Effects of Intraoperative Glucose on Protein Catabolism and Plasma Glucose Levels in Patients with Supratentorial Tumors

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Animal studies suggest that hyperglycemia (glucose concentrations > 225 mg/dl) occurring prior to periods of brain ischemia exacerbates neurologic damage. Neurosurgical patients, a group at risk for intraoperative brain ischemia, often receive glucose. Therefore, the effects of intraoperative glucose administration (IGA) on these patients were studied. Sixteen patients undergoing supratentorial craniotomy were randomly assigned to receive either 5% glucose in 0.9% sodium chloride solution (G) or 0.9% sodium chloride solution (S) infusion (both at a rate of 3-4 ml·kg⁻¹·h⁻¹) during the first 4 h of surgery. All patients received glucose infusions postoperatively. Plasma glucose, insulin, free fatty acids, alanine, ketones, base excess, pH, triglycerides, and lactate were measured during the infusion period and 24 h postoperatively. Urinary nitrogen was measured, commencing with the infusion and continuing for 24 h. Neurologic testing included preoperative and postoperative neurologic and psychomotor exams, time to extubation (min), and degree of alertness at the completion of anesthesia. The G group had significantly greater intraoperative plasma glucose concentrations at all time periods studied during the infusion (P < 0.05). Glucose levels ranged from 200–242 mg/dl compared with 120–160 mg/dl in G and S groups, respectively. G group hyperglycemia was within the range associated with exacerbation of ischemic brain damage in animal studies. Free fatty acids and ketones were significantly greater (P < 0.05) intraoperatively in the S group. Lactate and insulin were significantly greater in the G group at 4 h. Total urinary nitrogen was comparable in both groups but was significantly greater intraoperatively (P < 0.05) in the G group (13 ± 2 vs. 7 ± 1 mg·kg⁻¹·h⁻¹). No differences in the other metabolic indices were found. Likewise, no difference between groups was found in the neurologic variables; however, the number of patients studied was small. In summary, IGA produced plasma levels that have been associated with potentiation of ischemic neurologic damage, while patients receiving saline had much lower glucose levels. Because there does not appear to be any metabolic compromise in those not receiving glucose, the results suggest that glucose should be avoided during intracranial surgery. (Key words: Anesthesia; neurosurgical. Brain: infarction. Metabolism: fasting; fatty acids; glucose; hyperglycemia; lactate. Surgery: neurologic.)

THERE IS CONSIDERABLE controversy regarding glucose administration during intracranial surgery. The administration of 100–150 g of glucose per day produces protein sparring in starving individuals,1 decreases fat and protein mobilization during a short fast,2 and provides free water.3 Many feel that these effects benefit patients undergoing general surgery.4,5 Glucose administration during neurosurgery has also been advocated6–8 for the previously mentioned reasons. However, recent animal and human studies suggest that hyperglycemia exacerbates ischemic brain damage5,9–20 and may, therefore, harm patients whose operations are associated with periods of decreased cerebral perfusion. Decreased cerebral perfusion to levels that may produce ischemia may occur during brain tumor resection with its attendant brain retraction,21,22 hypotension,22 and increased intracranial pressure.23

Intraoperative glucose administration increases blood glucose in diabetic and nondiabetic patients in proportion to the rate of glucose infusion. Glucose levels greater than 200 mg/dl were observed with glucose infusion rates as little as 12.5 g/h.24 Moreover, the corticosteroids that many neurosurgical patients receive in an attempt to decrease peritumor brain edema could alter glucose tolerance, increase protein catabolism, and, thus, may counteract the protein-sparing effects of moderate doses of glucose.

This study addresses the following questions. To what extent does intraoperative glucose administration produce hyperglycemia? If hyperglycemia does occur intraoperatively during procedures at risk for brain ischemia, can it affect neurologic outcome, as evidenced by neurologic and psychomotor testing? Are there any counterbalancing benefits from glucose administration in these patients, as demonstrated by differences in protein sparing (total urine nitrogen) or fasting-state reversal (free fatty acids, ketones, alanine, triglycerides, and lactate levels)?

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Methods

Sixteen adult patients undergoing removal or biopsy of a supratentorial tumor were studied. No diabetic patients or patients with a history of previous intracranial surgery were included. After obtaining written, informed consent according to the institutional guidelines at the University of Pennsylvania, each patient was assigned randomly to one of two intraoperative fluid regimens: 5% glucose in 0.9% sodium chloride solution or 0.9% sodium chloride solution alone. Additional preoperative data included: age; sex; name of operation; tumor location, type, and size; neurologic exam; and psychomotor exam. All subjects fasted 8 h preoperatively and received at least 10 mg of dexamethasone during the 12 h before surgery. The fluid infusion rate was determined by the formula: body surface area \( \times 135 \text{ ml} \cdot \text{m}^{-2} \cdot \text{h}^{-1} \) (approximately 3–4 ml \( \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \)). This rate, which took into account urine, third space, and maintenance requirements, allowed a stable intraoperative crystalloid infusion.

Monitoring included five-lead ECG, radial artery catheter, central venous pressure catheter, urinary catheter, end-tidal CO\(_2\) analyzer, inspired oxygen analyzer, esophageal stethoscope, and peripheral nerve stimulator. Anesthesia was induced intravenously with 3–5 mg/kg sodium thiopental, 5–7 \( \mu \text{g} / \text{kg} \) fentanyl, and 0.1 mg/kg pancuronium and was maintained using 50–70% nitrous oxide in oxygen with supplemental doses of pancuronium and fentanyl. Seven patients in each group required isoflurane in concentrations up to 1% at various points during the procedure for blood pressure control. No patient received more than 1 MAC h isoflurane during the 4-h infusion period. The average MAC h values of isoflurane for the entire infusion period in the seven patients in each group were similar \((0.78 \pm 0.12\) and \(0.68 \pm 0.13\), mean \( \pm \text{SEM} \), MAC h isoflurane in the glucose and saline groups, respectively).

No patient received preoperative intravenous fluids. In the operating room, an intravenous catheter was inserted, and 0.9% sodium chloride was initially administered to both groups in an amount adequate to allow for intravenous induction of anesthesia (less than 200 ml). Immediately following induction of anesthesia, the urinary bladder was catheterized, and then the assigned crystalloid infusion was begun. The infusion rate was maintained for 4 h or until the end of surgery, whichever occurred first. At the end of the first 4 h of surgery, the infusion rate was reduced to 1 ml \( \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \). Postoperatively, all patients received 5% glucose in 0.45% sodium chloride solution (1 ml \( \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \)) until the following morning. Mannitol was given to all but two patients, one in each group \((0.5 \text{ g} \cdot \text{kg}^{-1} \text{ intravenously})\). Additional fluids that were required intraoperatively were given as blood or colloid and did not contain any lactate or glucose.

Blood samples were drawn from the arterial catheter into heparinized syringes and immediately placed in ice. Samples for acetocetate, beta-hydroxybutyrate, triglycerides, free fatty acids, alanine, insulin, arterial blood gases, and lactate were obtained just before the beginning of the infusion \((0\) h) then 1, 4, and 24 h from the start of infusion. Samples for glucose were obtained at time 0, \(1/2\), 1, 2, 3, 4, and 24 h. Urine output from 0 to 4 h and 4 to 24 h was collected in separate containers, the volumes were recorded, and aliquots were frozen at \(-20^\circ\) C.

The neurologic examination was recorded preoperatively and 24 h postoperatively. A psychometric test using a modification of the "Mini Mental State" exam was performed preoperatively and 2 and 24 h postoperatively. At the time of extubation, degree of awareness was determined on a scale of 1–5 as follows: 1 = patient unresponsive and unable to extubate; 2 = patient able to be extubated, follows simple commands; 3 = patient extubated, speaks when asked questions, follows simple commands; 4 = patient extubated, follows simple commands, speaks and moves with some spontaneity; 5 = patient wide awake and talking. In addition, the time (min) between placement of the dressing and extubation was recorded.

The psychometric tests and evaluations of awareness at extubation were all performed by the first author under the supervision of an experienced psychologist with expertise in the evaluation of altered mental states (B. Uzello). Preoperative and postoperative neurologic exams were performed by the same senior neurosurgical resident.

\(\text{PaO}_2\), \(\text{PaCO}_2\), pH and base excess were measured by a Corning® #168 Blood Gas Analyzer. Plasma glucose was measured by a Beckman® #2 Glucose Analyzer. Two milliliters of each plasma sample were frozen at \(-20^\circ\) C for free fatty acid, insulin, and triglyceride assays. The remainder of the sample was precipitated with 0.7% perchloric acid and centrifuged. The supernatant was recovered, and 2 ml was stored at \(-20^\circ\) C for lactate analysis. The remainder of the supernatant was neutralized with imidazole and stored at \(-20^\circ\) C.

Free fatty acids were determined by the method of Itaya, while insulin was quantitated using a single antibody radioimmunoassay. Triglycerides, lactate, beta-hydroxybutyrate, acetocetate, and alanine were measured by standard enzymatic techniques. Urinary nitrogen was measured by chemoluminescence (Antek® Model 720/772, Houston, TX) using urea as a standard.

\(\text{Sigma Tech Bulletin No. 320-UV (2-76), Sigma Chemical Company, St. Louis, MO, 1982, pp. 1–5.}\)

\(\text{Sigma Tech Bulletin No. 726-UV/826-UV (6-76), Sigma Chemical Company, St. Louis, MO, 1982, pp 1–19.}\)
Testing for statistical significance was accomplished using one- and three-way analysis of variance (ANOVA).\textsuperscript{31} Significance between selected groups was demonstrated using the method of least significant differences (LSD). Bonferroni inequalities were used to correct for multiple comparisons.\textsuperscript{92} The chi-square test was used to test for unequal distribution of characteristics between the two groups.

Results

Both treatment groups were comparable in age, body surface area, dexamethasone dosage, and length of operation (table 1). Females were the predominant sex, but there was no significant difference in sex distribution between the two groups. Meningioma was the most common diagnosis.

All patients had comparable 0-h and 24-h glucose values (fig. 1) and showed intraoperative increases in plasma glucose. The increase was greater in those receiving glucose. Significant differences ($P < 0.05$) were seen between treatment groups at all sample times from 0.5–4 h. Patients receiving glucose infusions intraoperatively had glucose levels that ranged between 200 to 242 mg/dl after 2 h. This resolved postoperatively. The glucose levels of those receiving saline remained between 120 to 165 mg/dl. Hypoglycemia (plasma glucose less than 57 mg/dl) was not seen in the saline group despite preoperative fasting and the absence of administered glucose; no patient had a glucose level less than 86 mg/dl.

Patients receiving only saline (table 2) showed increases in free fatty acid levels over initial values at 1 and 4 h ($P < 0.05$), which returned to normal by the next morning. Free fatty acid levels at 1 and 4 h in the saline group were significantly greater than in the glucose group. No differences in alanine or triglycerides were seen over time or between groups (table 2). Beta-hydroxybutyrate and acetoacetate were significantly increased at 1 h in the saline group (table 3). At 4 h, only acetoacetate remained increased ($P < 0.05$). Although plasma lactate was increased at 4 h ($P < 0.05$) in the glucose group (table 3), base excess changed in neither group. Over time, both groups became alkaloic (table 3) but returned to normal pH postoperatively. All patients were hyperventilated intraoperatively.

Intraoperative urinary nitrogen excretion was greater in patients receiving glucose ($13 ± 2$ vs. $7 ± 1$ mg $\cdot$ kg$^{-1}$ $\cdot$ h$^{-1}$, mean $\pm$ SEM, in the glucose and nonglucose groups, respectively, $P < 0.05$). Both groups had similar 24-h nitrogen excretion ($185 ± 29$ and $172 ± 24$ mg $\cdot$ kg$^{-1}$ $\cdot$ day$^{-1}$, mean $\pm$ SEM, in the glucose and nonglucose groups, respectively).

Plasma insulin concentration differed between groups with significantly greater ($P < 0.05$) levels obtained at 4 h in the glucose group (fig. 2). In the saline group insulin levels ranged from 0.44 to 1.61 ng/ml and were within the normal intraoperative range described in previous studies of nondiabetic patients.\textsuperscript{24}

There were no statistically significant differences between group mean scores for psychomotor testing at all times tested (preoperatively, 2 h, and 24 h postoperatively). Three patients in the glucose group sustained permanent postoperative motor deficits. These included

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<th>Table 1. Characteristics of Study Population</th>
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* Values are either totals or mean $\pm$ SEM.

![Fig. 1. Plasma glucose concentration in patients receiving intraoperative infusion of 5% glucose in 0.9% sodium chloride solution (x) or 0.9% sodium chloride solution alone (c). Time 0 to 4 h represents the intraoperative period. Values represent mean $\pm$ SEM of eight patients. In both groups, glucose levels increase over time ($P < 0.05$, one-way ANOVA), and glucose levels were significantly different between groups from 0.5 to 4 h ($P < 0.05$, three-way ANOVA, least-squares difference testing).](https://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931400/ on 11/23/2018)
right-sided weakness following resection of a left-sided temporal glioma; a left cranial nerve III and VI palsy, and left cranial nerve V anesthesia following a pterional craniotomy for resection of a left-sided chordoma; and left-lower-extremity weakness following parasagittal meningioma removal. No patients in the saline group had postoperative changes in neurologic exam. No statistically significant difference between groups was found in the degree of alertness (2.6 ± 0.4 vs. 2 ± 0.3, [mean ± SEM] in glucose and nonglucose groups, respectively) or time to extubation (3.6 ± 1.6 vs. 4.5 ± 0.7 min [mean ± SEM] in glucose and nonglucose groups, respectively).

**Discussion**

The data show that moderate rates of glucose infusion (11–15 g/h) produce glucose levels greater than 200 mg/dl. These findings are similar to those reported by Schwartz.24 In addition, intraoperative saline administration did not lead to hypoglycemia (plasma glucose less than 57 mg/dl) in that no patient in this study had an intraoperative plasma glucose concentration less than 86 mg/dl. Although isoflurane may modestly increase blood glucose,25 the dose of isoflurane was similar in both groups, and thus would not invalidate the comparison between treatment groups.
Few metabolic differences were found between treatment groups. Of note was the increase in ketone bodies and free fatty acids in patients not receiving glucose. Because these products of lipolysis provide a major energy source during stress and starvation, the acute nutritional needs of the body were probably being met. Concern might be raised that the increased ketone levels observed in the saline group could lead to metabolic decompensation. The ketone-body levels obtained in the saline group (0.33–0.873 mM) represented values seen with starvation and are not in the same range (much greater than 1 mM) as diabetic ketoacidosis (DKA). The insulin levels present in this group were in the range associated with half-maximal suppression of glucose production in normal humans (plasma insulin concentration of 29 ± 2 μU/ml, which approximates the levels of 1.2 ng/ml reported in “Results” where 25 μU insulin = 1 ng). Although the dose–response relationships of insulin are probably altered intraoperatively, our data indicate that the insulin levels present in the saline group, although not sufficient to prevent ketone-body values in the range of starvation, are able to prevent severe hyperglycemia in the face of surgical stress. As substantiated by the similarities in acid–base status between groups, it is unlikely that the degree of ketosis observed in the saline group would lead to major metabolic alterations.

Total 24-h nitrogen excretion values in our patients are in the same range as previous studies in neurosurgical patients. The findings that intraoperative nitrogen excretion was greater in the group receiving glucose seems paradoxical; however, there have been few studies of protein loss during the operation itself. Previous studies, showing protein sparing with moderate glucose intake, examined 24-h time periods over several days. With respect to our findings, immobilization during the operation may decrease the anabolic effects of glucose administration, as might steroids. In addition, protein catabolism is inhibited by hyperketonemia, as has been observed in starving patients receiving beta-hydroxybutyrate infusions. This may be a factor in our patients, considering the marked differences in ketone bodies between the two groups. The important observation, however, is that glucose did not produce protein sparing in this group of patients.

Our results show that intraoperative glucose administration causes hyperglycemia without additional protein sparing despite some reversal of the fasting state. In addition, not giving glucose does not result in hypoglycemia or acidosis. With this in mind, animal studies showing a less-favorable neurologic outcome when blood-glucose levels are increased before the ischemic insult should not be ignored. Glucose concentrations as low as 225 mg/dl in mice and 300 mg/dl in rats have been reported to exacerbate ischemic brain damage. In addition, a retrospective study in humans following cardiac arrest has found a statistically significant association between glucose levels greater than 341 mg/dl and neurologic residua.

Glucose concentrations above 120 mg/dl in nondiabetic stroke patients have been associated with a poorer neurologic outcome in a prospective series, although this data did not reach levels of statistical significance (P = 0.061). Interpretation of these human studies, however, is complicated by the possibility that severe insulins may produce a proportional reactive hyperglycemia.
The neurologic and psychomotor evaluations in this study examined changes during the 24-h perioperative period. The postoperative deficits observed in the glucose group were interesting, but difficult to interpret. It is not known, for example, whether these changes were secondary to ischemia or surgical trauma. The fact that increased neurologic damage in the glucose group was not found in this study was not surprising in view of the small number of patients and the good outcome usually obtained after initial supratentorial craniotomy for tumor at our institution.

Our findings suggest that glucose should be avoided during resection of supratentorial tumors. Although glucose does prevent ketosis, the insulin levels observed in the saline group appear to be sufficient to prevent ketacidosis. In addition, hypoglycemia did not occur in patients not receiving glucose, and nitrogen loss at 24 h was the same regardless of the intraoperative therapy. However, patients receiving intraoperative glucose achieved plasma-glucose levels that have been associated with increased brain damage if ischemia had occurred. Therefore, the risk of enhancing ischemic damage by giving glucose may be a major consideration during surgical procedures where the risk of brain ischemia is increased. That increased neurologic damage in the glucose group was not found is not a major consideration in these recommendations. The metabolic data suggest a potential risk that may only apply to a small, but important, subgroup. However, the authors studied patients for only 4 h, and these recommendations may not hold for operations of longer duration.

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