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Umer Shoukat, MD
Department of Neurological Surgery, Thomas Jefferson University, umer.shoukat@jefferson.edu

Umer Mukhtar, MD
Department of Neurological Surgery, Thomas Jefferson University, umer.mukhtar@jefferson.edu

M. Kamran Athar, MD
Department of Medicine, Thomas Jefferson University, kamran.athar@jefferson.edu

Managing Hyperglycemia in Critically Ill Patients: Where Are We Now?

Umer Shoukat, MD[1,2]; Umer Mukhtar, MD[1,2]; M. Kamran Athar, MD[1,2]

[1]Department of Neurology, Thomas Jefferson University, Philadelphia,PA
[2]Department of Neurological Surgery, Thomas Jefferson University, Philadelphia,PA

Hyperglycemia is common in critically ill patients and is associated with increased morbidity, mortality, rate of infections and length of hospital stay. For decades, hyperglycemia in critically ill population was considered an adaptive response and interventions were only considered if diabetic ketoacidosis (DKA) or severe hyperosmolar states developed. Furnary et al published studies showing lower sternal wound infection rates in cardiac surgical patients with control of glucose (180-220 mg/dl). This led to the dissemination of the "Portland Protocol," but it was not widely accepted.[1, 2]

Management of hyperglycemia changed with the publication of Van Den Berghe study.[3] This was a prospective, randomized, controlled study involving adults admitted to a surgical intensive care unit (ICU) who were receiving mechanical ventilation (MV). A total of 1548 patients were enrolled with patients randomly assigned to two groups. One group received intensive insulin therapy (IIT) with goal blood glucose of 80-110 mg/dl. The second group received conventional treatment whereby insulin was given only if the blood glucose level exceeded 215 mg/dl with goal glucose level of 180-200 mg/dl.

The primary outcome measure was death from any cause during intensive care. The main secondary outcome measures were in-hospital death; the number of days in the intensive care unit and the need for prolonged intensive care (more than 14 days) or readmission; the need for ventilatory support, renal replacement therapy, or inotropic or vasopressor support. At 12 months, IIT reduced mortality during intensive care from 8.0% with conventional treatment to 4.6% (P<0.04) in intensive treatment group. The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2% with conventional treatment, as compared with 10.6% with IIT; P=0.005). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. IIT also reduced overall in-hospital mortality by 34%.

Subsequently, in another single center study,[4] Van Den Berghe randomly assigned 1200 patients in medical ICU to strict normalization of blood glucose levels (80-110 mg/dl) with the use of insulin infusion or to conventional therapy. The study showed no significant difference in hospital mortality (40.0% in the conventional-treatment group vs. 37.3% in the intensive-treatment group, p=0.33). However, IIT reduced morbidity and mortality in patients that stayed in ICU for three or more days. The reasons for reduced morbidity in patients who received IIT were the prevention of acquired kidney injury, earlier weaning from MV, and earlier discharge from the medical ICU and hospital.

A number of multicenter studies were performed following the initial Van Den Berghe trial in an attempt to replicate the earlier results. VISEP (Volume Substitution and Insulin Therapy in Severe Sepsis) study[5] and Glucocontrol study[6] were prospective, multicenter randomized control trials whereas Wiener study[7] was a meta-analysis of 29 randomized controlled trials having a total of 8432 patients. The results of these studies showed no significant difference in mortality in the conventional and tight control groups but increased episodes of severe hypoglycemia.

Given the conflicting data regarding tight glycemic control, the NICE-SUGAR study [8] was undertaken. This was a multicenter randomized control trial which enrolled 6104 patients. Study compared intensive target glucose of 80 to 108 mg/dl to the conventional target of 180 mg/dl or less.

Primary outcome was death from any cause within 90 days after randomization. Secondary outcomes were survival in first 90 days, cause-specific death, duration of MV, length of stay in the ICU, and total length of stay in the hospital. The intervention was discontinued when patients were discharged from ICU or eating and were resumed if the patient was readmitted within 90 days. Blood glucose <40 mg/dl was considered a serious adverse event. One-third of the patients were surgical patients and two-thirds were medical patients. Mortality in intensive target group was 27.5% compared to 24.9% in conventional group (p=0.02). The incidence of severe hypoglycemia (<40 mg/dl) was 6.8% in intensive group compared with 0.5% in conventional group (p<0.001).

There were a number of differences between Van Den Berghe trial and NICE-SUGAR trial, which may help explain their divergent results. Van Den Berghe study was performed at a single center and considered reduction of glucose level only if it was markedly elevated (>215 mg/dl). In contrast, NICE-SUGAR study was multinational and the glucose level in conventional group was targeted at only a mildly elevated range of 144 to 180 mg/dl. Most patients in Van Den Berghe trial received parenteral nutrition whereas enteral nutrition was the rule in NICE-SUGAR study.

The strengths of NICE trial include its large, multicenter patient population, vigorous statistical analysis and broad representative spectrum of critically ill patients. However, some of the downfalls were open-label study design and premature discontinuation of treatment in 10% of the patients. Increased risk of death from IIT in NICE-SUGAR study can be attributed to multiple factors including direct harmful effects of insulin and neuroglycopenia that warrants further studies.[9]

An summary, IIT seems to save lives in the initial Van Der Berghe trial but its results are yet to be replicated, particularly in any multicenter trial. Critical care and endocrinologic societies have backed away from recommending intensive insulin therapy. ADA/AACE Inpatient Task Force recommends that insulin infusion should be used to control hyperglycemia with the starting threshold of 180 mg/dl. Once IV insulin is started, the target glucose is between 140 and 180 mg/dl. Lower glucose targets (110-140 mg/dl) may be appropriate in selected patients. Targets <110 mg/dl are not recommended.[10]

HYPERGLYCEMIA IN BRAIN INJURED PATIENTS

Hyperglycemia is a common secondary insult in traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and acute ischemic stroke and has been consistently associated with poor neurological outcome.[11]

ISCHEMIC STROKE

Several studies have evaluated the effect of IIT in acute ischemic stroke patients with hyperglycemia.[12,13] UK Glucose Insulin in Stroke Trial was the largest randomized clinical trial, which enrolled 933 patients and showed no clinical benefit of IIT.[14]

INSULINFARCT trial randomized 180 patients with acute stroke to receive IIT or subcutaneous insulin treatment during the first 24 h.[15] It demonstrated that IIT in the first 24 h was associated with larger infarct growth and was not recommended.

Mortality

Study	IIT (%)	Conventional (%)	p value
Van Den Berghe (2001)	4.6	8	<0.04
Van Den Berghe (2006)	37.3	40	0.33
VISEP (2008) (At 28 days)	24.7	26	0.74
Glucocontrol (2009) (At 28 days)	18.7	15.3	0.14
NICE-SUGAR (2009)	27.5	24.9	0.02

Hypoglycemia

Study	IIT (%)	Conventional (%)	p value
VISEP (2008)	17	4.1	<0.001
NICE-SUGAR (2009)	6.8	0.5	<0.001
Glucocontrol (2009)	8.7	2.7	<0.0001

Sample Size

Study	n (Total)	n (Conventional)	n (IIT)
Van Den Berghe (2001)	1548	783	765
Van Den Berghe (2006)	1200	605	595
VISEP (2008)	537	290	247
Glucocontrol (2009)	1101	551	550
NICE-SUGAR	6104	3050	3054

AHA/ASA recommends that it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dl and to closely monitor to prevent hypoglycemia in patients with acute ischemic stroke[16] (Class II a; Level of Evidence C).

SUBARACHNOID HEMORRHAGE

Hyperglycemia may have detrimental effects in patients with subarachnoid hemorrahge by increasing chances of infection, cerebral ischemia and by facilitating the progression from ischemia to irreversible infarction.

The majority of the studies using IIT reported episodes of hypoglycemia. Insulin therapy inducing episodes of low glucose was associated with cerebral infarction, vasospasm, and worse functional outcome 3 months following SAH.[17] There is only one randomized trial where 40 patients receive IIT. This study showed no significant improvement in clinical outcome or the incidence of vasospasm.[18]

Currently there is no evidence that hyperglycemia in SAH patients should be treated with IIT. This treatment is accompanied by an increase in hypoglycemic episodes.

AHA/ASA recommends that glucose management with strict avoidance of hypoglycemia may be considered as part of the general critical care management of patients with Aneurysmal SAH[19] (Class IIb; Level of Evidence B).

TRAUMATIC BRAIN INJURY

Hyperglycemia contributes to poor outcome in TBI patients. Hyperglycemia has been shown to worsen ischemic brain injury in experimental studies with animals. One study analyzing cortical contusion injury in rats found that hyperglycemia worsens the injury with superimposed ischemia.[20] In two class III human studies, hyperglycemia has been associated with worsened outcome.[21,22] A randomized controlled trial of 97 patients with severe TBI compared a regimen of IIT versus conventional management. No significant differences were observed in mortality and poor functional outcome at 6 months. Meanwhile, the incidence of hypoglycemic events was markedly increased among patients treated with IIT.[23] This was confirmed in an additional randomized trial with total of 523 patients including 94 TBI patients. IIT was not associated with improved survival and was associated with increased occurrence of hypoglycemia.[24]

Current clinical trials do not show any benefit of tight glucose control with IIT in TBI patients with increased episodes of hypoglycemia.[25]

CONCLUSION

In summary, significant body of literature has shown that hyperglycemia is common in patients with TBI, SAH, and ischemic stroke and that it is related to poor outcome. However, no concrete evidence exists that tight glycemic control improves outcome in these patients. It might on the contrary lead to hypoglycemic episode with deleterious effects on the injured brain due to secondary neuronal injury.

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