Glycemic control in acute stroke: ‘balancing the risks’
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EFFICACY AND SAFETY OF TWO 5 DAY INSULIN DOSING REGIMENS TO ACHIEVE STRICT GLYCEMIC CONTROL IN PATIENTS WITH ACUTE ISCHEMIC STROKE
ABSTRACT

Background
In patients with acute ischemic stroke and hyperglycemia, prolonged strict glycemic control may improve clinical outcome. The question is how to achieve this prolonged strict glycemic control. In this study, the efficacy and safety of two regimens with different basal to meal related insulin ratio are described.

Methods
Thirty-three patients with ischemic stroke and hyperglycemia on admission were randomized in an open design to receive: (1) conventional glucose-lowering treatment, (2) strict glucose control with predominantly basal insulin using intravenous insulin or (3) strict glucose control with predominantly meal related insulin using subcutaneous insulin in the first 5 days after stroke. The target range of glucose control for the last two groups was 4.4 to 6.1 mmol/L. Sixteen consecutive patients without hyperglycemia on admission were included to serve as normoglycemic controls.

Results
The median area under the curve (AUC) in the meal related insulin group was 386 mmol/L x 658 hours (range 286 to 662) for days 2 to 5, and did not differ from the hyperglycemic control group (median AUC 444 mmol/L x 658 h; range 388 to 620). There was also no difference in median AUC of the basal insulin group (453 mmol/L x 658 h, range 347 to 629) and the hyperglycemic control group on days 2 to 5. In the first 12 hours, glucose profiles were lower in the groups treated with strict glucose control; median AUC was 90 mmol/L x 612 hours (range 77 to 189) for the hyperglycemic control group versus 81 mmol/L x 612 hours (range 60 to 118) for the meal related insulin group (p=0.03) and 74 mmol/L x 612 (range 52 to 97) for the basal insulin group (p=0.008).

Conclusion
In intermittently fed ischemic stroke patients, strict glycemic control between day 2 and day 5 with two different basal bolus regimens did not result in lower glucose profiles due to postprandial hyperglycemia. Continuous enteral feeding may therefore be needed to achieve prolonged strict glycemic control in acute stroke patients.
INTRODUCTION

Hyperglycemia after ischemic stroke is associated with adverse outcome. Patients with ischemic stroke and hyperglycemia on admission have a larger infarction volume, with less penumbral salvage. This suggests that hyperglycemia plays a pathophysiological role in stroke progression, and lowering hyperglycemia after ischemic stroke may improve clinical outcome. However, the recently published multicentre GIST-UK study did not show a benefit of strict glucose control in the first 24 hours after stroke. The effect of strict glycemic control may only become evident with a longer duration of treatment. In myocardial infarction and intensive care patients, only prolonged glycemic control has yielded positive results. Furthermore, prolonged hyperglycemia after acute ischemic stroke has a stronger association with infarct growth and clinical outcome than hyperglycemia on admission. There is currently no clear pathophysiological explanation. One of the hypotheses is that increased glucose availability and a limited amount of oxygen in the ischemic border zone results in cerebral tissue damage through anaerobic glycolysis and lactate formation.

In this study, we evaluated two insulin therapy regimens for prolonged glycemic control in patients with acute ischemic stroke, with a different route of administration and basal to meal related insulin ratio.

METHODS

Patients with an acute neurological deficit for which no other cause than cerebral ischemia could be found, with a time of onset less than 24 hours before presentation, were recruited in the Academic Medical Centre, Amsterdam, and the University Medical Centre, Utrecht, The Netherlands. Patients were included between March 2004 and September 2005, before it was editorial policy to require trial registration. Patients using insulin were excluded. Oral glucose lowering drugs were continued in the conventionally treated group. Subcutaneous short acting insulin aspart was only administered when glucose values exceeded 16.6 mmol/L, as recommended at the time of patient recruitment. Oral glucose lowering drugs were discontinued in the groups receiving strict glycemic control. They were treated with predominantly basal insulin or predominantly meal related insulin. Intravenous insulin administration in the group of patients treated with predominantly basal insulin was adjusted every hour until glucose values were < 6.1 mmol/L, and at all standard measuring points thereafter, according to a sliding scale regimen. Meal related insulin was intravenously administered as a bolus insulin in a dose equal to the newly calculated hourly insulin infusion rate.

In the group receiving predominantly meal related insulin, long acting insulin glargine (Lantus, Sanofi-Aventis, Gouda, The Netherlands) was administered subcutaneously as basal insulin and rapid acting insulin aspart (Novorapid, Novo Nordisk, Alphen aan de Rijn, The Netherlands) as meal related insulin. Basal and meal related insulin doses were further titrated using a sliding scale regimen. Hypoglycemia was defined as glucose <3.5 mmol/L. Patients unable to eat received enteral feeding (Nutrison standard; Nutricia, Zoetermeer, The Netherlands) within 24 hours after admission. Enteral feeding was gradually increased over the first 2 or 3 days, aiming at 2000 kcal/day. Other patients were stimulated to eat a balanced diet of about 2000
kcal/day. Caloric intake was quantified by scoring the constituents of consumed meals. Glucose on admission was measured by the HK/G-6PD method (Roche/Hitachi, Indianopolis, USA). Subsequent samples were analyzed with a bedside Hemocue analyzer (Hemocue Diagnostics, Ängelholm, Sweden). Twice during the study period simultaneous measurements were performed with the HK/G-6PD method, for quality control. Meal related glucose measurements were taken immediately before and 2 hours after each meal, and around 22:30. In patients treated with strict glucose control, glucose values were also measured twice during the night to detect possible hypoglycemia. Randomization was performed using consecutive numbered envelopes, stratified for dysphagia on admission and diabetes mellitus on admission. Glucose levels over time were calculated as areas under the curve (AUC) for each patient. AUC was computed for day time measurements only. Differences in AUC between groups were analyzed using the Mann–Whitney rank test. The primary endpoint was the difference in AUC for days 2 to 5. Day 2 started at the first measurement on the day after inclusion. Differences in AUC in the first 12 hours after inclusion were calculated as a secondary endpoint. In patients included in the late evening or night, day 2 and the first 12 hours after inclusion overlapped. All patients gave written informed consent. The study protocol was approved by the local ethics committee of both institutions.

RESULTS

Baseline characteristics of the study patients are displayed in table 1. Twelve patients discontinued the trial for the following reasons: withdrawal of informed consent (n=4; two in the control group and two in the treatment group); imminent death (n=4, all in the control group); rapid clinical improvement (n=1, in the control group); transfer to regional hospital (n=1); and logistic failure (n=2).

The amount of insulin administered per 24 hours was similar in the two experimental groups (median 34 (range 21 to 41) IU/24 hours in the of insulin administered was differently distributed over the days: in the predominantly basal insulin group, the amount of insulin remained relatively constant (decrease from 40 IE/24 hours at day 1 to 33 IE/24 hours at day 5) while in the predominantly meal related insulin group the amount of insulin increased from 20 to 34 IE/24 hour. In the hyperglycemic control group, subcutaneous rapid acting insulin was administered to three patients on one, three and five occasions, respectively, when glucose values exceeded 16.6 mmol/L.

There was no significant difference in AUC between the group treated with predominantly meal related insulin or predominantly basal insulin and the hyperglycemic control group on days 2, 3, 4 and 5 (median AUC 386 (range 286 to 662) mmol/L x 658 hours and median 453 (range 347 to 629) mmol/L x 658 hours vs. 444 (range 388 to 620) mmol/L x 658 h; p=0.15 and p=0.9 for predominantly meal related and basal insulin, respectively). In the first 12 hours after inclusion, glucose profiles were lower in the groups treated with strict glucose control (median 81 (range 60 to 118) mmol/L x 612 hours and median 74 (range 52 to 97) mmol/L x 612 hours vs. median 90 (range 77 to 189) mmol/L x 612 h, p=0.03 and p=0.008 for predominantly meal related insulin and predominantly basal insulin vs. the hyperglycemic control group, respectively).

More hypoglycemic events occurred in patients treated with predominantly basal insulin than in patients who received predominantly meal related insulin (18/476 vs. 7/422; p=0.05). In
the predominantly basal insulin group, 9/18 (50%) hypoglycemic events occurred during the night compared with 0/7 hypoglycemic events in the predominantly meal related insulin group. In patients receiving predominantly meal related insulin, all seven hypoglycemic episodes occurred postprandially. One patient who received predominantly meal related insulin complained of heavy perspiration during hypoglycemia (2.6 mmol/L) which disappeared with glucose administration. All other occurrences of hypoglycemia were asymptomatic.

Food intake was highly variable between patients. However, in all four groups, the caloric intake almost doubled from day 1 to day 5 (data not shown).

### Table 1 | Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Predominantly basal insulin (n=13)</th>
<th>Predominantly meal related insulin (n=10)</th>
<th>Hyperglycemic control group (n=10)</th>
<th>Normoglycemic control group (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>6 (46)</td>
<td>6 (60)</td>
<td>3 (30)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Mean age (years ± sd)</td>
<td>77.7 ± 9.5</td>
<td>72.0 ± 14.0</td>
<td>64.7 ± 17.5</td>
<td>68.8 ± 14.0</td>
</tr>
<tr>
<td>Type 2 DM (%)</td>
<td>6 (46)</td>
<td>2 (20)</td>
<td>4 (40)</td>
<td>–</td>
</tr>
<tr>
<td>Mean admission HbA1c (± sd)</td>
<td>6.5 ± 2.1</td>
<td>6.3 ± 1.4</td>
<td>7.6 ± 2.3</td>
<td>5.6 ± 0.57</td>
</tr>
<tr>
<td>Tube fed patients (%)</td>
<td>3 (23)</td>
<td>2 (20)</td>
<td>3 (30)</td>
<td>3 (19)</td>
</tr>
</tbody>
</table>


### Figure 1: Mean glucose levels in time.

![Figure 1](image)

(A) Mean (SEM) glucose values pooled per time point per group. (B) Mean (SEM) glucose values pooled per day per group. ■: hyperglycemic control group; △: predominantly meal related insulin group; ○: predominantly basal insulin group; ◆: normoglycemic control group.
DISCUSSION

This study shows that prolonged strict glycemic control in patients with ischemia stroke is difficult to achieve with both of the studied regimens. This was mainly caused by postprandial hyperglycemia (fig 1A). In common with others, we were able to achieve lower glucose profiles in the initial phase after acute stroke. Achieving adequate glucose lowering in the early stage of an acute illness is notoriously difficult. A previous randomized but uncontrolled study also found postprandial hyperglycemia to be the main obstacle in achieving prolonged strict glycemic control in acute stroke patients. A large international randomized clinical trial that investigated the use of strict glycemic control in acute myocardial infarction failed because glucose lowering in the experimental group was inadequate. Also, in the GIST-UK study, resuming oral intake was the likely reason that the effect of treatment discernable after 8 and 16 hours had waned after 24 hour. So how can we adequately lower hyperglycemia in the first 5 days after stroke? Administering less basal insulin and more meal related insulin is likely to result in more favorable glucose profiles. However, it is hard to predict if a patient is going to eat and if so, how much. In our study, we found that the amount of caloric intake was highly variable between patients. A potential danger is that too much meal related insulin is administered, resulting in hypoglycemia. All hypoglycemic events in the predominantly meal related insulin group occurred postprandially. Successful regimens for strict glucose control in other settings are limited to continuously fed patients. Continuous enteral feeding, although more invasive, may facilitate strict glycemic control in patients with acute ischemic stroke.

Is hyperglycemia a potential treatment target 3 days after stroke? We found that after an initial decline in glucose levels, from day 3, glucose levels increased again in control patients with hyperglycemia on admission, and that hyperglycemia persisted until at least the fifth day after stroke (fig 1B). It is possible that glucose values decrease on the second day after stroke as a result of attenuation of the stress reaction following stroke after 24 to 36 hour. The increase on day 3 is likely to be explained by a further increase in caloric intake and the presence of pre-existent insulin resistance.

CONCLUSION

Two insulin dosing regimens with a different basal to bolus insulin ratio failed to lower glucose in intermittently fed patients in the first 2 to 5 days after stroke, despite an initial lowering of glucose levels. This was likely due to unpredictable meal related rises in glucose levels. A possible solution might be to give continuous enteral feeding to patients receiving treatment with strict glucose control.