Moderate hypothermia for 359 operations to clip cerebral aneurysms

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Background. Experimental data have suggested that hypothermia (32–34°C) may improve outcome after cerebral ischaemia, but its efficacy has not yet been established conclusively in humans. In this study we examined the feasibility and safety of deliberate moderate perioperative hypothermia during operations for subarachnoid aneurysms.

Methods. A total of 359 operations for intracranial cerebral aneurysms were included in this prospective study. By using cold intravenous infusions (4°C) and convective cooling our aim was to reduce the patient's core temperature to more than 34°C within 1 h before operation. The protocol assessed postoperative complications such as infections, prolonged mechanical ventilation, pulmonary complications and coagulopathies.

Results. During surgery, the body temperature was reduced to a mean of 32.5 (SD 0.4) °C. Cooling was accomplished at a rate of 4.0 (SD 0.4) °C h−1. All patients were normothermic at 5 (SD 2) h postoperatively. Peri/postoperative complications included circulatory instability (n=36, 10%), arrhythmias (n=17, 5%) coagulation abnormalities and blood transfusion (n=169, 47%), infections (n=29, 8%) and pulmonary complications (infiltrate or oedema while on ventilatory support) (n=97, 27%). Eighteen patients died within 30 days (5%). There was no significant correlation between the extent of hypothermia and any of the complications. However, there was a strong correlation between the occurrence of complications and the severity of the underlying neurological disease as assessed by the Hunt and Hess score.

Conclusion. Moderate hypothermia accomplished within 1 h of induction of anaesthesia and maintained during surgery for subarachnoid aneurysms appears to be a safe method as far as the risks of peri/postoperative complications such as circulatory instability, coagulation abnormalities and infections are concerned.


Keywords: arteries, cerebral, aneurysm; complications, hypothermia; surgery, neurological

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The mortality of aneurysmal subarachnoid haemorrhage is reported to be 19–45%,1 2 and this has forced physicians to re-evaluate therapeutic options. Even experienced surgeons meet with unforeseen difficulties during these operations,2 3 so we have adopted a protocol that combines very early referral for operation with aggressive anti-ischaemic adjunctive treatment based on several principles, of which perioperative moderate (32–34°C) hypothermia is the most important. The protective effect of hypothermia to below 32°C on cerebral ischaemia has been claimed for a long time, based on theoretical calculations, data from animal experiments and recently through several published studies concerning the benefit of hypothermia after cardiac arrest.1–6 The benefits of moderate (32–34°C) hypothermia have been shown in several experimental studies7 8 but there have been few prospective randomized controlled trials in humans.9 10

Assuming a cerebral protective effect of moderate hypothermia (range 32–34°C), the aim of the present study was to achieve moderate hypothermia (32–34°C) within 1 h after the induction of anaesthesia and before the commencement of surgery, and to maintain this temperature until the aneurysm had been clipped. Because the operations were done at a single centre and the number of patients was limited, a randomized controlled trial was deemed inappropriate. The main aim of this study was to determine the incidence and extent of peri/postoperative complications such as circulatory instability, coagulopathies and infections that could be related to the hypothermia. We also looked for a possible
correlation between these complications and the extent of hypothermia (the depth of hypothermia and the total hypothermic time). To take account of the effects of the underlying cerebral condition and variations in operative technique on outcome they were adjusted for the Hunt and Hess score.\textsuperscript{11}

**Patients and methods**

The study was approved by the hospital ethics committee (Institutional Review Board). All patients admitted to the neurosurgical intensive care unit at Linköping University Hospital between 1994 and 2000 with the diagnosis of subarachnoid cerebral aneurysm were prospectively considered for this study. Patients who had atrial fibrillation, had a recent myocardial infarction or were in renal failure were excluded, as were those who were pregnant. If the neurosurgical condition of a patient was considered too critical to delay surgery for the period required to establish hypothermia, the patient was not included. During the initial period pilot experiments were done to optimize the protocol, and these patients were excluded from analysis.

**Protocol**

The anti-ischaemic protocol combined early diagnosis of the lesion and the prevention of ischaemia by pharmacological treatment and hypothermia. As soon as patients entered the operating room, where the temperature was set at 18°C, a central venous line was inserted for injection of inotropic drugs and nimodipine if they were considered clinically appropriate.\textsuperscript{12} Immediately after induction of anaesthesia about 450 ml of blood was withdrawn through the central venous line. Saline 0.9% (2000–3000 ml) and hetastarch (500 ml) at 4°C were given intravenously together with a high dose of thiopental (15 mg kg\textsuperscript{−1}). We aimed to achieve a core body temperature below 34°C before the dura was opened. The core temperature was measured using a temperature probe (Datex-Ohmeda\textsuperscript{TM}, Finland) placed in the mid-portion of the oesophagus. Anaesthesia was maintained with sevoflurane at an end tidal concentration in the range 0.8–1.2 minimal alveolar concentration (MAC). Monitoring included continuous electrocardiography, direct arterial and central venous pressures, end tidal carbon dioxide (ventilation was adjusted to maintain normocapnia), pulse oximetry and urinary output. Blood gas and other analyses (including measurements of concentrations of haemoglobin, sodium and potassium) were made regularly. Potassium was infused if needed to ensure normokalaemia (3.5–5.0 mmol litre\textsuperscript{−1}). After the aneurysm had been clipped the patient was actively rewarmed using convection warmers and warmed intravenous infusions. Postoperatively, patients were kept in the Neurosurgical Intensive Care Unit. If an operation was complicated or the surgical procedure or recovery was expected to be delayed, the patient was sedated with a combined infusion of midazolam (1 mg ml\textsuperscript{−1}) and morphine (10 mg ml\textsuperscript{−1}). All others were sedated with propofol (10 mg ml\textsuperscript{−1}) until the temperature returned to normal (36.8°C) and were then extubated. The criteria for extubation were normothermia, haemodynamic stability, no neurological deficiency, and adequate ventilation (P\textsubscript{O\textsubscript{2}}<0.40) and inspiratory pressure support (<10 cm H\textsubscript{2}O).

**Outcome measures**

**Cardiovascular complications**

The number of patients who required inotropic support, other than preoperatively or during cooling, and the number who developed an arrhythmia (atrial fibrillation or flutter, heart rate <50 or >120 beats min\textsuperscript{−1} or other arrhythmia requiring pharmacological intervention) was recorded.

**Perioperative bleeding**

This was measured as units of blood transfused; a postoperative haemoglobin concentration of 12 g dl\textsuperscript{−1} was aimed at. All surgeons were asked about any unusual bleeding and this information was added to the charts.

**Infection**

The possibility of infection was raised when there was an increase in C-reactive protein concentration, which was measured in all patients. Infections were confirmed by cultures, by infiltrates on chest radiographs or by the need to prescribe additional antibiotics.

**Postoperative ventilatory support**

This was considered to be an important endpoint as an indicator of complications of the hypothermia. Patients who had bilateral pulmonary infiltrates without any clear sign of infection were considered to have pulmonary oedema (from cardiac failure, neurogenic factors or treatment).

**Statistics**

Data are presented as mean (SD). Associations between variables were assessed by multiple regression analyses. To reduce any effect of the underlying cerebral condition the complication rates were adjusted for the Hunt and Hess score.\textsuperscript{11} As there was no contemporary control group we attempted to find a correlation between the above endpoints and the extent of hypothermia, measured by the maximal decline of temperature and the total hypothermic time.

**Results**

Three hundred and fifty-eight patients were considered for inclusion in the study. One was excluded because she was pregnant, one because of recent myocardial infarction, one because of renal failure and five because of the urgency of
Further patients were excluded from analysis because of missing data (n = 8) or because they were piloting the hypothermia protocol (n = 16). Therefore, 326 patients who had 359 operations for clipping of cerebral aneurysms were included in the analysis (Table 1). From the induction of hypothermia the target temperature (<34°C/14°C) was reached in a mean of 1 (SD 0.3) h. Obese patients took a longer time to cool. After the aneurysm had been clipped, warming was started and the patients were normo-thermic (36.8°C/14°C) in a mean of 5 (2) h (Fig. 1). The lowest temperature was at the time of clipping. A substantial number (n=334, 93%) of the patients were still hypothermic (<36.8°C) when they arrived at the Neurosurgical Intensive Care Unit. After 197 operations (55%) transient hyperthermia was noted.

The incidence of complications is indicated in Table 2. There was no significant correlation between the extent of hypothermia and any of the complications. However, there was a strong correlation between the occurrence of complications and the severity of the underlying neurological disease as assessed by the Hunt and Hess score.

**Discussion**

Our protocol was based on rapid infusion of cold solutions to replace blood that had been withdrawn (isovolaemic haemodilution) together with external cooling. This has been shown to be successful for rapid induction of moderate hypothermia for patients treated by hypothermia after stroke or cardiac arrest.13-14 Our technique produced hypothermia more rapidly than has been reported previously10 and in practice worked well.

Although we had a number of perioperative events and considerable postoperative morbidity we found no correlation with either the maximum reduction in temperature or the duration of hypothermia. Postoperative complications (Table 2) correlated strongly with the Hunt and Hess score, suggesting that these complications were related more to the underlying cerebral condition than to the hypothermia. The complications that we found were in the same range as those presented by others after non-hypothermic subarachnoid operations.1-15
The incidence of 10% of patients who required inotropic support during operation is in line with, or less than, that which was reported in a large multicentre study.1 The incidence of arrhythmias (5%) was low and in line with that reported by Solenski and colleagues.1 The adverse circulatory effects in our study were also less common than had been reported in a study of hypothermia in patients with brain trauma.19 Our rate of haemodynamic complications was also lower than has been described in normothermic patients with subarachnoid haemorrhage.17 It is our strategy to maintain high haemoglobin concentrations (>12 g dl⁻¹) to assist oxygen transport to the brain. Therefore on neurological grounds we did not minimize volumes transfused. Although there were 266 ruptured aneurysms, only 74 (27%) of our patients were given blood transfusions perioperatively. This is comparable with another study (normothermia) in which 30% of the patients with ruptured aneurysms were given transfusions perioperatively.18

The infection rate (8% of the cultures of blood or cerebrospinal fluid grew pathogens) is comparable with that reported by Shapiro and colleagues19 (11.7%). Solenski and colleagues1 reported an infection rate of 30%. They also reported that, after a subarachnoid hemorrhage, 45% of patients developed either pulmonary oedema (23%) or pneumonia (22%). In the more recent study by Friedman and colleagues15 pulmonary complications were recorded in 22% of the patients. Two factors are relevant, both of which are related to increases in extravascular pulmonary water. The first is that the pharmacological treatment is thought to increase the risk of pulmonary oedema. The second is that neurogenic pulmonary oedema is thought to result from a large increase in sympathetic vascular tone. Our results (pulmonary complications in 27–44%) are within the reported range.1,15 As these complication rates were strongly correlated with the Hunt and Hess score, we consider that the effect of hypothermia is minor compared with the underlying cerebral condition, which is known to be a significant risk factor for respiratory problems. However, it needs to be stressed that, from a scientific viewpoint, we cannot exclude that there might be a negative synergistic effect of the hypothermia and neurological injury with increased risk of pulmonary complications. It might be argued that more aggressive warming would have allowed more patients to be extubated in the operating room and that this might have reduced the incidence of postoperative ventilatory complications.20

Conclusion

We recommend the setting up of a large multicentre clinical study to establish whether moderate hypothermia for operations on intracranial aneurysms does improve neurological outcome and can therefore be established for routine clinical use.

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