Sugar and NICE – Aggressive Hyperglycaemic Control in Ischaemic Stroke and What Can We Learn from Non-Neurological Intensive Glucose Control Trials in the Critically Ill?

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Hyperglycaemia is a common phenomenon after cerebral ischaemia (for that matter, after most acute medical or surgical conditions), and clinicians have certainly been itching to treat. But should we? The devil is in the details.

Continuous assessment of blood glucose levels and qualified treatment are often noted to be core components of specialized stroke care [1]. Expert statements have taken a somewhat sinusoidal course when discussing the matter. In 1994, the Stroke Council of the American Heart Association said that it may be a good idea to treat hyperglycaemia in patients with stroke just as one would treat hyperglycaemia in 'other persons with elevated blood glucose' [2]. The guideline was substantiated in 2003, with treatment then being warranted should blood glucose levels exceed 16.6 mmol/l (300 mg/dl) [3]. Europeans were more stringent, finding that a cut-off of 10 mmol/l (180 mg/dl) would be optimal [4, 5]. The American Stroke Association followed this lead and in 2007 revised its suggestions and noted that treatment should begin above 11.1 mmol/l (200 mg/dl), possibly as low as 7.8 mmol/l (140 mg/dl) [6]. In 2008, instead of continuing on the downward track and effectively postulating fasting normoglycaemia below 5.5 mmol/l (99 mg/dl), the European Stroke Organization retained its previous recommendation of 10 mmol/l (180 mg/dl) [7].

There are two lines of evidence that drove the evolution of these guidelines:

(1) The weight of arguments that suggest an association between high glucose levels and detrimental outcome has substantially increased in the last few years. Observational studies, both naturalistic [8, 9] and trial-associated [10–12], have reported higher morbidity and mortality in patients with initial hyperglycaemia. (Note that there is neither consensus as to what actually defines 'initial' – is it a 1-measurement baseline, continuously elevated levels within the first 24 h or other timelines? – nor is there a clear definition of when hyperglycaemia necessitates treatment [13].) Moreover, experimental data have underlined the association. Early neuropathological animal studies provided evidence that hyperglycaemia augments morphological brain damage in acute stroke [14, 15]. Imaging studies in hyperglycaemic animals subjected to ischaemic stroke corroborated these findings: hyperglycaemia is associated with enhanced MRI diffusion-weighted imaging alterations [16] and reduced hemispheric cerebral blood volume [17]. Importantly, equivalent correlations have been established in MRI studies in human subjects. Acute hyperglycaemia is associated with reduced salvage of perfusion-impaired tissue and larger final infarct size [18, 19]. This is also true for patients treated with intravenous tissue plasminogen

activator, where acute hyperglycaemia is further correlated with lower recanalization rates [20–22]. But is association really causality? Hyperglycaemia has been related to the size of the ischaemic lesion, stroke location, age and prior as well as unrecognized diabetes, among other variables [23–25]. There remains considerable controversy over whether hyperglycaemia as such is a truly independent predictor of detrimental effects or just plays a role as a prominent confounder or effect mediator [26].

(2) If one accepts a causal pathway, then (and only then) does it seem truly promising to treat hyperglycaemia. Undoubtedly, the development of the consensus guidelines was influenced by the very encouraging results from large non-neurological critical-care trials. Though the pathophysiology of specific end-organ damage due to hyperglycaemia in ischaemic stroke may be different to that expected in non-neurological cohorts [for a review, see 26–28], there is also clear overlap, paradoxically often scotomized in the literature: both populations are acutely and seriously ill, and share many complications contributing to higher morbidity and mortality. The first large randomized controlled trial addressing the question whether aggressive glucose normalization may be beneficial was performed in Leuven, Belgium, in 2001 ($n = 1,548$) [29] – it was to become highly influential. Patients having undergone cardiac surgery and other surgical procedures were either treated with an intravenous insulin regimen, targeting 4.4–6.1 mmol/l (80–110 mg/dl) or were treated only when blood glucose concentrations exceeded the renal threshold (i.e. 12 mmol/l or 215 mg/dl). The authors showed an absolute risk reduction in in-hospital mortality of 3.4% favouring treatment. Though a subsequent trial by the same study group, now also involving patients with serious medical conditions, missed significance in respect to mortality (overall morbidity was however reduced, especially in those having undergone longer periods of intervention), such a momentum was now there that many commentators were led to conclude that normoglycaemia should be a goal in the care of critically ill patients independently of anything else; those involved in the care of stroke patients were quick to follow [27, 30].

Recently Terence Quinn and Kennedy Lees thoroughly reviewed the ‘but should we’ question whether or not to treat hyperglycaemia in patients with ischaemic stroke in this journal [28]. They highlighted that though research has been intensified in recent years, there is little evidence that supports pro-active treatment, much less aggressive intervention resulting in normal fasting blood glucose concentrations. The only large-scale prospective

randomized trial to date (i.e. GIST-UK; $n = 933$) produced neutral results. The active normalization (4–7 mmol/l or 72–126 mg/dl) of blood glucose using glucose-potassium-insulin infusions (GKI) failed to reduce mortality at 90 days or ameliorate neurological outcome. Smaller studies, using different treatment regimens (there are numerous treatment modalities and algorithms of varying complexity suitable for glycaemic control: GKI, subcutaneous sliding scale schemes, varying intravenous insulin infusion protocols, with or without concomitant glucose administration), have also remained neutral as to the treatment goals studied (i.e. mortality, neurological outcome) [31–35]. The GIST-UK, besides not having reached the intended study size due to slow recruitment, may have ‘failed’ because the GKI regimen insufficiently lowered blood glucose concentrations (i.e. 0.57 mmol/l or 10.3 mg/dl) – Quinn and Lees conclude that ‘to achieve meaningful clinical improvements, glucose change must be substantial ...’ [28]. Intravenous insulin infusion protocols may in fact have a higher efficacy [31, 33, 35] and were successful in non-neurological trials, as noted above [29].

The GIST-UK had further potential shortcomings: The treatment duration was short (limited to 24 h), much shorter than in the medical and surgical study settings [36]; there is some evidence that glucose dysregulation persists after the first day following the onset of ischaemia and may be detrimental in the long run [11, 35]. Furthermore, study initiation was well after stroke onset (i.e. median ‘time-to-needle’ was 14 h), potentially missing the time window of the most effective treatment.

So were we stroke folks doing it all wrong? Well, maybe not. In the meantime, the results of the largest study to date (NICE-SUGAR study; $n = 6,104$), a multi-centre trial testing the effect of an intravenous insulin regimen, lowering blood glucose concentrations to the range of 4.5–6 mmol/l (81–108 mg/dl), versus an approach with target values of 8–10 mmol/l (144–180 mg/dl) in a non-neurological mixed acutely ill population (approx. one third surgical patients), have been published [37]. Though not completely unexpected, they were sobering: intervention actually increased the absolute risk of mortality by 2.6%. Though there are methodological differences between the Leuven and the NICE-SUGAR studies, and possible confounders may play a significant role in the latter trial [38], the results do lend serious support to commentators that have questioned the benefit of aggressive therapy in critically ill patients [39, 40].

Do the results of this trial, powerful as they are, effectively end attempts to ‘significantly’ treat hyperglycaemia

in the critically ill – including stroke patients? The devil is in the details:

- While there is now much rumination in the critical-care community as to ‘what went wrong’, a possible ‘compromise’ may be evolving, with reverberations also for patients with cerebral ischaemia: clearly at odds with previous thinking, clinical improvement may not depend on substantial glucose change; rather lower blood glucose levels, but not necessarily normoglycaemia, could be the optimal target. In fact in the Leuven trials, three quarters of the mortality reduction were accounted for by patients reaching a range of 6.1–8.3 mmol/l (110–150 mg/dl), but not lower; the NICE-SUGAR results effectively reflect benefit in this range (the mean concentration of the control group was 7.9 mmol/l or 142 mg/dl, with almost 70% of this arm actually having received insulin during the course of the study). There is also some indication that a mid-range glucose concentration (i.e. 8.6 mmol/l or 155 mg/dl) may represent a watershed in stroke patients, with outcomes of those lying below this value being better [41]. It must, however, be fairly said that no studies to date have tested interventions leading to intermediate glucose levels versus the conventional approach of ‘wait and see’, treating only when concentrations surpass the renal threshold.

Other considerations also seem relevant:

- Though diabetics have been routinely included in these trials (both stroke and other critical-care cohorts), they may in fact not benefit from stricter glycaemic control [36]. Diabetics are potentially adapted to higher blood glucose concentrations, and they do show a significantly lower mortality at higher glycaemic levels in the acute setting than non-diabetics, both in ischaemic stroke [8] and in other critical illnesses [42, 43]. Patients with non-diabetic hyperglycaemia, alternatively coined reactive [44] or stress [8] or non-diabetic post-stroke hyperglycaemia [28], may be the more suitable treatment target.

- Feeding strategies could play a pivotal role in light of high insulin load. Though there is no consensus as to when and how to initiate feeding, in the successful Leuven trial, insufficient enteral feeding was supplemented by a parenteral regimen, guaranteeing sufficient calories; the NICE-SUGAR trial relied solely on enteral feeding, effectively being hypocaloric. In the stroke setting, things become even more complicated; due to lack of specific trials that investigate the effect of different caloric regimens commencing very close to onset, there is evidence that enteral tube feeding starting within a couple of days reduces mortality versus avoiding tube feeding [45]. Moreover, under intensive insulin therapy, continuous

tube feeding has been shown to increase the efficacy of glycaemic control and to reduce hypoglycaemic events [46].

- The stress on caregivers is enormous. Frequent measurements and adjustments can only be performed in a highly dedicated setting. Glucometers should be accurate and standardized; optimally automated continuous measurements should be preferred, once available.

There are also stroke-specific pathophysiological issues:

- Treatment should be commenced early on, preferably in the same time window as applicable for thrombolysis, targeting salvageable tissue [28], and sustained for longer periods of time (e.g. 3–5 days [35, 47]).

- Direct and indirect potential toxic effects of hyperglycaemia are more prominent in larger infarctions. Moreover, patients with lacunar stroke seem to profit from hyperglycaemia up to a concentration of 12 mmol/l (216 mg/dl) [48, 49].

But then should we treat hyperglycaemia in ischaemic stroke? The answer is yes and no, applicable to both future trials and the individual basis. We believe that treatment is warranted, targeting an intermediate range (6.7–8.3 mmol/l or 110–150 mg/dl) in non-diabetic patients with non-lacunar stroke. We would advocate an immediate start of therapy, sustained for at least 3 days after onset, using an intravenous infusion protocol, but only if a highly dedicated monitoring and treatment infrastructure is available. Feeding should be started in parallel, enterally if possible, or otherwise parenterally, to guarantee sufficient calorie intake.

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