody>
</table>

12 fold and 5 fold risk of deaths if <2.2 and 4.4 mmol/l, respectively

Glycaemia as a predictor of case fatality

Hypoglycaemia

- very good specificity 98%
- poor sensitivity (10.5%)
- <6.1 mmol/l (110mg/dl)
- The most effective cut-off
- Good sensitivity 64.5%
- Specificity 75.1%
- But
- Moderate Predictive accuracy (AUC: 0.7)

Discussion

Intermediate levels of low glycaemia with increased risk of death from malaria (OR 11.8 and 5.2) not explained by other features of severe malaria

Observed irrespective of malaria positivity
- Low glycaemia also at risk in other childhood severe disease

<table>
<thead>
<tr>
<th></th>
<th>White et al, 1987 (Gambia)</th>
<th>Sikasso, 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>47</td>
<td>417</td>
</tr>
<tr>
<td>Overall case fatality</td>
<td>13%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Prevalence of glucose &lt;2.2mmol/l</td>
<td>32%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Case fatality for &lt;2.2mmol/l</td>
<td>33%</td>
<td>62%</td>
</tr>
<tr>
<td>Case fatality for &gt;2.2mmol/l</td>
<td>3%</td>
<td>15.6%</td>
</tr>
</tbody>
</table>
Why the differences?

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<th>White et al, 1987</th>
<th>Sikasso, 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement method</td>
<td>Laboratory, BM sticks</td>
<td>glucometer</td>
</tr>
<tr>
<td>Malaria diagnosis</td>
<td>Confirmed</td>
<td>Presumed</td>
</tr>
<tr>
<td>Treatment with i-v glucose</td>
<td>$&lt;2.2 \text{mmol/l}$</td>
<td>$&lt;4.4 \text{mmol/l}$</td>
</tr>
<tr>
<td>Patient selection</td>
<td>Not clear how many excluded</td>
<td>95.4% included</td>
</tr>
</tbody>
</table>

Discussion

• Should we keep 2.2 mmol/l to recommend treatment?

• This study suggest that the sensitivity is too low

• Is maintaining low glycaemia safe for infants and Children 'brain or giving glucose deleterious:
  – Limitant l’augmentation du lactate ds la cellule et baisse de Ph
  – Qui pourrait favoriser l’acidose lactique (White, 1987)
  – Pas d’aggravation après traitement par G 50%?
  – Pas d’élevation des lactates aprè 3-5 heures de perfusion D (in Taylor, 1998)

Need of research/a clinical trial to assess this question

Any treatment in remote areas when IV no feasible?

Sublingual sugar

- good effectiveness children,
  • severe hypoglycaemia*
  • moderate hypoglycaemia**

A few points to address
- dosages,
- timing of return to normal,
- effectiveness and safety in routine

Glycaemia of hypog4 after Sublingual sucre (SLS) and IV dextrose (IVG)*

Conclusion

• Unclear evidence for a low threshold at 2.2

• More research is needed the assess
  – whether treatment with intravenous glucose or sublingual sugar is beneficial to those
  – with low glycaemia,
  – above the current treatment threshold.

References


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Decrease the fatality due to malaria