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Efficacy and safety of two 5 day insulin dosing regimens to achieve strict glycaemic control in patients with acute ischaemic stroke

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ABSTRACT

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

Methods: 33 patients with ischaemic stroke and hyperglycaemia at admission were randomised in an open design to receive: (1) conventional glucose lowering therapy, (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 4.4–6.1 mmol/l. 16 consecutive patients without hyperglycaemia at admission were included to serve as normoglycaemic controls.

Results: The median area under the curve (AUC) in the meal related insulin group was 386 mmol/l×58 h (range 286–662) for days 2–5, and did not differ from the hyperglycaemic control group (median AUC 444 mmol/l ×58 h; range 388–620). There was also no difference in median AUC of the basal insulin group (453 mmol/l ×58 h, range 347–629) and the hyperglycaemic control group on days 2–5. In the first 12 hours, glucose profiles were lower in the groups treated with strict glucose control; median AUC was 90 mmol/l×12 h (range 77–189) for the hyperglycaemic control group versus 81 mmol/l×12 h (range 60–118) for the meal related insulin group ($p = 0.03$) and 74 mmol/l×12 h (range 52–97) for the basal insulin group ($p = 0.008$).

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

Hyperglycaemia after ischaemic stroke is associated with adverse outcome.[1 2] Patients with ischaemic stroke and hyperglycaemia at admission have a larger infarction volume, with less penumbral salvage.[3 4] This suggests that hyperglycaemia plays a pathophysiological role in stroke progression, and lowering hyperglycaemia after ischaemic 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 h after stroke.[5] The effect of strict glycaemic control may only become evident with a longer duration of treatment. In myocardial infarction and intensive care patients, only prolonged glycaemic control has yielded positive results.[6–8] Furthermore, prolonged hyperglycaemia after acute ischaemic stroke has a stronger relationship with infarct growth and clinical outcome than hyperglycaemia at admission.[9] There is currently no clear pathophysiological explanation. One of the hypotheses is that increased glucose availability and a limited amount of oxygen in the ischaemic border zone results in cerebral tissue damage through anaerobic glycolysis and lactate formation.[10]

In this study, we evaluated two insulin therapy regimens for prolonged glycaemic control in patients with acute ischaemic 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 ischaemia could be found, with a time of onset less than 24 h 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.[11] Oral glucose lowering drugs were discontinued in the groups receiving strict glycaemic 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. Hypoglycaemia was defined as glucose <3.5 mmol/l.

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Table 1 Baseline characteristics

	Predominantly basal insulin (n = 13)	Predominantly meal related insulin (n = 10)	Hyperglycaemic control group (n = 10)	Normoglycaemic control group (n = 16)
Men (n (%))	6 (46)	6 (60)	3 (30)	8 (50)
Age (years) (mean (SD))	77.7 (9.5)	72.0 (14.0)	64.7 (17.5)	68.8 (14.0)
Glucose at admission (mmol/l) (median (range))	9.6 (7.3–18.6)	8.6 (7.3–13.2)	10.5 (7.8–23)	5.8 (4.5–6.7)
Type 2 DM (n (%))	6 (46)	2 (20)	4 (40)	–
HbA1c at admission (%) (mean (SD))	6.5 (2.1)	6.3 (1.4)	7.6 (2.3)	5.6 (0.57)
Intermittent tube feeding (n (%))	3 (23)	2 (20)	3 (30)	3 (19)
Intravenous thrombolysis (n (%))	4 (31)	4 (40)	3 (30)	9 (56)
Location of stroke (n (%))				
Middle cerebral artery	9 (69)	7 (70)	4 (40)	11 (69)
Lacunar	2 (15)	1 (10)	3 (30)	4 (25)
Vertebral basilar	2 (16)	2 (20)	3 (30)	1 (6)
Time from stroke to admission (h) (mean (SD))	6.3 (6.7)	3.1 (3.0)	8.3 (8.4)	3.2 (4.3)
Time from admission to inclusion (h) (mean (SD))	6.9 (4.7)	10.8 (5.6)	8.9 (7.0)	6.2 (2.7)
NIHSS score at admission (median (range))	5 (1–20)	8.5 (2–20)	7 (1–24)	8 (2–25)
NIHSS score day 5 (median (range))	2 (0–21) (n = 12)	2 (0–6) (n = 8)	2 (0–19) (n = 8)	7 (0–17) (n = 11)

DM, diabetes mellitus; HbA1c, glycated haemoglobin; NIHSS, National Institute of Health Stroke Scale.

Patients unable to eat received enteral feeding (Nutrison standard; Nutricia, Zoetermeer, The Netherlands) within 24 h 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 at admission was measured by the HK/G-6PD method (Roche/Hitachi, Indianopolis, USA). Subsequent samples were analysed with a bedside Hemocue analyser (Hemocue Diagnostics, Ängelholm, Sweden).[12] 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 h 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 hypoglycaemia.

Randomisation was performed using consecutive numbered envelopes, stratified for dysphagia at admission and diabetes mellitus at 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 analysed using the Mann–Whitney rank test. The primary endpoint was the difference in AUC for days 2–5. Day 2 started at the first measurement on the day after inclusion. Differences in AUC in the first 12 h after inclusion were calculated as a secondary endpoint. In patients included in the late evening or night, day 2 and the first 12 h 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 h was similar in the two experimental groups (median 34 (range 21–41) IU/24 h in the predominantly basal insulin group vs median 30 (range 21–37) IU/24 h in the predominantly meal related insulin group). Patients with predominantly basal insulin received 86–95% of insulin as basal insulin compared with 16–28% in the predominantly meal related insulin group. However, the amount 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 h at day 1 to 33 IE/24 h at day 5) while in the predominantly meal related insulin group the amount of insulin increased from 20 to 34 IE/24 h. In the hyperglycaemic 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 hyperglycaemic control group on days 2, 3, 4 and 5 (median AUC 386 (range 286–662) mmol/l×58 h and median 453 (range 347–629) mmol/l×58 h vs 444 (range 388–620) mmol/l×58 h; $p = 0.15$ and $p = 0.9$ for predominantly meal related and basal insulin, respectively). In the first 12 h after inclusion, glucose profiles were lower in the groups treated with strict glucose control (median 81 (range 60–118) mmol/l×12 h and median 74 (range 52–97) mmol/l×12 h vs median 90 (range 77–189) mmol/l×12 h, $p = 0.03$ and $p = 0.008$ for predominantly meal related insulin and predominantly basal insulin vs the hyperglycaemic control group, respectively).

More hypoglycaemic 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%) hypoglycaemic events occurred during the night compared with 0/7 hypoglycaemic events in the predominantly meal related insulin group. In patients receiving predominantly meal related insulin, all seven hypoglycaemic episodes occurred postprandially. One patient who received predominantly meal related insulin complained of heavy perspiration during hypoglycaemia (2.6 mmol/l) which disappeared with glucose administration. All other occurrences of hypoglycaemia 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).

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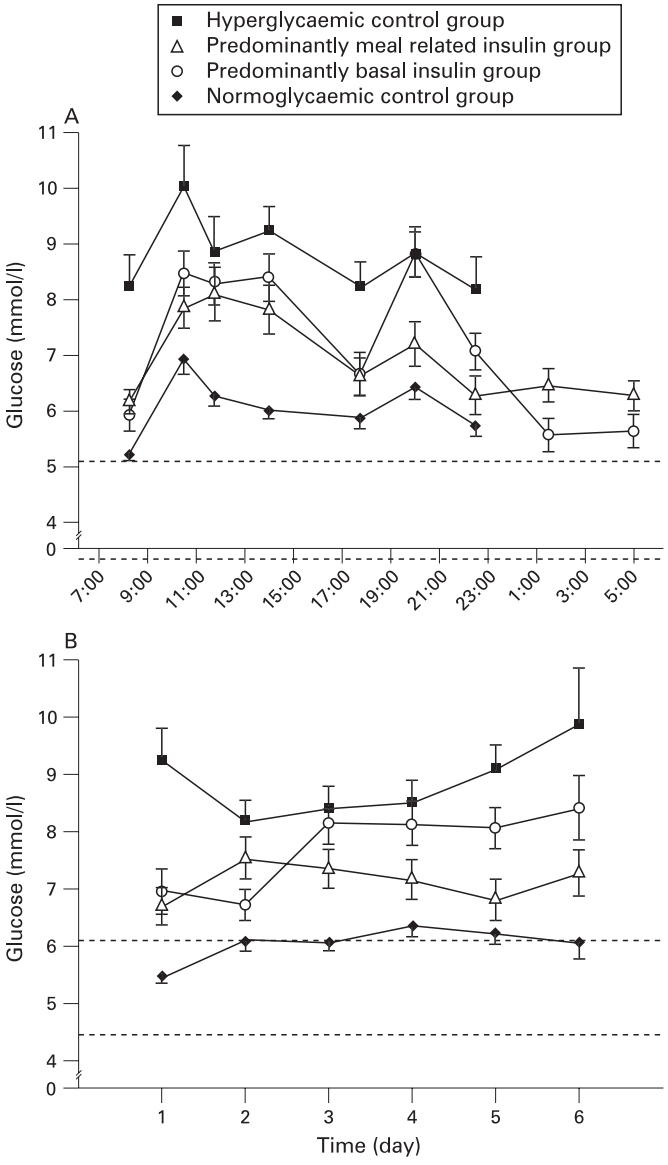

Figure 1 (A) Mean (SEM) glucose values pooled per time point per group. (B) Mean (SEM) glucose values pooled per day per group.

DISCUSSION

This study shows that prolonged strict glycaemic control in patients with ischaemia stroke is difficult to achieve with both of the studied regimens. This was mainly caused by postprandial hyperglycaemia (fig 1A). In common with others,[13 14] 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 randomised but uncontrolled study also found postprandial hyperglycaemia to be the main obstacle in achieving prolonged strict glycaemic control in acute stroke patients.[15] A large international randomised clinical trial investigating the use of strict glycaemic control in acute myocardial infarction failed because glucose lowering in the experimental group was inadequate.[16] Also, in the GIST-UK study, resuming oral intake was the likely reason that the effect of treatment discernable after 8 and 16 h had waned after 24 h.[5]

So how can we adequately lower hyperglycaemia in the first 5 days after stroke? Administering less basal insulin and more meal related insulin is likely to result in more favourable 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 hypoglycaemia. All hypoglycaemic 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.[17] Continuous enteral feeding, although more invasive, may facilitate strict glycaemic control in patients with acute ischaemic stroke.

Is hyperglycaemia 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 hyperglycaemia at admission, and that hyperglycaemia 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 24–36 h. 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 2–5 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.

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Competing interests: None.

Ethics approval: The study protocol was approved by the local ethics committee of the Academic Medical Centre, Amsterdam, and the University Medical Centre, Utrecht, The Netherlands.

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Neurological picture

Multiseptated post-traumatic cervicothoracic syrinx treated by two anatomically distant syringo-subarachnoid shunts

A 24-year-old man with a history of a complete T5 spinal cord injury requiring acute surgical decompression and stabilisation presented 4 months postinjury with progressive, ascending spinal cord symptoms consisting of upper-extremity weakness, paraesthesias and hypoesthesia. T_2-weighted MRI of the cervical and thoracic spine revealed central cystic dilation of the spinal cord (syringomyelia) from C6–T3 (fig 1A). Despite placement and subsequent revision of a T2–3 syringo-subarachnoid shunt with brief symptom resolution, the patient's symptoms recurred, and a repeat MRI demonstrated progression of the syrinx with multiple septations (fig 1B). He underwent a third operation for placement of a C5–6 syringo-subarachnoid shunt, which resulted in near complete resolution of his symptoms. Follow-up MRIs over the course of 2 years demonstrate complete and durable regression of the syrinx (fig 1C).

COMMENT

Post-traumatic syringomyelia, or formation of a cystic cavity within the spinal cord, is not uncommon and can occur in up to one-third of patients suffering spinal cord injuries. Syrinx formation is often associated with progressive neurological impairment including sensory or motor deficits, pain or autonomic dysfunction.[1] The mechanisms underlying syrinx formation are not known. One hypothesis suggests that the spinal cord becomes tethered at the injury site, and with fibrosis and scarring a subarachnoid block results in the transmission of CSF pressure to the syrinx cavity.[2] Treatment options are surgical and include shunting procedures (ie, syringo-subarachnoid shunts), subarachnoid reconstruction with duraplasty, or even cordectomy.[3 4] However, no approach has proven optimal for this difficult-to-treat problem. Herein, we present a rare and striking case of a large post-traumatic multiseptated syrinx that required placement of two anatomically distant syringo-subarachnoid shunts for successful symptom and radiographic resolution. In cases where imaging identifies multiple septations, it appears reasonable to attempt syringo-subarachnoid shunting at a second anatomical location.

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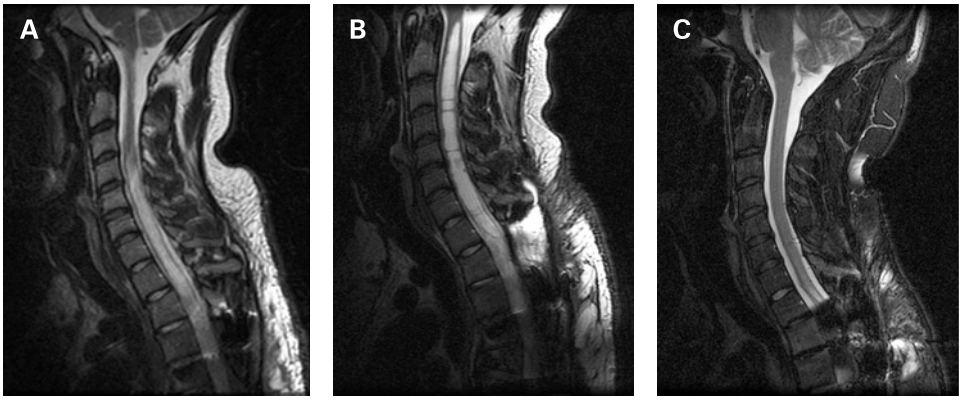

Figure 1 (A) T_2-weighted midline sagittal image at patient presentation demonstrating a cervicothoracic syrinx with associated oedema. (B) Subsequent sagittal T_2 image 1 month after the first surgery demonstrating cephalad expansion of the syrinx with the appearance of multiple septations. (C) Follow-up imaging 2 years after placement of the C5–6 syringo-subarachnoid shunt revealing resolution of the syrinx.

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