Commentary

Intensive glycemic control in traumatic brain injury: what is the ideal glucose range?

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See related research by Meier *et al*., http://ccforum.com/content/12/4/R98

Abstract

Intensive glycemic control has become standard practice. Existing data, however, suggest this practice may have adverse consequences for traumatic brain injury. The recent paper by Meier and colleagues suggests that intensive glycemic control may be deleterious. The present article explores existing literature surrounding this controversy, and outlines the literature that raises concern. Finally, I suggest an alternative course of action that may enable control of glucose in an optimal range.

The treatment of traumatic brain injury centers on diligent intensive care and the prevention of secondary insults. One of the suspected secondary insults is early hyperglycemia. There is significant literature that associates early systemic hyperglycemia with poor neurological outcome after traumatic brain injury.

The recent paper by Meier and colleagues raises new concerns about the control of hyperglycemia [1]. Hyperglycemia has repeatedly been associated with poor outcome after traumatic brain injury [2-5], with glucose values >300 mg/dl (16.6 mmol/l) uniformly associated with fatal traumatic brain injury in one study [3]. Continued hyperglycemia with glucose values >200 mg/dl (11.1 mmol/l) has been associated with poor outcome [4]. While intensivists are focused on preventing hyperglycemia, and expend much clinical effort in achieving normoglycemia, it remains unclear whether intensive glycemic control during the intensive care stay is beneficial.

There has been a great deal of enthusiasm for intensive glycemic control after landmark studies by Van Den Berghe and colleagues [6,7]. The initial prospective randomized single-center study of surgical intensive care unit patients included a small number of brain-injured patients. The overall results indicated convincingly that intensive glycemic control was beneficial, and subsequent *post-hoc* analysis indicated that intensive glycemic control resulted in less neurologic complications.

The most recent medical intensive care unit study of intensive glycemic control was less convincing [8]. In the latter study, mortality was not reduced in the overall intention-to-treat group, and a very small positive effect of intensive glycemic control on mortality was seen in patients treated for >3 days. At the same time, there remains some concern that intensive glycemic control (4.4 to 6.1 mmol/l) is not appropriate for brain-injured patients, and may elicit secondary injury [9]. Using cerebral microdialysis in brain-injured patients, Vespa and colleagues found that the infusion of insulin to achieve intensive glycemic control resulted in profound reductions of brain glucose and in elevation of biomarkers indicating cellular distress – namely glutamate and lactate/pyruvate ratio. This finding has been replicated in patients with subarachnoid hemorrhage [10], in which patients with intensive glycemic control have elevated microdialysis glycerol and elevated lactate/pyruvate. In addition, there is evidence that moderate hyperglycemia (12 to 15 mmol/l) is not associated with adverse events after brain injury [11].

A small single-center randomized trial comparing intensive glycemic control with moderate hyperglycemia in subarachnoid hemorrhage patients recently failed to demonstrate a benefit on mortality or vasospasm ischemic insults [12]. There is therefore great uncertainty about how best to control systemic glycemia after brain injury.

It is in this context that we consider the recent paper of Meier and colleagues [1]. In this paper, Meier and colleagues performed a retrospective study comparing the incidence of hypoglycemia and other adverse consequences when intensive glycemic control (goal of 3.5 to 6.5 mmol/l) was used versus when loose glycemic control (goal of 5 to 8 mmol/l) was used. The results are complex and do not indicate that

intensive glycemic control is beneficial overall. Specifically, the authors report that the incidence of hypoglycemia and intracranial hypertension is higher in those patients undergoing intensive glycemic control during the initial week after injury, and that the rate of bacteremia is higher and urinary tract infections are worse too. While there was a trend towards a better intracranial pressure profile during the second week after injury in the intensive control group, the preponderance of data points against the use of intensive glycemic control. This finding stands in sharp contrast to the results of Van Den Berghe and colleagues [8], in which the incidence of intracranial hypertension and of mean intracranial pressure was less in the group undergoing intensive glycemic control. Moreover, Meier and colleagues report a trend towards worsened survival at 21 days after brain injury in the intensive glycemic control group. This unexpected worsening of mortality is cause for great concern among those who advocate intensive glycemic control in brain trauma.

The stage is clearly set for prospective study of glycemic control. In our center we have begun to use cerebral microdialysis and positron emission tomography to prospectively identify the ideal lowest glycemic range that appears to be safe from the brain's metabolic perspective. The operational definition of a lowest safe glycemic range may not be uniform among patients, and is as yet unclear. The lowest safe glycemic range will probably be defined by the serum glucose value that does not elicit metabolic disturbance in the brain, as measured by sophisticated brain monitors such as microdialysis and positron emission tomography.

Once the lowest safe glycemic range is identified, a multicenter randomized control trial will be needed to determine whether some form of glycemic control is better than moderate hyperglycemia for brain-injured patients. For now – given the cumulative evidence that intensive glycemic control is associated with metabolic distress [9], with increased hypoglycemia, with worsened intracranial pressure, and with worsened mortality [1] – the ideal range for glycemic control is unclear.

Competing interests

PMV receives funding on the subject of glycemic control.

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