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Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke

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Hyperglycaemia in acute ischaemic stroke is traditionally associated with a worsened outcome. However, it is unclear whether the impact of hyperglycaemia on stroke outcome is similar in lacunar and non-lacunar infarctions.

The relation between serum glucose measured within 6 h after stroke onset and functional outcome was investigated in 1375 ischaemic stroke patients who had been included in two placebo-controlled trials with lubeluzole. The endpoint was a favourable outcome, defined as a modified Rankin Scale score ≤ 2 at 3 months. Classification into lacunar ($n=168$) and non-lacunar ($n=1207$) strokes was based on clinical criteria according to the Oxfordshire Community Stroke Project and findings on brain CT scan. Hyperglycaemia was defined as blood glucose >8 mmol/l. A possible concentration-dependent effect of glucose on outcome was investigated in both lacunar and non-lacunar stroke.

Multivariate analysis showed that hyperglycaemia was associated with decreased odds of a favourable outcome in non-lacunar stroke (OR 0.60; 95% CI 0.41–0.88, $P=0.009$), but with increased odds of a favourable outcome in lacunar stroke (multivariate OR for glucose >8 mmol/l: 2.70; 95% CI 1.01–7.13, $P=0.048$). In non-lacunar stroke, there appeared to be a concentration–effect relation, as the odds of favourable outcome gradually decreased with increasing glucose levels. In lacunar stroke, an association with favourable outcome was observed with glucose levels >8 mmol/l, but this beneficial effect diminished with more severe hyperglycaemia >12 mmol/l.

In conclusion, hyperglycaemia has a detrimental effect in non-lacunar stroke, but moderate hyperglycaemia may be beneficial in lacunar stroke.

Keywords: ischaemic stroke; hyperglycaemia; lacunar stroke; stroke subtype

Abbreviations: CGI = clinical global impression; CT = computed tomography; NSE = neuron-specific enolase

Introduction

Several studies have identified hyperglycaemia as an independent risk factor for death and more severe disability following acute ischaemic stroke (Woo *et al.*, 1988, 1990; Kiers *et al.*, 1992; Weir *et al.*, 1997; Capes *et al.*, 2001; Parsons *et al.*, 2002). Admission hyperglycaemia is common in acute stroke patients and exists across the range of stroke subtypes (Scott *et al.*, 1999). There is a great deal of interest in achieving glycaemic control in acute stroke patients (Walters *et al.*, 2006; Garg *et al.*, 2006), and a large randomized controlled trial, which employs the ‘Glucose–Potassium–Insulin’ infusion, is ongoing (Major ongoing stroke trials, 2002). However, the question is whether treating hyperglycaemia is warranted in all types of ischaemic stroke.

In animal models of reversible focal brain ischaemia, hyperglycaemia consistently increased infarct size (Lin *et al.*, 1998; Anderson *et al.*, 1999; Gisselsson *et al.*, 1999). Interestingly, however, in animals with end-artery infarcts hyperglycaemia had a beneficial effect and decreased infarct size (Ginsberg *et al.*, 1987; Prado *et al.*, 1988). The investigators suggested that these animal data might predict that lacunar infarctions would not be worsened by hyperglycaemia. A small study found that hyperglycaemia significantly increased serum levels of neuron-specific enolase (NSE), which is a biochemical marker for neuronal injury, in cortical strokes but not in lacunar strokes (Sulter *et al.*, 1998). Bruno and co-workers analysed the relation between admission blood glucose (within 24 h of stroke

onset) and clinical outcome in patients enrolled in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST), a placebo-controlled, randomized, double-blind trial to test the efficacy of a low-molecular weight heparinoid in acute ischaemic stroke. They found that hyperglycaemia worsened the outcome in non-lacunar stroke, but not in lacunar stroke; in the placebo arm, hyperglycaemic patients with lacunar stroke had a better outcome than normoglycaemic patients (Bruno *et al.*, 1999). This observation has not been widely taken into account by the medical community.

The aim of this study was to further explore a possible different response to hyperglycaemia in lacunar versus non-lacunar strokes.

Material and Methods

Patient selection

Data were obtained from the United States and Canadian Lubeluzole in Acute Ischaemic Stroke Study (LUB-INT-9) (Grotta, 1997), and the European and Australian Lubeluzole Ischaemic Stroke Study (LUB-INT-5) (Diener, 1998). Both studies were multicentre, randomized, placebo-controlled trials that investigated efficacy and safety of lubeluzole in acute ischaemic stroke and found that lubeluzole given within 6 h after stroke onset did not improve outcome at 3 months.

The target population was at least 18 years of age, presenting with substantial neurological deficit within 6 h of onset of an acute cerebral hemispheric ischaemic stroke. They had to be alert to or arousable by minor stimulation, and exhibit a significant motor deficit of the arm or leg.

Analyses

Blood was obtained within 6 h after stroke onset, and glucose concentration was determined at the local study centres. In accordance with previous studies hyperglycaemia was defined as a blood glucose >8 mmol/l (Weir *et al.*, 1997; Alvarez-Sabin *et al.*, 2003). To investigate a possible concentration-dependent effect, patients were stratified into five groups on the basis of increasing glucose levels: <7, 7–8, 8–10, 10–12 and >12 mmol/l.

Patients were divided into lacunar and non-lacunar stroke groups on the basis of clinical criteria according to the Oxfordshire Community Stroke Project (typical clinical lacunar syndrome and absence of evidence of cerebral cortical dysfunction) (Bamford *et al.*, 1991) and findings on brain Computed Tomography (CT) scans performed at baseline and between 4 and 7 days after admission. Stroke severity was assessed with the National Institute of Health Stroke Scale (NIHSS) in the LUB-INT-9 and with the European Stroke Scale (ESS) in the LUB-INT-5. In both studies, baseline stroke severity was also stratified into mild, moderate or severe by a clinical global impression (CGI). The modified Rankin Scale (mRS) was used to measure the

degree of residual disability at 3 months after stroke onset. Favourable outcome was defined as mRS ≤ 2 , which means that a patient has no or only slight disability while functionally independent (Uyttenboogaart *et al.*, 2005).

Statistical methods

For univariate analyses, Mann–Whitney U or Pearson Chi square tests were used, where appropriate. The relation between initial stroke severity (CGI) and glucose levels was assessed using Kruskal Wallis tests.

We performed logistic regression analysis to investigate whether hyperglycaemia was an independent predictor for functional outcome. We adjusted for possible confounders: age, stroke severity (CGI), lubeluzole/placebo treatment and diabetes. CGI was used instead of the stroke scales in order to analyse the pooled data of both trials. Interaction terms between glucose and CGI, and glucose and diabetes were tested.

SPSS version 12 was used for statistical analyses. Statistical significance was defined as a (two-sided) *P*-value <0.05.

Results

Out of the 1446 patients included, 1375 had confirmed ischaemic stroke, and these were the ones selected for this study. There were 168 patients with lacunar stroke and 1207 patients with non-lacunar stroke. Baseline characteristics of the patients are given in Table 1. There were 13 (8%) missing glucose values in the lacunar group and 107 (9%) in the non-lacunar group. At 3 months, 5 (3%)

Table 1 Patient characteristics at admission

	Lacunar (n = 168)	Non-lacunar (n = 1207)	<i>P</i>
Mean age, years (SD)	70 (12)	70 (13)	0.442*
Male gender	102 (61)	653 (54)	0.107
Left hemisphere	56 (33)	558 (46)	0.002
CGI			<0.001
Mild	26 (16)	34 (3)	
Moderate	102 (61)	446 (37)	
Severe	40 (24)	727 (60)	
Mean blood glucose, mmol/l (SD)	7.3 (3.3) [†]	7.9 (3.3) [‡]	<0.001*
<7 mmol/l	99 (64)	573 (52)	
7–8 mmol/l	17 (11)	188 (17)	
8–10 mmol/l	18 (12)	156 (14)	
10–12 mmol/l	9 (6)	74 (8)	
> 12 mmol/l	12 (8)	109 (10)	
Previous hypertension	109 (65)	659 (55)	0.012
Atrial fibrillation	21 (13)	369 (31)	<0.001
Coronary artery disease	53 (32)	450 (37)	0.148
Diabetes	33 (20)	255 (21)	0.658

Note: Values are numbers (%). SD = standard deviation. *P*-values calculated with Pearson χ^2 -test, unless otherwise indicated.

[†] = 13 missing and [‡] = 107 missing values. * = Mann–Whitney U test.

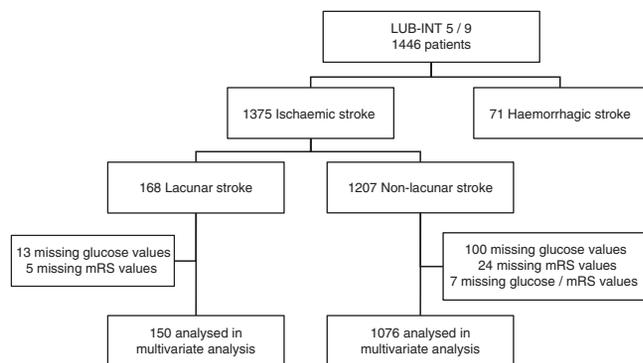


Fig. 1 Selected patients for the multivariate analyses.

and 31 (3%) mRS scores were missing in the lacunar and non-lacunar group, respectively (Fig. 1).

The distribution of glucose levels was not significantly different between the three categories of the CGI in lacunar stroke; median values: 6.3 mmol/l in mild, 6.2 mmol/l in moderate and 6.6 mmol/l in severe stroke ($P=0.79$). Median glucose values in the non-lacunar group were 6.4 mmol/l in mild, 6.8 mmol/l in moderate and 6.9 mmol/l in severe stroke ($P=0.09$).

In the univariate analysis (Table 2), hyperglycaemia was significantly associated with worse outcome in the non-lacunar group, and there was a trend towards better outcome in the lacunar group. Less severe stroke and younger age were significantly associated with a favourable outcome in both groups. Diabetes was associated with an unfavourable outcome in non-lacunar stroke.

The results of the multivariate analyses are presented in Table 3. Hyperglycaemia, defined as blood glucose >8 mmol/l, independently reduced the chance of a favourable outcome in non-lacunar stroke (OR 0.60; 95% CI 0.41–0.88, $P=0.009$), but increased the chance of a favourable outcome in lacunar stroke (2.70; 95% CI 1.01–7.13, $P=0.048$) (Table 3).

Concentration-dependent effects of glucose levels as assessed with multivariate analyses are shown in Fig. 2. In the non-lacunar infarction group, there was a concentration-dependent effect of higher glucose levels and lower odds of favourable outcome. In the lacunar group, the association with better outcome was mainly observed for glucose levels between 8 and 12 mmol/l, and diminished with levels above 12 mmol/l. There were no significant interactions between hyperglycaemia and CGI or diabetes in both the lacunar ($P=0.09$; $P=0.32$) and non-lacunar groups ($P=0.79$; $P=0.41$). In all regression models, higher age and more severe stroke were significant risk factors for an unfavourable outcome, but diabetes and lubeluzole treatment were not.

Discussion

This study confirms the detrimental effect of hyperglycaemia in non-lacunar stroke, and replicates the findings by

Bruno and co-workers that hyperglycaemia has no adverse effect on functional outcome in lacunar stroke; instead it may have a beneficial effect in this type of stroke (Bruno *et al.*, 1999). In our study, a beneficial effect of hyperglycaemia on functional outcome in lacunar stroke was independent of stroke severity, age, diabetes and treatment with lubeluzole. In the TOAST study population, a significant favourable effect on lacunar stroke was demonstrated only in the placebo group (Bruno *et al.*, 1999). Although limited by low patient numbers, stratification of patients on the basis of increasing glucose levels suggested that the beneficial effect in lacunar stroke may be confined to moderate hyperglycaemia, as it diminished with glucose levels above 12 mmol/l. In non-lacunar stroke, a concentration-dependent effect was observed, in a sense that increasing glucose levels decreased the chance of favourable outcome.

These findings may have important consequences for the treatment of hyperglycaemia in acute ischaemic stroke. Currently, the Glucose Insulin in Stroke Trial (GIST) is investigating whether glycaemic control in patients with acute stroke improves outcome. Patients with acute stroke, including lacunar infarctions, who are found to have raised plasma glucose >6.0 mmol/l, are treated with a controlled infusion of glucose/potassium/insulin to maintain glucose at 4–7 mmol/l (Major ongoing stroke trials, 2002). There is interest in setting up additional acute stroke studies using insulin infusion therapy (Garg *et al.*, 2006; Walters *et al.*, 2006). It is important to define the stroke type because treating hyperglycaemia to levels <7 mmol/l may not be necessary in lacunar infarctions, where, based on animal experiments (Ginsberg *et al.*, 1987; Prado *et al.*, 1988), it might adversely affect outcome. A standard symptom list could be used for this purpose, which has been validated to distinguish between different stroke subtypes in the acute phase (Aerden *et al.*, 2004).

Infarct size and outcome in cortical stroke is highly dependent on collateral circulation and the fate of the hypoperfused but still viable brain tissue, the penumbra. By using perfusion-weighted and diffusion-weighted magnetic resonance imaging, Parsons and colleagues showed that hyperglycaemia in patients with acute ischaemic stroke had a detrimental effect on the penumbra and led to an increased infarct size (Parsons *et al.*, 2002). Lacunar strokes are located in end-arteriolar vascular territories, with no collateral supply. Studies with diffusion weighted MRI and magnetic resonance spectroscopy suggest that a metabolically compromised area surrounding subcortical infarctions also exists (Labelle *et al.*, 2001).

The detrimental effects of hyperglycaemia on the cortical penumbra are not clearly understood, but can include increasing tissue acidosis secondary to anaerobic glycolysis, increased blood–brain barrier permeability, and vascular changes (Dietrich *et al.*, 1993; Anderson *et al.*, 1999; Martini and Kent, 2006). In the vasculature hyperglycaemia causes a pro-vasoconstrictive, pro-thrombotic and

Table 2 Univariate analysis: variables associated with functional outcome

Characteristic	Lacunar			Non-lacunar		
	Favourable outcome (n = 84)	Unfavourable outcome (n = 79)	OR (95%CI)	Favourable outcome (n = 329)	Unfavourable outcome (n = 847)	OR 95%CI)
Hyperglycaemia	24 (31) [†]	14 (19) [‡]	1.9 (0.9–4.1)	65 (22) [§]	267 (34) [¶]	0.5 (0.4–0.7)
Male gender	51 (61)	49 (62)	0.9 (0.5–1.8)	174 (56)	448 (53)	1.1 (0.9–1.4)
Mean age, years (SD)	67 (14)	73 (9)	–*	65 (15)	73 (11)	–*
CGI						
Mild	18 (21)	6 (8)	10.0 (3.1–33) ¹	21 (6)	12 (1)	9.4 (4.5–19.7) ¹
Moderate	57 (68)	43 (54)	4.4 (1.9–10.3) ²	197 (60)	236 (28)	4.5 (3.4–6.0) ²
Severe	9 (11)	30 (38)		111 (34)	599 (71)	
Left hemisphere	25 (30)	28 (35)	0.8 (0.4–1.5)	153 (47)	393 (46)	1.0 (0.8–1.3)
Diabetes	15 (18)	18 (23)	0.7 (0.3–1.6)	55 (17)	193 (23)	0.7 (0.5–0.9)
Hypertension	57 (68)	50 (63)	1.2 (0.6–2.3)	174 (53)	466 (55)	0.9 (0.7–1.2)
Lubeluzole	53 (63)	38 (48)	1.8 (1.0–3.4)	163 (50)	431 (51)	0.9 (0.7–1.2)

Note: Values are numbers (%). Favourable outcome means a modified Rankin score of 0–2. Hyperglycaemia defined as >8 mmol/l. OR = odds ratio (95% confidence intervals). CGI = clinical global impression of stroke severity. * Mann–Whitney U test, P < 0.001. † = 7 missing, ‡ = 6 missing, § = 33 missing and ¶ = 67 missing values. ¹ Odds ratio's comparing mild with severe stroke. ² Odds ratio's comparing moderate with severe stroke.

Table 3 Multivariate analysis: predictors for favourable outcome

	Lacunar			Non-lacunar		
	OR	95% CI	P	OR	95% CI	P
Hyperglycaemia	2.70	1.01–7.13	0.048	0.60	0.41–0.88	0.009
Age (years)	0.94 [†]	0.91–0.97	<0.001	0.95 [†]	0.94–0.97	<0.001
CGI	0.21 [‡]	0.10–0.42	<0.001	0.23 [‡]	0.17–0.30	<0.001
Diabetes	0.44	0.15–1.29	0.133	1.00	0.66–1.53	0.993
Lubeluzole	2.03	0.94–4.37	0.072	1.01	0.75–1.36	0.963

Note: Hyperglycaemia defined as blood glucose > 8 mmol/l. Favourable outcome means a modified Rankin score of 0–2. † Odds ratio for each year increase. ‡ Odds ratio for comparing severe stroke with mild stroke.

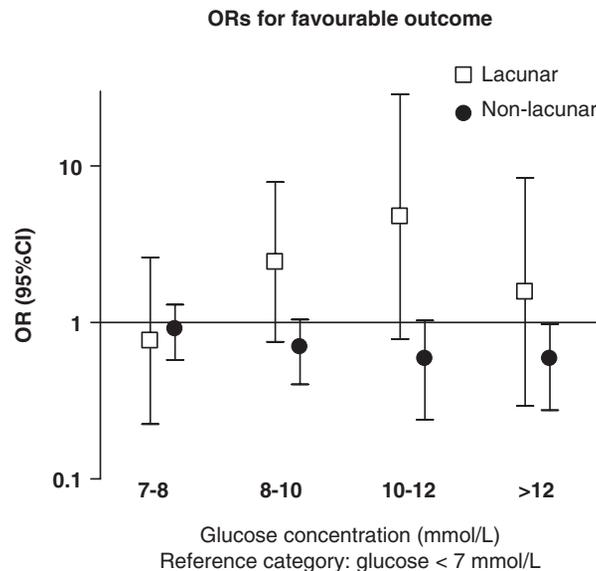


Fig. 2 Relation between hyperglycaemia and functional outcome in lacunar and non-lacunar stroke. Adjusted for clinical global impression, age, lubeluzole treatment and diabetes. Favourable outcome defined as mRS score 0–2 at 3 months.

pro-inflammatory phenotype, which severely compromises the microvasculature and collateral circulation and enhances reperfusion injury (Martini and Kent, 2006). Lacunar stroke associated with limb weakness, such as in our study, is situated in white matter and damages axons and glial cells. Lactate produced by astrocytes is an important rescue source of energy for axons (Brown *et al.*, 2003) and perhaps also for oligodendrocytes (Sanchez-Abarca *et al.*, 2001). Therefore, it is tempting to speculate that increased lactate production due to hyperglycaemia in lacunar ischaemia might fuel and salvage axons and oligodendrocytes.

A strong point of this study is that all patients were well documented, and that blood glucose was measured within 6 h of stroke onset. A limitation of the study is the relatively low number of patients with lacunar strokes and the fact that the study was not powered to detect effects of hyperglycaemia.

In conclusion, our study suggests that moderate hyperglycaemia in acute lacunar stroke may be beneficial. This finding stresses the need to distinguish lacunar stroke from cortical stroke in an early stage, especially when therapies to normalize blood glucose are considered.

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