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Clinical Study

Effects of glycaemic control on cerebral neurochemistry in primary intracerebral haemorrhage

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Abstract

This was a pilot study to compare the cerebral haemodynamics and neurochemical changes in patients with primary basal ganglia haemorrhage (PBGH), who underwent conventional blood glucose level (BGL) control and intensive BGL control with continuous titrated insulin therapy. Patients admitted over an 18-month period with PBGH after evacuation of haematoma were retrospectively divided into two groups according to the method used for BGL control: the 'intensive' group consisted of patients who underwent continuous titrated insulin infusion to maintain a lower normoglycemic level of 4–8 mmol/L, and the 'conventional' group consisted of patients whose BGL was maintained at between 8.1 and 10.0 mmol/L using conventional 'sliding scale' bolus subcutaneous insulin administration. Data on cerebral haemodynamics, interstitial brain oxygenation ($PtiO_2$) and neurochemical monitoring were collected via microcatheters inserted in the perihaemorrhagic penumbral region. A homogenous group of 12 patients with haemorrhage originating in the deep basal nuclei was identified. Five patients (42%) were included in the intensive group, and seven patients (58%) were included in the conventional group. The mean intracranial pressure, mean arterial pressure, BGL, extracellular (EC) lactate, EC glutamate, EC pyruvate and EC glycerol levels and the lactate/pyruvate ratio were found to be significantly lower ($p < 0.001$) in the intensive group compared with the conventional group, but the mean $PtiO_2$ and amount of insulin administered were higher ($p < 0.001$) in the intensive group. The mean cerebral perfusion pressure and EC glucose did not differ significantly between the two groups of patients. Maintenance of lower normoglycaemia (4–8 mmol/L) with continuous titrated insulin therapy is associated with improved cerebral haemodynamics, oxygenation and neurochemistry in the perihaemorrhagic penumbral region.

Keywords: Cerebral metabolism; Hyperglycaemia; Insulin; Microdialysis; Perihaemorrhagic penumbra

1. Introduction

While primary insults causing the onset of spontaneous intracerebral haemorrhage are beyond our control, the secondary insults and ischaemia that occur during intensive care can be prevented. Episodes of hyperglycaemia are of particular interest during intensive care, because increased blood glucose level (BGL) has been shown to adversely affect clinical outcome in stroke patients.[1–4] Hyperglycaemia has been shown to worsen the brain damage produced by cerebral ischaemia in animals and humans,[5–8] and stroke-related damage is augmented by hyperglycaemia regardless of whether diabetes is present or not, thus having a direct impact on neurological outcome.[2–4,9,10] Numerous studies examining the effect of insulin on the condition of critically ill patients in the intensive care setting have been published,[2–4,11,12] including a large trial conducted in a heterogeneous group of critically ill patients, which demonstrated that the use of intensive insulin treatment to prevent hyperglycaemia in diabetic and non-diabetic patients is associated with a significant decrease in mortality.[2–4] Van den Berghe et al.[3,4] recently reported that a reduction in blood glucose (achieved by insulin titration according to a simple algorithm, instead of the actual amount of insulin given) was significantly related to an observed reduction in the mortality rate and incidence of anaemia, bacteraemia, inflammation and critical illness polyneuropathy.

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However, there is little data available regarding the effects of insulin on cerebral haemodynamic and neurochemical changes in critically ill patients with spontaneous intracerebral hematomas. The cerebral microdialysis (CMD) technique has been used to detect neurochemical changes in patients with subarachnoid haemorrhage and severe head injury.[13–16]

In this pilot study, CMD was used for patients with primary basal ganglia haemorrhage (PBGH) to sample the small molecules present in the interstitial brain fluid in the perihaemorrhagic penumbra region. We hypothesised that intensive BGL control with continuous titrated insulin therapy would have a more favourable impact on cerebral haemodynamic parameters and neurochemistry compared with conventional BGL control using sliding scale insulin therapy in patients with PBGH.

2. Materials and methods

2.1. Patient selection and characteristics

This pilot study included patients who had undergone surgery for PBGH between January 2004 and August 2005. All patients were admitted to a dedicated 18-bed neuro-intensive care unit (NICU) for postoperative monitoring.

Patients were divided into two groups: those admitted between January and August 2005, who had undergone intensive BGL control using continuous titrated insulin therapy, were classified as the 'intensive' group, and those admitted between January and December 2004 were selected as the control group because they had received conventional BGL control with sliding scale insulin before intensive glycaemic control with continuous titrated insulin therapy was implemented as a standard treatment protocol in our NICU. Patients who were haemodynamically unstable and close to brain death on admission, or those for whom informed consent could not be obtained (for surgery) from their spouses or relatives were excluded from this study. The research protocol was approved by the local ethics committee.

2.2. General management of patients

On admission, the diagnosis of spontaneous basal ganglia intracerebral haematoma (ICH) was confirmed by computed tomography (CT) imaging. Surgery for PBGH was only carried out for non-elderly patients (<60 years of age) with deteriorating Glasgow Coma Scale (GCS) scores, in whom a large-volume haematoma (>50 mL) was detected on CT imaging.

Microdialysis (CMA 70; Microdialysis, Solna, Sweden) catheters were inserted to less than 1.5 cm from the edge of the haematoma cavity in the perilesional brain region, together with $PtiO_2$ (LICOX; Integra Neuroscience, Plainsboro, NJ, USA) and brain temperature probes, which were inserted in the standard fashion via a triple lumen skull bolt. Postoperative CT scans were performed to ascertain the depths of the catheters relative to the clot cavity.

Intracranial pressure (ICP) was monitored continuously by means of a ventricular catheter and/or intraparenchymal device (Codman and Shurtleff, Raynham, MA, USA). The patients underwent ICP/cerebral perfusion pressure (CPP)-directed management, in which intracranial hypertension (ICP > 20 mmHg) was managed according to standard guidelines for the management of intracerebral haemorrhagic stroke: cerebrospinal fluid (CSF) drainage was carried out via ventricular catheters, boluses of mannitol (0.5–1 g/kg body weight over a period of 20 min) were administered and moderate hyperventilation ($PaCO_2$ between 30 and 35 mmHg) was applied. Attempts were made to maintain CPP above 60 mmHg, if necessary using colloidal and non-colloidal agents.

2.3. Physiological monitoring

The mean duration of neuro-monitoring at the NICU was 5.5 days (range 3–10 days) and data from all patients throughout the period of monitoring are analysed in this study. The data collected for each patient included the following: heart rate; systemic systolic, diastolic, and mean arterial pressure (MAP); peripheral blood gases, and glycaemia. After admission to the NICU, all patients' arterial and central venous pressures were measured invasively using arterial and venous catheter lines, and the values were recorded as mean arterial pressure (MAP) and central venous pressure (CVP).

CPP was calculated as the difference between MAP and ICP. $PtiO_2$ monitoring was continuously carried out using a polarographic Clark-type microcatheter (LICOX: Integra Neuroscience) beginning 3 h after insertion of the probe (to allow it to stabilise). The mean hourly values of MAP, ICP and CPP were matched with CMD readings collected during the same hour. The different variables were continuously digitalised, displayed and stored on a software program for multimodal data acquisition.

2.4. Microdialysis procedure

CMD was performed using a catheter (CMA 70; Microdialysis, Solna, Sweden) with a membrane length of 10 mm, a diameter of 0.52 mm, and a molecular mass cut-off of 20 000 Da, which was perfused using a microinjection pump (CMA 106; Microdialysis) with artificial CSF at a rate of 0.3 μL/min. The dialysates (9–18 μL) were collected every hour, and were immediately analysed for glucose, lactate, pyruvate and glutamate with a microdialysis analyser (CMA 600; CMA/Microdialysis) by using an enzyme reagent and colorimetric measurements.

2.5. Conventional BGL control

BGL was monitored every 6 hours after determination of the initial BGL at admission. When BGL was between