Prolonged hyperglycemia in the early subacute period after cerebral infarction: effects on short term prognosis

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Abstract

Although the adverse effect of admission hyperglycemia in cerebral infarction on prognosis is well known, studies generally have not questioned the effect of hyperglycemia in the early subacute period on prognosis after a stroke.

Forty-six patients with acute ischemic stroke were separated into 3 groups: Group 1) Known diabetes or admission blood glucose (ABG) ≥ 140 mg/dl and HbA1c ≥ 8,0%; Group 2) ABG ≥ 140 mg/dl and HbA1c < 8,0%; and Group 3) ABG < 140 mg/dl and HbA1c < 8,0%. Blood glucose was followed-up 4 times a day for 10 days after the stroke and the mean of these measurements was calculated as the mean of glycemic regulation (MGR). Neurological evaluation was done at presentation and on day 10 and 30 with the National Institute of Health (NIH) scale. Oedema, lesion size and presence of hemorrhagic transformation were evaluated using CT.

The MGR was significantly higher in group 1 compared to the other two groups (p < 0.001 and p < 0.01) and in group 2 compared to group 3 (p < 0.001). Patients with clinical worsening had a significantly higher MGR (p < 0.05). Patients with marked cerebral edema had a significantly higher MGR (p < 0.01) compared to patients with lesser edema. No correlation was found between MGR and lesion size or hemorrhagic transformation.

Our results show that hyperglycemia in the early subacute period after cerebral infarction is associated with more pronounced cerebral edema and has an adverse effect on short term prognosis. We suggest that studies investigating the effect of insulin infusion on stroke prognosis should also consider infusions for a longer period than 24 hours.

Key words: Cerebral infarction; hyperglycemia; prognosis; cerebral edema.

Introduction

Diabetic patients have a worse prognosis and higher mortality rate compared to non-diabetics after acute stroke (Pulsinelli et al., 1983; Weinberger et al., 1983). In the past 10-15 years it has been shown that this is not only true for diabetics but that patients with high blood glucose levels prior to or shortly after a stroke have a worse prognosis independent from the presence of diabetes (Pulsinelli et al., 1983; Candelise et al., 1985; Weir et al., 1987; Woo et al., 1988; O’Neill et al., 1991; Capes et al., 2001; Bruno et al., 2002; Williams et al., 2002). Experimental studies have shown that high blood glucose levels prior to an occlusion of the middle cerebral artery lead to a greater infarct size and it has been suggested that this is caused by enhanced intra- and extracellular acidosis due to anaerobic glycolysis (de Courten Myers et al., 1988; Vasquez Cruz et al., 1990). Hyperglycemia at the time of ischemia also contributes to clinical worsening by increasing cerebral edema (Berger and Hakim, 1986; Chen et al., 1986) or increasing the probability of hemorrhagic transformation (Bruno et al., 2002). Although the reason for the high blood glucose concentrations which are frequently encountered after stroke even in non-diabetics is still a matter of debate it is generally thought that this is due to a stress response (Candelise et al., 1985; Woo et al., 1988; Power et al., 1988; O’Neill et al., 1991).

Even though the main damage occurs within the first 24 hours it is known that infarct volume can still expand beyond 24 hours (Bryan et al., 1991; Heiss et al., 1992). In a proton MR spectroscopic study, loss of cerebral metabolites in an infarcted region continued up to 10 days after the acute event, suggesting that damage is ongoing for an extended period (Saunders et al., 1995). In an experimental study on permanent middle cerebral artery occlusion in cats, de Courten-Myers showed that hyperglycemia at the time of occlusion increased infarct volume while hyperglycemia after the occlusion increased mortality secondary to cerebral edema (de Courten Myers et al., 1987).

Although it is now generally accepted that high blood glucose levels prior to or shortly after cerebral infarction have an adverse effect on prognosis studies generally have not questioned the effect of...
hyperglycemia in the early subacute period on prognosis after a stroke. In this study we aimed to assess whether high blood glucose levels in the first 10 days after a stroke had an additional effect on prognosis.

Subjects and Methods

Forty-six patients (19 women and 27 men) with acute ischemic stroke who presented to the emergency unit of the Akdeniz University Hospital within 24 hours of onset were included into the study. Their mean age was 63.9 ± 13.5 years. All patients informed consented to participate in the study.

All patients had a CT scan done to exclude other causes than ischemic stroke in the acute period. A second CT scan was done in the first week to assess lesion size, cerebral edema and development of hemorrhagic transformation. Lesion size was assessed in three categories: 1) Small infarct: Lesion not visible on CT scan or smaller than 10 mm, being visible on no more than 2 slices; 2) Medium size infarct: Lesions lying between small and large infarct; 3) Large infarct: Lesions involving at least one vascular territory. Ischemic edema was graded by modifying the scale suggested by Wardlaw and Sellars (Wardlaw and Sellars, 1994): 0) No edema; 1) Effacement of cortical sulci; 2) 1+ compression of the ipsilateral ventricle; 3) 1+ complete effacement of the ipsilateral ventricle or midline shift or effacement of the basal cisternae. Hemorrhagic transformation was evaluated as 0 = absent or 1 = present.

In all patients a random admission blood glucose (ABG) level was measured as soon as they entered the emergency unit and HbA1c was determined within the first 24 hours. According to these two parameters patients were categorized into one of three groups: Group 1) Previously known diabetes or ABG ≥ 140 mg/dl and HbA1c ≥ 8.0%; Group 2) ABG ≥ 140 mg/dl and HbA1c < 8.0%; and Group 3) ABG < 140 mg/dl and HbA1c < 8.0%.

Neurological status evaluation was done within 24 hours and at the 10th and 30th day following the event using the National Institute of Health (NIH) scale (Brott et al., 1989).

All patients had blood glucose determinations done 4 times daily (at 06, 12, 18 and 24 o’Clock) for 10 days following the insult. The admission blood glucose determination was not included into this analysis. Blood glucose measurements were always done by one of our three collaborators (AE, EM or CO) using a Medisense Precision-G, Abbot Laboratories glucometer. The mean of these 40 measurements was calculated as the mean of glycemic regulation (MGR). Analyses were based on the MGR. Blood glucose levels were aimed to be kept below 250 mg/dl by appropriate doses of insulin. Five patients received subcutaneous insulin treatment adjusted to the blood glucose level. These patients were not excluded because it was our aim to assess the effect of blood glucose levels on prognosis.

Statistical analysis was done by the SPSS for Windows 10.0 software program. Students’ t-test was used for equally distributed variables and Mann Whitney U and Kruskall Wallis tests were used for not equally distributed variables. Correlation analysis was done using the Spearman’s rho test. Statistical significance level was set at p < 0.05.

Results

The distribution of patients and mean MGR values within patient groups are given in Table 1. In group 1 the MGR was significantly higher compared to the other two groups (p < 0.001 and p < 0.01). In group 2 the MGR also was higher than group 3 (p < 0.001).

MGR values in the patients who showed improvement on the NIH scale or who deteriorated or died on assessment at day 10 and 30 are given in Table 2. MGR values were significantly higher in the patients who showed deterioration or died, both on day 10 and on day 30 (p < 0.05).

The distribution of CT features and the mean MGR’s according to lesion size, edema and hemorrhagic transformation are given in Table 3. Neither admission blood glucose levels nor blood glucose levels in the first 10 days after the event were associated with lesion size. MGR’s were significantly higher in the patients with pronounced cerebral edema. The MGR in the patients with massive edema (edema category 3) was significantly higher compared to the patients with no edema (p < 0.01) and the other two edema categories (edema categories 1 and 2) (p < 0.05). When edema categories 0, 1 and 2 were compared with each other no significant difference could be found. The MGR was higher in the patients with hemorrhagic

<table>
<thead>
<tr>
<th>Admission glycemia group</th>
<th>N</th>
<th>MGR</th>
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</thead>
<tbody>
<tr>
<td>Group 1 (Known DM or Admission blood glucose ≥ 140 mg/dl and HbA1c ≥ 8.0%)</td>
<td>7</td>
<td>176.9 ± 22.1*</td>
</tr>
<tr>
<td>Group 2 (Admission blood glucose ≥ 140 mg/dl and HbA1c &lt; 8.0%)</td>
<td>13</td>
<td>131.5 ± 18.4*</td>
</tr>
<tr>
<td>Group 3 (Admission blood glucose &lt; 140 mg/dl and HbA1c &lt; 8.0%)</td>
<td>26</td>
<td>113.8 ± 18.8</td>
</tr>
</tbody>
</table>

* p < 0.01 (Group 1 compared to Group 2).  
* p < 0.001 (Group 1 compared to Group 3).  
* p < 0.001 (Group 2 compared to Group 3).
transformation but this difference was not significant.

**Discussion**

The results of this study show that the admission blood glucose level after an acute stroke is conclusive about the degree of glycemic regulation in the following 10 days and that high glucose concentrations in the early subacute period after a stroke have an adverse effect on cerebral edema and a negative effect on short-term prognosis.

The adverse effect of elevated blood glucose levels in the acute period on the ischemic brain have been well documented (Pulsinelli et al., 1983; Weinberger et al., 1983; Candelise et al., 1985; Weir et al., 1987; Woo et al., 1988; O’Neill et al., 1991; Kawai et al., 1997; Bruno et al., 1999; Capes et al., 2001; Williams et al., 2002). This acute hyperglycemia can be seen not only in diabetic patients but also in patients who were previously normoglycemic and who are not diagnosed as diabetic afterwards, due to the stress caused by the acute event (Candelise et al., 1985; Woo et al., 1988; Power et al., 1988; O’Neill et al., 1991). It has been suggested that the negative prognostic effect of hyperglycemia in the acute period is independent from the presence of diabetes (Candelise et al., 1985; Weir et al., 1987). But it has not been questioned how the course of glycemia in patients with hyperglycemia after an acute stroke is and whether the blood glucose concentrations in the early subacute period affect outcome.

In this study admission hyperglycemia after a stroke was associated with high blood glucose concentrations in the first 10 days following the event and this hyperglycemic course was more profound in patients with high ABG and high HbA1c but also significant in the patients with only high ABG. The hyperglycemia in the early subacute period in the patients with high HbA1c is probably due to the already impaired glycemic regulation which becomes more compromised due to the acute stressfull event because this group also included patients with diabetes. The persisting hyperglycemia in the patients with high ABG and normal HbA1c could be explained by a prolonged adverse effect of the acute stressor event on glycemic regulation.

It has also been suggested that the hyperglycemia in the acute phase is related to stroke severity, independent from the presence of diabetes (Candelise et al., 1985; Woo et al., 1988; Power et al., 1988). It has been shown that acute phase hyperglycemia is associated with an increased infarct size and that in large infarcts the hyperglycemia is more profound (Candelise et al., 1985; de Courten Myers et al., 1987; Prado et al., 1988; de Falco et al., 1993; Kawai et al., 1997; Bruno et al., 1999). But whether hyperglycemia is the cause or the result of a large infarct remains unclear. We could not demonstrate an association between infarct size and neither acute hyperglycemia nor blood glucose levels in the first 10 days after the stroke. The reason for this could be the small number of small and medium sized infarcts in our study.

Several studies have shown that hyperglycemia in the acute phase of a stroke enhances cerebral edema (Berger and Hakim, 1986; Chen et al., 1986). We also showed that blood glucose levels in the early subacute period in patients with marked cerebral edema were significantly higher than patients with less pronounced edema or no edema.

In the GIST study, which was a randomized, controlled trial investigating the effect of insulin infusion in the acute phase on prognosis, it was shown that glucose-potassium insulin infusion did not have an effect on mortality and neurological scores on the 30th day but caused a slight improvement in neurological scores measured at the 48th hour after the stroke (Scott et al., 1999). In this study insulin infusion was only given during the first 24 hours. Taking the results of our study into regard we would suggest that studies investigating

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### Table 2

Mean of glycemic regulation (MGR) according to clinical improvement and survival

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>MGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10th day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>24</td>
<td>119.5 ± 21.6</td>
</tr>
<tr>
<td>Deteriorated or dead</td>
<td>22</td>
<td>138.2 ± 33.2</td>
</tr>
<tr>
<td>30th day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>26</td>
<td>119.2 ± 22.2</td>
</tr>
<tr>
<td>Deteriorated or dead</td>
<td>20</td>
<td>140.5 ± 32.8</td>
</tr>
</tbody>
</table>

*p < 0.05 (Improved vs Deteriorated or dead).

### Table 3

Mean of glycemic regulation (MGR) according to CT characteristics

<table>
<thead>
<tr>
<th>CT lesion size</th>
<th>N</th>
<th>MGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smaller infarct</td>
<td>9</td>
<td>124.9 ± 17.5</td>
</tr>
<tr>
<td>Medium infarct</td>
<td>10</td>
<td>117.0 ± 26.0</td>
</tr>
<tr>
<td>Larger infarct</td>
<td>27</td>
<td>133.8 ± 32.3</td>
</tr>
<tr>
<td>Cerebral edema category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17</td>
<td>117.0 ± 23.7</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>127.9 ± 24.5</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>123.7 ± 20.2</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>163.9 ± 35.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemorrhagic transformation</th>
<th>N</th>
<th>MGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>6</td>
<td>141.9 ± 21.8</td>
</tr>
<tr>
<td>Absent</td>
<td>40</td>
<td>126.4 ± 29.6</td>
</tr>
</tbody>
</table>

*p < 0.01 (Category 3 vs 0)

*p < 0.05 (Category 3 vs 1)

*p < 0.05 (Category 3 vs 2).
the effect of insulin infusion on stroke prognosis should also consider infusions for a longer period than 24 hours.

The results of this study show that in acute stroke patients with hyperglycemia the blood glucose levels continue to be high during the first 10 days after the stroke and that this hyperglycemia in the early subacute period has an adverse effect on cerebral edema and on short term prognosis. Larger scale studies involving treatment with insulin infusion are needed to confirm our results.

REFERENCES


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