

What goes up should come down?

Hyperglycaemia following stroke

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'Most cases of stroke improve and many recover.....the tendency to improve by cerebral compensation and the spontaneous disappearance of indirect symptoms is very marked thus making it difficult to estimate the actual influence of treatment employed' (Gowers 1888)

More than a century after William Gowers first acknowledged the difficulties that exist in demonstrating the influence of treatment in acute stroke, there is still no safe, simple and effective medical therapy that can be administered to the majority of patients to limit neuronal damage and improve recovery. Recent advances in acute stroke treatment have been either consistently disappointing (neuroprotective therapy) or fraught with controversy regarding risk/benefit (thrombolysis) and attention is once again being directed towards physiological variables that may influence stroke outcome.

In the absence of a proven medical therapy there is increasing evidence that the provision of specialist stroke care within acute and rehabilitation stroke units is associated with reductions in mortality, dependency and subsequent need for institutional care [1]. It was initially proposed that these benefits are the result of co-ordinated care, staff specialization and education, however most recent evidence from acute stroke unit studies suggests that factors such as early hydration and mobilization are also important in distinguishing specialist from conventional care [2]. In parallel to the evidence supporting stroke unit care there has been a plethora of clinical studies linking global and local metabolic factors to stroke outcome and it is only now that clinical trials are being conducted to explore these associations.

One of the strongest and indeed first described associations between a physiological variable and stroke outcome exists for hyperglycaemia where there is increasing evidence from both animal and clinical studies that Diabetes Mellitus (DM) and/or hyperglycaemia is associated with an adverse prognosis. Hyperglycaemia is a frequent finding following acute stroke [3] and may reflect the metabolic stress of the acute event, so-called

stress hyperglycaemia, and/or underlying impaired glucose metabolism (DM or Impaired Glucose Tolerance).

Both insulin dependent and non-insulin dependent diabetes are major risk factors for stroke [4, 5]. Diabetes has also been shown to be associated with increased mortality and reduced functional outcome after stroke [5–7]. Several large clinical studies have now demonstrated a positive association between a raised blood glucose and poor outcome from stroke; greater mortality and reduced functional recovery [6, 8–10]. What is not entirely clear is to what extent hyperglycaemia is a 'normal' physiological response to stroke or whether hyperglycaemia per se increases cerebral damage in the acute phase. There are many potential mechanisms by which hyperglycaemia can exert a harmful effect upon cerebral tissue and it is probable that an important relationship exists, not only between glucose and stroke outcome, but also between insulin and neuroprotection [11]. It now remains to be determined whether lowering and maintaining 'normal' glucose levels in the immediate aftermath of stroke, combined with the administration of insulin as an acute treatment, can modify this outcome. The United Kingdom Glucose Insulin in Stroke Trial (GIST UK) is a multi-centre randomized controlled trial, which seeks to determine whether outcome from acute stroke can be favourably influenced by glucose/potassium/insulin (GKI) induced and maintained euglycaemia [12]. Treatment comprises intravenous GKI or normal saline therapy for 24 hours in acute stroke patients presenting with mild to moderate hyperglycaemia (admission plasma glucose 6.1–17 mmol/l) within 24 hours of symptom onset. The objective of the GKI treatment is to maintain capillary blood glucose between 4–7 mmol/l for the duration of the infusion. The primary outcome measures for the study are all cause mortality and the proportion of patients with a poor outcome (modified Rankin score 4–6 including death) at 12 weeks between treatment groups.

Associations between other physiological variables and stroke outcome have also been demonstrated including blood pressure (hypertension and hypotension), temperature, oxygen saturation and markers of inflammation. Whilst each of these may indeed exert a direct harmful effect upon cerebral metabolism it is probable that they also have a synergistic effect with glucose through their association with the acute stress response following stroke [13].

The Royal College of Physicians National Clinical Guidelines for Stroke highlight the importance of organized stroke care and the need to consider the early management of hyperglycaemia, blood pressure, hydration and pyrexia [14]. Recognizing that there is no true evidence base to direct intervention for these variables they add the caveat that local clinicians should discuss their own guidelines. Unfortunately these guidelines have become slightly misinterpreted when translated into the National Service Framework for Older People [15]. In Standard 5 (Stroke) the Framework specifically states that 'immediate management to improve chances of survival and minimize risk of complications should include; appropriate control of blood pressure, maintenance of hydration and oxygen saturation and management of hyperglycaemia and fever'. Regrettably these are precisely the areas where there is no evidence and a pressing need exists for clinical trials to clarify the risks/benefits of such routine interventions. Current studies such as ENOS (blood pressure lowering) and PISA-PAPAS (reduction in body temperature) should help to expand the evidence base in these areas. [16, 17] Furthermore, the haphazard implementation of local strategies for these physiological variables is a missed opportunity to properly evaluate and implement proven interventions to correct physiological variables. A good analogy for this comes from cardiology where clinical trials in patients with acute myocardial infarction (MI) and DM/hyperglycaemia have shown that treatment with a glucose/potassium/insulin infusion (GKI) conferred significant reductions in mortality (52% relative risk reduction) up to 12 months after the acute event [18]. As a result treatment of hyperglycaemia post MI using an evidence-based regimen is now routine practice.

Recognition of the benefits of organized and co-ordinated stroke care has led to the wide-scale introduction of acute stroke units and specialist stroke rehabilitation services. In addition, clinical trial evidence demonstrates that thrombolysis with alteplase is a promising treatment for acute stroke if given <3 hours from symptom onset [19]. There is accumulating evidence that the risks of thrombolytic therapy (intracranial haemorrhage) may be directly influenced by physiological variables that include not only blood pressure but also blood glucose levels [20]. The design and implementation of clinical trials in acute stroke in the future will need to take into account the importance of physiological variables in influencing not only patient

outcome but also the potential safety and thereby efficacy of the treatment being evaluated.

Advances in the management of stroke have been extremely limited when compared with acute myocardial infarction. It is only following the widespread introduction of specialist stroke services that comparable clinical trials can be undertaken. Stroke remains a disease primarily of older people for whom a multidisciplinary approach will always be essential. It is incumbent upon physicians with a special interest in and responsibility for older people to lead the development of future clinical trials to ensure their applicability to the majority affected by this disease.

Key points

- Hyperglycaemia following acute stroke is associated with increased mortality and poor functional recovery.
- The Glucose Insulin in Stroke Trial (GIST – UK) is investigating whether treatment of mild – to – moderate hyperglycaemia in patients with acute stroke improves clinical outcomes.
- Clinical trials are required to explore the risks and benefits of clinical interventions which modify other physiological variables e.g. hypoxia, fever, blood pressure.

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