Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury*

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**Objective:** To determine that intensive glycemic control does not reduce microdialysis glucose concentration brain metabolism of glucose.

**Design:** Prospective monitoring followed by retrospective data analysis of cerebral microdialysis and global brain metabolism.

**Setting:** Single center, academic neurointensive care unit.

**Patients:** Forty-seven moderate to severe traumatic brain injury patients.

**Interventions:** A nonrandomized, consecutive design was used for glycemic control with loose insulin (n = 33) for the initial 2 yrs or intensive insulin therapy (n = 14) for the last year.

**Measurements and Main Results:** In 14 patients treated with intensive insulin therapy, there was a reduction in microdialysis glucose by 70% of baseline concentration compared with a 15% reduction in 33 patients treated with a loose insulin protocol. Despite this reduction in microdialysis glucose, the global metabolic rate of glucose did not change. However, intensive insulin therapy was associated with increased incidence of microdialysis markers of cellular distress, namely elevated glutamate (38 ± 37% vs. 10 ± 17%, p < .01), elevated lactate/pyruvate ratio (38 ± 37% vs. 19 ± 26%, p < .03) and low glucose (26 ± 17% vs. 11 ± 15%, p < .05), and increased global oxygen extraction fraction. Mortality was similar in the intensive and loose insulin treatment groups (14% vs. 15%, p = .9), as was 6-month clinical outcome (p = .3).

**Conclusions:** Intensive insulin therapy results in a net reduction in microdialysis glucose and an increase in microdialysis glutamate and lactate/pyruvate without conveying a functional outcome advantage. (Crit Care Med 2006; 34:850–856)

**Key Words:** brain injury; microdialysis; insulin; glucose; intensive insulin therapy

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Intensive glycemic control has become a mainstay of intensive care unit treatment following the seminal study by van den Berghe et al. (1), which convincingly demonstrated that control of serum glucose within a narrow range resulted in decreased mortality among surgical intensive care unit patients. In addition, hyperglycemia has been repeatedly found to correspond with worsened clinical outcome after traumatic brain injury and a variety of other acute central nervous system injuries, including ischemic stroke, brain hemor-
been previously described (9). Acute-phase studies were carried out during the initial 10 days of intensive care. Determination of the injury severity score was done using the loose assessment tool (10). Outcome was prospectively assessed using the Glasgow Outcome Score by office visits at 6 months after discharge.

Cerebral microdialysis was performed as described previously (9) using the CMA70 probe (10-cm flexible shaft, 10-mm membrane length, 20-kd cutoff, CMA, Stockholm, Sweden) inserted via a twist drill burr hole adjacent to an existing ventriculostomy. Probe location was in normal appearing white matter. The location was in the nondominant frontal lobe. The CMA103 perfusion pump was used to perfuse normal saline through the catheter at 1 μL/min, and fluid was collected in 60-min samples and then placed into dry ice or directly into the CMA600 instrument. The initial 60-min sample was not used for analysis, allowing for stabilization of the probe. Microdialysis was not interrupted for transport or bedside testing. The sampling was done for the initial 96 hrs after injury. Microdialysis samples were analyzed on the CMA600 (Stockholm, Sweden) with standard CMA600 reagents. These hourly samples were run twice each for each analyte, and the mean final value was used. Quality control methods have been previously published (9).

Positron emission tomography was performed using a quantitative method previously described (11, 12). Intracranial pressure (ICP) was kept under 20 mm Hg, CO2 was kept 30–34 mm Hg, and temperature was kept 37–37.6°C. Patients underwent quantitative, dynamic 0-15 PET scans (C15O, O15O, H215O) to determine regional cerebral blood flow (ml/100 g/min), oxygen extraction fraction (OEF, %), and the cerebral metabolic rate of oxygen (mg/100 g/min) (12). The extracranial tissue and CSF were excluded as described by Coles et al. (13). This was followed by an FDG-PET scan obtained using a quantitative technique for the calculation of the global cerebral metabolic rate of glucose (CMRg, mg/100 g/min) (7, 11, 12). The regional rates of metabolism near the microdialysis probe have been previously reported (9).

Daily global values of glucose and oxidative metabolism were conducted in the intensive care unit using methods previously published (14). The Xenon-133 modified Kety-Schmidt technique was used to determine the global measures of cerebral blood flow, glucose metabolic rate (JCmRg), and oxygen metabolic rate. These were measured once daily for both loose patients and intensive glycemic control patients. Simultaneous samples of arterial and jugular bulb venous blood, in quadruplicate samples, were taken daily and matched to the corresponding hourly microdialysis glucose sample. The quadruplicate samples each for arterial and venous blood were then analyzed and the results were averaged for each arterial and venous daily time point. Blood glucose levels were determined using the glucose oxidase method. The jugular bulb venous glucose value obtained at the time of the test was used to segregate the rates of metabolism during data analysis (discussed subsequently). No change in insulin infusion rate or injection of subcutaneous insulin occurred before 2 hrs before the determination of the global metabolic rates or PET metabolic rates. Samples taken during burst-suppression coma using propofol or pentobarbital were excluded from study.

Glycemic Control Protocol. The initial 33 patients (2001–2003) underwent routine glycemic control consisting of serial serum glucose checks every 4 hrs after a glucose-directed sliding-scale regular insulin subcutaneous injections by the bedside nurse to control the serum glucose within the target range of 120–150 mg/dL. The subcutaneous injections were administered into the skin overlying the abdomen in 15 mins of determining the serum glucose value. A second cohort of 14 patients, from 2003 to 2004, underwent intensive glycemic control using a continuous intravenous infusion of insulin using a protocol resembling that previously published by van den Berghe (1), but with the serum target range of 90–120 mg/dL. Serum glucose values were checked every 4 hrs using the Accu-check® system in the loose group and every 1 hr in the intensive group. Both the routine and the intensive glycemic control were done while blinded to the microdialysis glucose values. Subcutaneous insulin injections were given in the subcutaneous tissue overlaying the abdomen. In this loose control group, the glycemic goals were achieved and maintained for 71 ± 14% of all sampled time points.

General Management Protocol. Our general management protocol has been previously published (9). ICP was kept <20 mm Hg using a stepwise management strategy (i.e., cerebrospinal fluid drainage, hyperventilation to Pco2 of 30–34, and hypertonic saline). Jugular venous oximetry (jugular venous oxygen saturation) was performed to monitor for jugular venous desaturation, and blood pressure was adjusted to keep the jugular venous oxygen saturation between 60% and 70%. Core temperature from the jugular vein was used and kept between 37°C and 37.6°C through the use of medications (acetaminophen) and surface cooling devices. All patients received phenytoin for >7 days. None of the patients studied received intravenous or oral steroids. In both groups, patients were maintained on intravenous crystalloids without glucose (normal saline with potassium chloride) for the initial 12 hrs after injury. Enteral nutrition (Isocal HN®, Novartis) was provided via nasogastic tube at a rate of 1 mL/kg, with feedings adjusted for gastric residuals and caloric goals on an individual basis. Enteral feedings were started within 12 hrs after injury and were adjusted to maintain caloric goal of 30 kcal/kg of adjusted ideal body weight. Audit of nutritional records indicates that this goal was met during the period of microdialysis observation. Intravenous sedation consisted of continuous propofol at dose ranging from 10 to 50 μg/kg/min, with titration adjusted to maintain intracranial pressures <20 mm Hg or Ramsay scale of 3.

Data analyses included Pearson product-moment correlations, analyses of proportions, analyses of variance (ANOVA), computation of odds ratios with 95% confidence intervals, and linear regression. Data acquisition was handled in Access 97 (Microsoft, Redmond WA), whereas statistical procedures were conducted within SPSS (SPSS, Chicago, IL) and Statistics 5.3 (StatSoft, Tulsa, OK). Univariate analyses were performed as outlined subsequently. For repeated measures of microdialysis over time across the two cohorts of patients, linear mixed effects model fitting was used to account for within-subjects covariance of values and variable number of individual samples across subjects. Multivariable logistic regression was used to determine whether probability of 6-month outcome was determinant on patient specific variables (e.g., age, admission GCS, admission serum glucose concentration) and/or on insulin treatment group (e.g., loose or intensive).

RESULTS

Forty-seven subjects were studied overall, 33 of whom comprised the loose glycemic control group with 14 subjects in the intensive glycemic control group. The groups were evenly matched with respect to injury severity, age, and admission glucose values (Table 1). Using serial measures of jugular venous oxygen saturation and ICP, we found similar rates jugular venous desaturation (<50%) and intractable ICP (>25 mm Hg × 2 hrs) between the two treatment groups (Table 1).

Effect of Glycemic Level on Glucose Metabolism. To evaluate the impact of steady-state glucose value on global cerebral glucose metabolism, we compared the JCMRg values across three steady states of glycemic control, namely intensive control 90–120, loose control 120–150, and hyperglycemia 151–200. To account for the varying number of patients in each steady-state condition, a linear mixed effects model analysis was used. The linear mixed effects model fitting identified no effect due to the level of actual glycemic control (90–120, 120–150, 150–200) (p = .199), although a significant effect on brain glucose metabolism due to glycemic control protocol,
The interaction of these two factors (treatment group vs. glycemic range) was marginally nonsignificant \( (p = .064) \). Further modeling showed no additional contribution to model fit from either age or gender. Figure 1 demonstrates a nonsignificant trend of increasing jCMRG in the intensive group. In all cases, the absolute rate of glucose metabolism was depressed, as has been previously reported by our group (14). On intensive glycemic therapy in those patients with cerebral microdialysis monitoring, the jCMRG decreased by a nonsignificant amount \( (p = .52) \) compared with baseline metabolic rate (Fig. 2).

**Effect of Glycemic Level on Brain Oxidative Metabolism.** In a subgroup of 19 patients, brain metabolism was measured using positron emission tomography. These patients represented nonrandomized, consecutive patients from a separate study to determine brain metabolism and consisted of ten patients from the loose group and nine patients from the intensive group. Global and regional rates of oxidative and glucose metabolism were determined using methods previously described (12). There was no relationship between serum venous glucose concentration and global rates of glycolysis \( (r = - .32, p < .29) \) for the group as a whole or for each treatment group. However, serum glucose correlated negatively with oxygen extraction fraction \( (OEF, r = - .52, p < .001) \), with the highest values for OEF corresponding with serum glucose values within the glucose range of 90–120. The intensive insulin group demonstrated higher values of OEF \( (0.51 \pm 0.15 \text{ vs. } 0.30 \pm 0.13, \text{ univariate } p < .005) \) compared with the loose group. The intensive group had three of eight subjects with OEF > 0.5 compared with none of the conventional group. The remainder of the metabolic values was similar between the two groups. Table 2 shows the summary of results that compared serum glucose to global metabolism.

### Table 1. The groups were evenly matched

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive</th>
<th>Loose</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>14</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Age, mean</td>
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<td>47.8</td>
<td>.3</td>
</tr>
<tr>
<td>Admission GCS, mean</td>
<td>8</td>
<td>9</td>
<td>.8</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>26</td>
<td>.5</td>
</tr>
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<td>Female</td>
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<td>7</td>
<td>.4</td>
</tr>
<tr>
<td>ISS</td>
<td>32</td>
<td>32</td>
<td>.9</td>
</tr>
<tr>
<td>Admission glucose</td>
<td>157 ± 40</td>
<td>161 ± 42</td>
<td>.8</td>
</tr>
<tr>
<td>% intractable ICP</td>
<td>7</td>
<td>9</td>
<td>.8</td>
</tr>
<tr>
<td>SjO2 desaturation, %</td>
<td>2</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Mortality, 30-day, %</td>
<td>14</td>
<td>15</td>
<td>.9</td>
</tr>
<tr>
<td>% GOS 1–3, 6 mos</td>
<td>43</td>
<td>33</td>
<td>.5</td>
</tr>
<tr>
<td>% GOS 5+, 6 mos</td>
<td>43</td>
<td>60</td>
<td>.3</td>
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GCS, Glasgow Coma Scale; ISS, injury severity scale; Intractable ICP, percentage of patients with intracranial pressure ≥ 25 mm Hg for ≥ 4 hrs; SjO2, percentage of jugular desaturation hours/total hours/group; GOS 1–3, percentage of patients within each group with a 6-month Extended Glasgow Outcome Score of 1–3; GOS 5+, percentage of patients within each group with a 6-month Extended Glasgow Outcome Score of ≥ 5.

**Response of Cerebral Microdialysis to Insulin.** Under conditions of systemic hyperglycemia, the microdialysis glucose values ranged from 0.4 to 1.5 mmol/L. These baseline microdialysis glucose values did not correlate with the extent of systemic hyperglycemia \( (r = .08) \). On continuous insulin infusion, there was a decrease in microdialysis glucose values in 11 of 14 subjects. Compared with baseline values at hour 0, the microdialysis glucose concentration decreased by 70 ± 852 Crit Care Med 2006 Vol. 34, No. 3

**Figure 1.** The jugular-derived global metabolic rate for glucose (cerebral metabolic rate, \( \text{CMR}_g \)) in both conservative and intensive glycemic control patients. Segregated by the steady-state glycemic level during the metabolic measurement. There is no statistical difference in the metabolic rate in patients with normoglycemia (90–120) compared with moderate hyperglycemia (120–150 or 151–200) in either treatment group.

**Figure 2.** Changes in jugular-derived global metabolic rate for glucose (jCMRG) in the intensive glycemic control cohort. The mean values for jCMRG were obtained during conditions of baseline hyperglycemia, during intensive insulin drip resulting in normoglycemia (90–120 mg/dL), and again after removal of insulin drip (during moderate hyperglycemia (130–200 mg/dL). The time interval between the three time points averaged > 48 hrs.
11% during insulin infusion by hour 11 of infusion (Fig. 3). The mean time to reaching the nadir of microdialysis glucose was 11 ± 1 hrs after onset of infusion, which was similar to that of the serum glucose values. Systemic hypoglycemia (<80 mg/dL) was present 1% of the time during insulin infusion. After reaching this nadir, microdialysis glucose was persistently low for about 96 hrs and returned to baseline concentration at 120 hrs. In the loose insulin group, the response of cerebral microdialysis glucose to subcutaneous injections of insulin was analyzed. Within 4 hrs of subcutaneous insulin injections of 2–9 units of regular insulin, microdialysis glucose values were reduced by 15.3 ± 26%. The time course of the changes in glucose is demonstrated in Figure 4. Exploratory analysis of microdialysis values up to 8 hrs after injection of regular insulin did not reveal a further reduction in glucose values, and the 4-hr postinjection time point was therefore used for further analysis. The mean dose of subcutaneous insulin injected was 3.5 ± 1.5 units. There was no relationship between the administered insulin dose and the percent change in microdialysis glucose (Pearson r = .06).

We next examined the potential adverse effects of the insulin infusion by examining the microdialysis markers of cellular distress. For comparison, Table 3 contains the mean values of microdialysis glucose, glutamate, and lactate/pyruvate ratio (LPR) for each subgroup during the 96-hr period. The intensive group demonstrated lower mean glucose values (ANOVA, df = 3, F = 4.2, p < .01) and higher mean glutamate (ANOVA, df = 3, F = 30, p < .001) during the initial 96 hrs. LPR was nonsignificantly higher in the intensive group (ANOVA, df = 3, F = 1.6, p < .18). We used criteria for microdialysis markers of cellular distress based on accepted literature standards: microdialysis glucose <0.2 mmol/L, LPR >40, and glutamate >5 µM (15, 16). We compared the percent time in which each of these microdialysis markers of distress was present in the loose glycemic control subjects to that of the intensive glycemic control group during the initial 96 hrs after injury. The intensive glycemic control subjects experienced a greater percentage of time of elevated glutamate (p < .01), elevated LPR >40 (p < .03) and low glucose (p < .05) compared with the loose glycemic control subjects (Table 4).

Effect of Glycemic Control on Outcome. The effect of glycemic control on outcome was assessed in three ways. First, admission serum glucose values >150 mg/dL were associated with higher mortality (39% vs. 11%, chi-square = 5.4, Fisher’s exact t-test p < .03). In contrast, admission serum glucose was not associated with differences in the 6-month Extended Glasgow Outcome Score (4.8 ± 2.1 vs. 4.8 ± 1.9, p < .5). Using regression analysis with admission GCS and age covariates, we found that admission glucose was not an independent predictor of outcome.

<table>
<thead>
<tr>
<th>Table 2. Summary of results</th>
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<tr>
<td>Group</td>
</tr>
<tr>
<td>Intensive, n = 9</td>
</tr>
<tr>
<td>Loose, n = 10</td>
</tr>
</tbody>
</table>

CMRG, cerebral metabolic rate of glucose; CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction.

Figure 3. The time course of systemic (top) and microdialysis (bottom) glucose (GLU) during intensive insulin drip in 14 patients. Top, the hourly mean (SD) values for systemic glucose taken 6 hrs before the start of the insulin drip and for the duration of the insulin drip in all subjects. Bottom, the mean percent change (SD) in the hourly microdialysis glucose across all 14 subjects during intensive insulin drip. The baseline microdialysis value consisted of the mean value from 6 hrs before the onset of insulin drip and during which time no insulin was administered. There is a mean 70% reduction in microdialysis glucose with intensive insulin drip, reaching a nadir at 12 hrs after drip onset. The dotted line represents the onset of insulin drip.
regression, there was no effect of treatment group on 6-month Extended Glasgow Outcome Score (ANOVA F = 4.83, \(d^2 = 1.46, p = .153\)). However, similar to our previous work (9), the percent time of low microdialysis glucose (i.e., <0.2 mmol/L) did predict mortality (\(R^2 = .39, p < .04\)).

**DISCUSSION**

There are five principal findings of the current study. First, admission hyperglycemia was correlated with mortality but not functional outcome after TBI. Second, intensive glycemic control did not lead to a reduction in global cerebral metabolic rate compared with routine glycemic control. Third, intensive glycemic control was associated with a higher global mean oxygen extraction fraction compared with loose control. Fourth, intensive glycemic control resulted in a reduction in microdialysis glucose concentrations and an increase in microdialysis markers of brain metabolic distress, namely increased LPR and glutamate. Fifth, although this study was not powered to determine efficacy of intensive glycemic control, we did not find any differences in mortality rate or functional outcome between the intensive and loose glycemic control arms.

**Hyperglycemia Predicts Poor Outcome After TBI.** Acute hyperglycemia after traumatic brain injury is a common finding and has been associated with poor outcome (4, 17, 18), and the extent of hyperglycemia has been correlated with the severity of injury (3, 19). Hence it is not clear whether hyperglycemia is an independent predictor or merely a covariate of severity of injury. The level of delayed hyperglycemia (>200 mg/dL) was found to be associated with poor outcome (18) in a single study. Experimentally, immediate but not persistent posttraumatic hyperglycemia may exacerbate final lesion volume, but this has not been well studied in humans (20). Our study confirms that hyperglycemia at the time of admission is a negative prognostic factor for mortality.

**Glycemic Control in Intensive Care.** There has been widespread agreement that glycemic control is beneficial since the seminal randomized control study of van den Berghe (1). More recently, several single-center cohort control studies have confirmed decreased mortality and lower incidence of infections and multiple organ failure (21). Not all studies have demonstrated benefit from intensive insulin therapy, and one study reported a higher mortality rate in the treated group (22). Recently, a subgroup analysis of brain-injured patients within van den Berghe’s original study confirmed better outcomes in patients with a variety of brain injuries treated with intensive glycemic control (23). This subgroup analysis, however, grouped several types of brain-injured patients together, which limits the interpretability of the study. Thus, despite the convincing level 1 evidence of the utility of intensive glycemic control in intensive care patients in general (1), questions remain regarding the utility of intensive glycemic control in severe traumatic brain injury patients.

**Regulation of Brain Glucose Levels After TBI.** Given that the brain exhibits compensatory response to injury, which includes increased glucose utilization and an increase in glucose transport via up-regulation of GLUT 3 (24–26), one may be concerned that a reduction in
We have demonstrated very low microdialysis levels of glucose after TBI limitation in the injured brain. Several serum glucose could create substrate conditions of profound hypoglycemia. Normally, the brain is capable of maintaining neural activity in glucose hypoglycemia did not occur. Our data appear to suggest that marked reductions in glucose supply may occur during intensive glycemic control even in the absence of profound hypoglycemia. Although the reduction in microdialysis glucose level did not result in reduction in the whole brain glycolytic rates, the brain exhibited signs of metabolic distress. These signs were increased oxygen extraction fraction to near-ischemic level and increased levels of microdialysis glucose and LPR. The microdialysis markers and the PET OEF data suggest that the brain is behaving as if it is ischemic, even though cerebral blood flow is maintained (34). These markers have been previously found to predict poor outcome (9, 27–29, 33, 35). This constellation of PET and microdialysis markers suggests that intensive insulin may provoke further metabolic distress in TBI. In our study, the intensive group did not demonstrate improved functional outcome, as determined by similar 6-month Extended Glasgow Outcome Scores in both treatment groups. We hypothesize that intensive glycemic control may have had a negative effect on outcome in our cohort, and thus we could not replicate the findings of van den Bergh (23).

Limitations of This Study. We recognize several limitations to this study. First, the study was retrospective rather than a prospective randomized controlled trial. However, the findings in this study may be useful in designing a definitive study. Second, the Roche Accuchek method used to titrate insulin is less reliable at very low glucose concentrations and may have affected the titration of insulin. Third, the number of subjects is small and as such the study is not powered to show a difference in functional outcome or mortality between groups.Fourth, the differences in brain metabolism and microdialysis between groups may be due to injury characteristics and many aspects of treatment other than glycemic control.

CONCLUSION

Hyperglycemia is a known risk factor for poor outcome after traumatic brain injury and requires early and persistent intensive care to maintain normoglycemia. However, the optimal level of glycemia is presently unknown after TBI. Intensive glycemic control using insulin infusions may result in decreases in extracellular glucose concentrations and increases in microdialysis markers of cellular distress. The cellular distress may be a result of decreased glucose utilization in glycolytic pathways or may result from diversion of glucose away from other metabolic pathways that sustain diverse cell functions. The use of cerebral microdialysis monitoring of extracellular glucose and other markers of metabolic distress during intensive glycemic control may one day be a useful strategy by which to maximize the benefits of glycemic control while avoiding its complications.

REFERENCES