Letters to the Editor

Stroke welcomes Letters to the Editor and will publish them, if suitable, as space permits. They should not exceed 750 words (excluding references) and may be subject to editing or abridgment. Please submit letters in duplicate, typed double-spaced. Include a fax number for the corresponding author and a completed copyright transfer agreement form (published in every issue).

Poststroke Hyperglycemia Management: More Answers Required

To the Editor:

We read with interest the latest article discussing the immediate management of poststroke hyperglycemia.1 Gray and colleagues advocate the use of glucose-potassium-insulin (GKI) infusions to maintain euglycemia within the first 24 hours poststroke, the rationale for this being that plasma glucose level peaks and exerts its harmful effects on the ischemic penumbra within this time period.

However, in reality, nonphysiological surges of plasma glucose levels are also likely to occur beyond 24 hours and may be caused by a number of factors including early enteral feeding, use of solutions containing glucose, and secondary complications (eg, sepsis). Therefore, it may be conceivable that the detrimental effects of hyperglycemia persist beyond the first 24 hours of stroke, which Gray and colleagues have not addressed. Indeed, we demonstrated that changes in glycated serum protein levels in the first 2 weeks after stroke were significantly associated with an increase in death and disability at 3 months, after adjusting for stroke severity.2 In vitro studies have suggested that glycated proteins induce proinflammatory cytokines leading to endothelial cell damage and subsequent vascular occlusion.3

The use of intensive insulin therapy in maintaining blood glucose <6.1 mmol/L in critical care patients beyond 24 hours has also been shown to be beneficial in reducing in hospital mortality, sepsis, and renal failure.4 The benefits were seen irrespective of whether patients were rendered hyperglycemic with enteral or parenteral feeding. From the study by Gray and colleagues, it is not clear whether patients included in their trial were fed enterally, parenterally, or not at all during the first 24 hours of their stroke. Whether the complexity of maintaining euglycemia coupled with early enteral feeding in stroke patients can be achieved practically with insulin remains to be seen. If so, this would suggest that intensive insulin therapy may be warranted in all stroke patients who develop hyperglycemia while receiving early nutritional support.

There are a number of unanswered questions with regard to glycemic control poststroke, including what insulin regime should be used (GKI infusion or continuous insulin infusion), the duration of glycemic control, and the level of plasma glucose that should be attained. It is also conceivable that insulin could have potential benefits independent of its euglycemic effects. In vitro studies have shown that insulin inhibits tumor necrosis factor and macrophage inhibitory factor, reducing prothrombotic sequelae and septic complications, respectively.5 Both these actions could be crucial in limiting further tissue damage within the ischemic penumbra. We would agree with Gray and colleagues that the lack of evidence of immediate glycaemic control poststroke has led to wide variations in the use of insulin acute.6 The lack of evidence, however, should not be used as a form of justification for nonintervention pending the results of randomized controlled trials. Until more data are available, current consensus suggests that restoration of hyperglycemia should be encouraged.7 We look forward to the results of the GIST-UK outcome data.


Response:

We are pleased to respond to the letter from Dr Bhalla et al regarding our manuscript entitled Poststroke Hyperglycemia: Natural History and Immediate Management.8 In opening they suggest that we have advocated the use of glucose, potassium, and insulin infusions to maintain euglycemia. Unfortunately, they have not understood the gist (sic) of our paper. Although we have demonstrated the safety and efficacy of glucose, potassium, and insulin infusions in maintaining euglycemia, we clearly state in our concluding paragraph that the “GIST GKI regimen is the only evidence-based approach from which we can describe ‘how’ to manage acute PSH.”

In discussing late nonphysiological surges in hyperglycemia the authors are presumably attempting to differentiate between early poststroke hyperglycemia and sustained hyperglycemia. Sustained hyperglycemia is more likely to be unrelated to the acute neurological event rather than a consequence of underlying dysglycemia, and thus potentially reflects medium- and longer-term management of diabetes, impaired glucose tolerance, and nutrition. We refer the authors to our recently published data demonstrating the high prevalence of recognized and unrecognized glucose intolerance in acute stroke: one third of all acute stroke patients may have diabetes; for patients presenting with poststroke hyperglycemia, impaired glucose tolerance or diabetes mellitus is present in two thirds of survivors.2 Of course, persisting hyperglycemia may influence outcome, but this was not the aim of an acute stroke study into the first 24 hours of acute care.

Although sustained hyperglycemia may be negatively associated with stroke outcome, the process of care leading to sustained hyperglycemia is important in explaining such an association. Whether our patients received supplemental feeding or not, the point of the study was to show the safety and efficacy of the GKI infusion in maintaining early euglycemia. For information, none of our patients received supplemental feeding during the GKI

Anthony Rudd, FRCP
Division of Stroke Medicine
St Thomas’ Hospital
London, UK


Letters to the Editor

Stoke welcomes Letters to the Editor and will publish them, if suitable, as space permits. They should not exceed 750 words (excluding references) and may be subject to editing or abridgment. Please submit letters in duplicate, typed double-spaced. Include a fax number for the corresponding author and a completed copyright transfer agreement form (published in every issue).
infusion (which on average was delivered within 12 hours of stroke symptom onset), and none of our patients were “rendered hyperglycemic.” Patients received enteral feeding as soon as they were able to safely swallow. Despite this, mean plasma glucose levels remained significantly lower in the GKI treatment group throughout the study.

As Dr Bhalla and colleagues acknowledge, there are a number of unanswered questions regarding poststroke glycemic control, and for a review of these issues we refer them to our previous publications in this area.3,4 The work of Van den Berghe5 is of interest, although it remains to be determined whether benefit is conferred through glucose lowering per se rather than intensive insulin plus nutrition. In that study there was a mean morning blood glucose lowering of 2.8 mmol/L between intensive and conventional insulin treatment groups. We would also point out that all patients initially received intravenous glucose (200 to 300 g per 24 hours) before feeding the following day. We would argue that it is premature to suggest that intensive insulin therapy is warranted in all stroke patients who develop hyperglycemia while receiving early nutritional support; rather, we first need to determine whether correcting hyperglycemia plus early maintenance of euglycemia is beneficial, and then whether nutritional support plus euglycemic control confers additional benefit.

If, as the authors acknowledge, the early care of hyperglycemia in stroke patients remains subjected to such variation, then the practicalities of delivering a trial with standardized nutrition, hydration, and glycemia will be a major challenge. The message from our study is that early GKI infusions as delivered in the GIST protocol are effective and safe in maintaining early euglycemia following stroke. Thus, there is an evidence base from which guidelines for managing hyperglycemia can be derived, rather than relying on the development of local protocols.6

Finally, in our study we present evidence for the safety and efficacy of GKI infusion in the early management of poststroke hyperglycemia. This is hardly a justification for nonintervention and we again refer the authors to our published conclusions: GKI infusions as described in the GIST trial are a safe and effective means of correcting PSH and maintaining euglycemia in the acute phase of stroke. The clinical benefits of routine management of hyperglycemia remain to be determined.

Christopher S. Gray, MD, FRCP
Professor of Clinical Geriatrics
University of Newcastle upon Tyne
Sunderland, UK

Janice E. O’Connell, BSc, MBChB, FRCP
Senior Lecturer in Geriatric Medicine
University of Newcastle upon Tyne
Sunderland, UK

Poststroke Hyperglycemia Management: More Answers Required
Ajay Bhalla, David Hargroves and Anthony Rudd

Stroke. 2004;35:e341-e342
doi: 10.1161/01.STR.0000135299.31445.0f
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/7/e341

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/