Preoperative high dose methylprednisolone attenuates the cerebral response to deep hypothermic circulatory arrest

Stephen M. Langley*, Paul J. Chai, James J. Jaggers, Ross M. Ungerleider

Department of Pediatric Cardiac Surgery, Duke University Medical Center, Durham, NC, USA

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Abstract

Objective: The aim of this study was to assess the effects of preoperative high dose methylprednisolone on cerebral recovery following a period of deep hypothermic circulatory arrest (DHCA). Methods: Sixteen 1-week-old piglets were randomized to placebo (n = 8), or 30 mg/kg intramuscular methylprednisolone sodium succinate (MPRED) given at 8 and 2 h before induction of anaesthesia. All piglets underwent cardiopulmonary bypass, cooling to 18°C, 60 min of circulatory arrest followed by 60 min of reperfusion and rewarming. The radiolabelled microsphere method was used to determine the global and regional cerebral blood flow (CBF) and cerebral oxygen metabolism (CMRO₂) at baseline before DHCA and after 60 min of reperfusion. Results: In controls, mean global CBF (± 1 standard error) before DHCA was 53.7 ± 2.4 ml/100 g per min and fell to 23.8 ± 1.2 ml/100 g per min following DHCA (P < 0.0001). This represents a post-DHCA recovery to 45.1 ± 3.3% of the pre-DHCA value. In the MPRED group recovery of global CBF post-DHCA was significantly higher at 63.6 ± 5.2% of the pre-DHCA value (P = 0.009). The regional recovery of CBF in the cerebellum, brainstem and basal ganglia was 80, 75 and 69% of pre-DHCA values in the MPRED group respectively compared to 66, 60 and 55% in controls (P < 0.05). Global CMRO₂ in controls fell from 3.9 ± 0.2 ml/100 g per min before to 2.3 ± 0.2 ml/100 g per min after DHCA (P = 0.0001). This represents a post-DHCA recovery to 58.6 ± 4.4% of the pre-DHCA value. In the MPRED group, however, recovery of global CMRO₂ post-DHCA was significantly higher at 77.9 ± 7.1% of the pre-DHCA value (P = 0.04). Conclusions: Treatment with high dose methylprednisolone at 8 and 2 h preoperatively attenuates the normal cerebral response to a period of deep hypothermic ischaemia. This technique may therefore offer a safe and inexpensive strategy for cerebral protection during repair of congenital heart defects with the use of DHCA. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Methylprednisolone; Congenital heart defects; Circulatory arrest

1. Introduction

The use of deep hypothermic circulatory arrest (DHCA) during the repair of congenital heart defects is followed by a period of abnormal cerebral hyperperfusion and impaired cerebral oxygen metabolism (CMRO₂) that may last for some hours afterwards [1,2]. These changes are associated with impairment of intracellular brain oxygenation [3]. Paediatric patients exposed to a period of DHCA have a higher incidence of postoperative neurological disturbance and delayed motor development compared to those in whom low flow cardiopulmonary bypass (CPB) is used [4]. The reduction in CMRO₂ that follows DHCA is often regarded as a marker for neuronal injury as CMRO₂ recovers normally after hypothermic CPB when DHCA is not used [3].

The precise mechanism for the changes observed after DHCA is incompletely defined. There appears to be an imbalance between various cerebral vascular constricting and dilating factors [5,6]. The development of cerebral oedema following DHCA is also a major contributory factor to the subsequent reduction in CBF and CMRO₂. Indirect evidence for this comes from work showing an improvement in cerebral recovery with the use of modified ultrafiltration after DHCA [7]. More recently, however, direct evidence of perivascular cerebral oedema has been demonstrated using electron microscopy to visualize the cerebral microcirculatory bed under various conditions of deep hypothermic cerebral ischaemia and reperfusion [8].

Ever since the early reports of corticosteroid treatment in the context of neuro-oncology in the 1950s the role of corti-
corticosteroids in cerebral pathological states has received considerable attention. Their use in the reduction of tumour-induced cerebral oedema has become well established [9]. Their use in cerebral trauma, and following both stroke (focal) and global cerebral ischaemia, however, remains controversial. There have been many studies concluding that corticosteroids can reduce cerebral oedema [10].

Additional uses of MPRED in cerebral pathological conditions include the reduction of cerebral vasospasm following subarachnoid haemorrhage [11]. The mechanism for this is believed to be inhibition of haemorrhage-initiated vasoconstrictor prostanoid action [12]. There is now considerable evidence that MPRED is also a direct neuroprotectant. It was demonstrated in the 1980s that a single large dose of MPRED-protected spinal cord tissue following subarachnoid haemorrhage [11]. The mechanism for this is believed to be inhibition of haemorrhage-initiated vasoconstrictor prostanoid action [12]. One of the most striking things about this study was the very large dose of 30 mg/kg that was required. Treatment with lower doses was ineffective and doubling the dose to 60 mg/kg resulted in a loss of the effect. A repeated finding in studies demonstrating neuroprotection with MPRED, has been the need for much larger doses than those employed in conventional clinical treatment.

The aim of the current study was to determine the effects of high dose preoperative MPRED (30 mg/kg) on cerebral recovery following DHCA. The null hypothesis for this study is that MPRED given at 8 and 2 h before the induction of anaesthesia does not affect cerebral blood flow or metabolism following 60 min of DHCA in the neonatal piglet.

2. Materials and methods

2.1. Animal preparation

All animal experiments were conducted with the approval of the institution’s Animal Care and Use Committee. The animals received humane care in compliance with the ‘Guide for the Care and Use of Laboratory Animals’ published by the National Institutes of Health (NIH publication 85-23, revised 1995) and were housed in the institution’s NIH-approved animal facility before the experiments.

Sixteen neonatal piglets (1–2 weeks old) were anaesthetised with an intramuscular injection of ketamine (50 mg/kg) and acepromazine (15 μg/kg). Orotracheal intubation was performed and mechanical ventilation (Infant Ventilator, Sechrist Industries, Anaheim, CA) was commenced to achieve arterial oxygen tensions of 150–250 mmHg and carbon dioxide tensions of 35–45 mmHg. The animals were paralyzed with intravenous pancuronium (300 μg/kg) and anaesthetized with fentanyl (100 μg/kg). Thereafter, anaesthesia was maintained with a continuous infusion of fentanyl (25 μg/kg per h). An 18-gauge cannula was placed in the descending aorta via the femoral artery for blood pressure monitoring and arterial blood sampling. The animal’s temperature was monitored throughout the study by an indwelling nasopharyngeal temperature probe (Yellow Springs Instrument Inc, Yellow Springs, OH). Temperature was maintained at 36°C except for the period of induced hypothermia.

The heart was exposed through a median sternotomy. Cardiac instrumentation consisted of a 3F micromanometer (Millar Instruments Inc, Houston, TX) inserted into the superior vena cava for central venous pressure monitoring and placement of an 8-mm flow probe (Transonic Systems, Ithaca, NY) around the proximal pulmonary artery for cardiac output monitoring.

2.2. Sagittal sinus access

The animals were anticoagulated with intravenous heparin (500 IU/kg) before access of the sagittal sinus. A 1-cm strip of scalp was raised in the midline over the vertex of the skull. Two separate 2-mm burr holes were made over the superior sagittal sinus for repeated sagittal sinus venous blood sampling and continuous sagittal sinus venous pressure monitoring with a 3F micromanometer (Millar Instruments Inc, Houston, TX).

2.3. Cardiopulmonary bypass and circulatory arrest

An 8F arterial cannula and a 20F venous cannula (DLP Inc., Grand Rapids, MI) were inserted through purse string sutures into the ascending aorta and the right atrium, respectively. Cardiopulmonary bypass (CPB) was commenced at a flow rate of 120 ml/kg per min. The pump-oxygenator system consisted of a Sarns non-pulsatile roller pump (Sarns Inc., Ann Arbor, MI) and a Medtronic® Minimax PLUS™ hollow fibre membrane oxygenator (Medtronic Inc., Anaheim, CA). No arterial filter was used. The circuit was primed with heparinized fresh blood from a donor pig. Ringer’s lactate and sodium bicarbonate solutions were added to the prime to achieve a haematocrit of 0.25 and a pH of 7.4 at 37°C. The total prime volume was approximately 450 ml. The temperature of the perfusate was controlled with the integral heat exchanger in the venous reservoir of the oxygenator and a BIO-CAL 370 water bath system (Biomedicus, Minneapolis, MN). Animals were cooled to a temperature of 18°C over a standard duration of 20 min by the circulation of ice water through the heat exchanger. At the end of the cooling period, the circulation was arrested and the animal drained. DHCA was therefore established and the aortic and right atrial cannulae were clamped. After 60 min of DHCA, the aortic and venous cannulae were unclamped. Perfusion was re-established at 120 ml/kg per min with the perfusate initially at room temperature (20–22°C). Rewarming was accomplished by circulating warm water to the heat exchanger in the venous reservoir. A nasopharyngeal temperature of 36°C was generally reached by 45 min of reperfusion. During cooling
and rewarming, blood gases were managed according to the ‘alpha-stat’ strategy. The arterial pH was maintained at 7.35–7.45 and carbon dioxide tension at 35–45 mmHg measured at 37°C and uncorrected for the temperature of the animal. Arterial oxygen tension was kept between 150 and 250 mmHg and the haematocrit between 0.23 and 0.28. Sodium bicarbonate (8.4%) was given when necessary but not immediately before cerebral blood flow measurements. At the end of the study, the animals were killed by a bolus injection of fentanyl and cessation of CPB.

2.4. Measurement of cerebral blood flow

Cerebral blood flow (CBF) measurements were determined by the reference-sample, radiolabelled microsphere technique [14] during CPB at 36°C. The technique described in the current study is the same as that used in previous reports from our laboratory [6]. At the end of the experiment, the brain was removed and divided into left and right cerebral hemispheres, basal ganglia, cerebellum and brain stem (midbrain,pons, and medulla oblongata). In addition the kidneys were also removed for determination of renal blood flow (RBF). After measurement of fresh weights, the brain parts and kidneys were dissolved in 2 M potassium hydroxide solution and analyzed, together with the reference blood sample, in a gamma counter (Auto-Gamma 5530; Packard Instrument Co, Meriden, CT) to estimate the quantity of each type of radiolabelled microsphere present in the specimen. Cerebral blood flow measurements are expressed in ml/100 g of brain per min by normalizing for fresh tissue weight. The weighted sum of regional cerebral blood flow allowed calculation of global cerebral blood flow.

Cerebral perfusion pressure (CPP) was taken as the difference between the mean arterial pressure and the sagittal sinus venous pressure. Cerebral vascular resistance was the ratio of cerebral perfusion pressure to global cerebral blood flow (in units of mmHg100 g.min/ml). Systemic vascular resistance was taken as the ratio between the systemic perfusion pressure and the total bypass pump flow rate (systemic vascular resistance = [mean arterial pressure – right atrial pressure]/[pump flow rate] in units of mmHg.100 g.min/ml).

2.5. Measurement of cerebral oxygen handling

Arterial and sagittal sinus blood samples were taken just before each microsphere injection for estimation of oxygen tension, carbon dioxide tension, oxygen saturation, pH, and base excess using a GEM-Stat Blood Gas/Electrolyte Monitor (Mallinckrodt Sensor Systems Inc., Ann Arbor, MI). Haemoglobin levels (in g/dl) were measured from arterial blood samples (482 Co-Oximeter; Instrumentation Laboratory Corp, Lexington, MA). Cerebral delivery of oxygen (CDO$_2$ in ml/100 g brain per min), cerebral metabolic rate of oxygen (CMRO$_2$ in ml/100 g brain per min) and cerebral oxygen extraction (CEO$_2$ as a percentage) were calculated as follows: CDO$_2$ = cerebral blood flow × arterial oxygen content; CMRO$_2$ = cerebral blood flow × (arterial oxygen content – sagittal sinus venous oxygen content), and CEO$_2$ = (CMRO$_2$/CDO$_2$ × 100%. The oxygen content (in units of ml O$_2$/ml of blood) was calculated by the following formula: O$_2$ content = 0.01 × [(1.36)(haemoglobin)(oxygen saturation) + (0.003)(oxygen tension)].

2.6. Experimental protocol and data collection

The animals were randomized into two groups with eight animals in each group. The study group received 30 mg/kg MPRED (Pharmacia and Upjohn Company, Kalamazoo, MI) at 8 and 2 h before induction of anaesthesia. For practical reasons the preoperative doses of MPRED were administer by the intramuscular (i.m.) route. In terms of both the bioavailability and pharmacokinetics of MPRED the i.m. route is equally as efficacious as the intravenous (i.v.) route and the extent of absorption of free MPRED following i.v. and i.m. administration is equivalent. Although the i.v. route results in a higher initial peak concentration, at 1 h after administration there is no difference in the plasma levels [15]. The control group received 1 ml of sterile water for injection i.m. at the same time points. All animals were cannulated for CPB and normothermic perfusion was commenced at 120 ml/kg per min. The animals were stabilised on normothermic CPB for a minimum of 20 min before the pre-DHCA measurement was taken. During this time the pump flow was adjusted to provide a constant CPP of 50 mmHg. Following the pre-DHCA measurement, pump flow was returned to 120 ml/kg per min and the animals cooled for DHCA. At the end of 60 min of DHCA circulation was recommenced and the animals rewarmed. At 45 min of reperfusion, pump flow rate was again adjusted to provide a CPP of 50 mmHg for 15 min before the post-DHCA cerebral blood flow measurement was made at 60 min of reperfusion. Data collected at the two time points included nasopharyngeal temperature, mean arterial blood pressure, right atrial pressure, sagittal sinus venous pressure, arterial and sagittal sinus blood gases, CPB flow rate, electrolytes, hematocrit, hemoglobin, CBF and RBF.

2.7. Statistical analysis

All the results were entered into an ‘IBM compatible’ Excel 97 spreadsheet (Microsoft® Corporation, Redmond, WA) for further analysis. Repeating formulae were set up to calculate the mean and standard error of the mean for all the data collected. Further repeating formulae were programmed for calculation of the CBF, CDO$_2$, CEO$_2$, CMRO$_2$ and the percentage change between these, before and after DHCA for all animals. A two-tailed paired samples t-test was used to compare means at different time points within a group. An unpaired (independent samples) t-test was used to compare means between the groups. Statistical significance was tested at the 95% confidence limit.
3. Results

Nasopharyngeal temperature, arterial blood gases, pH, haemoglobin, haematocrit, and cerebral perfusion pressure were similar before DHCA in both the control and the MPRED groups ($P > 0.33$, data not shown). Within the two groups no significant differences were detected between pre-DHCA and post-DHCA measurements of these variables ($P > 0.07$). Before DHCA global cerebral blood flow, cerebral vascular resistance and cerebral oxygen handling were also similar in the two groups ($P > 0.37$).

3.1. The effects of DHCA in control animals

Sixty minutes of DHCA followed by 60 min of rewarming in the control group resulted in a significant fall in the SVR from $0.43 \pm 0.05$ mmHg·100 g·min/ml pre-DHCA to $0.33 \pm 0.02$ mmHg·100 g·min/ml post-DHCA ($P = 0.05$). This fall necessitated a rise in mean pump flow from $144 \pm 0.02$ ml/kg per min before DHCA to $182 \pm 9$ ml/kg per min after DHCA ($P = 0.03$) in order to maintain the preset CPP of 50 mmHg at the time of CBF measurement. The mean global CBF was $53.7 \pm 2.4$ ml/100 g per min and fell to $23.8 \pm 1.2$ ml/100 g per min following DHCA ($P < 0.0001$). This represents a post-DHCA recovery to $45.1 \pm 3.2\%$ of the pre-DHCA value. There was a significant reduction in blood flow to all regions of the brain in the control group following DHCA ($P < 0.001$). Different brain regions were affected to varying degrees (Table 1).

Recovery of blood flow was lowest in the cerebral hemispheres ($43.3 \pm 2.8\%$ of pre-DHCA level) and greatest in the cerebellum ($66.4 \pm 5.6\%$ of the baseline) (Fig. 1).

Changes in global cerebral oxygen handling and CVR following DHCA are shown in Table 2. The CDO$_2$ and CMRO$_2$ fell to $48.5 \pm 3.8$ and $58.6 \pm 4.4\%$ of the pre-DHCA levels, respectively, ($P = 0.0001$) and the CEO$_2$ and CVR were both significantly higher following DHCA ($P = 0.03$, $P = 0.0001$). Finally, in the control group the renal blood flow fell after DHCA to $67.3 \pm 5.9\%$ of the flow before circulatory arrest ($P = 0.003$) (Fig. 2).

3.2. The effects of methylprednisolone

In the MPRED group, as in the controls, the SVR fell after DHCA ($0.40 \pm 0.02$ mmHg·100 g·min/ml compared to $0.46 \pm 0.03$ mmHg·100 g·min/ml pre-DHCA, $P = 0.005$). This fall necessitated a rise in pump flow from $129 \pm 9$ ml/kg per min before to $154 \pm 9$ ml/kg per min after DHCA ($P = 0.006$). The change in pump flow again reflects maintenance of the preset level of CPP at $50$ mmHg despite changes in the SVR. The change in SVR and pump flow after DHCA, however, were significantly less in the MPRED group than in the control group ($P = 0.04$, $P = 0.05$).

The mean global CBF was $49.7 \pm 5.0$ ml/100 g per min and fell to $31.2 \pm 4.2$ ml/100 g per min following DHCA ($P = 0.001$). This represents a post-DHCA recovery to $63.6 \pm 5.2\%$ of the pre-DHCA value which is significantly higher than the $45.1 \pm 3.3\%$ recovery in CBF seen in control animals ($P = 0.009$). As in the control group the post DHCA regional blood flows in the MPRED group fell following DHCA ($P < 0.001$) (Table 1). When compared to the post DHCA values in the control group, however, the regional blood flows were higher in the MPRED group in all brain regions – significantly so in the brain stem and cerebellum ($P < 0.04$) (Table 1). Furthermore, when expressed as a percentage of the pre-DHCA value, recovery of regional CBF following DHCA in the MPRED group was significantly greater than in controls ($68.9 \pm 2.5\%$ vs. $55.2 \pm 5.7\%$ in the basal ganglia ($P = 0.04$), $75.3 \pm 3.0\%$ vs. $60.2 \pm 4.7\%$ in the brain stem ($P = 0.02$) and $79.8 \pm 2.9\%$ vs. $66.4 \pm 5.6\%$ in the cerebellum ($P = 0.05$) (Fig. 1).

The CVR in the MPRED group was higher following DHCA than before (Table 2). Compared with the control group, however, the increase in CVR in the MPRED group (169 $\pm 15\%$) was significantly lower ($P = 0.025$) than in the control group (228 $\pm 18\%$). The results in terms of the cerebral oxygen handling in the MPRED group are shown in Table 2 and Fig. 3. The CDO$_2$ fell to $68.4 \pm 5.9\%$ of the pre-DHCA level which was significantly higher than the recovery to $48.5 \pm 3.8\%$ of baseline in the control animals ($P = 0.01$) and the CMRO$_2$ recovered to $77.9 \pm 7.1\%$ of the pre-DHCA level which was also significantly greater.

### Table 1

<table>
<thead>
<tr>
<th>Cerebral and renal blood flow in control and MPRED groups before and following deep hypothermic arrest$^*$</th>
<th>Group</th>
<th>Pre-DHCA</th>
<th>Post-DHCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global CBF</td>
<td>Control</td>
<td>$53.7 \pm 2.4$</td>
<td>$23.8 \pm 1.2^*$</td>
</tr>
<tr>
<td></td>
<td>MPRED</td>
<td>$49.7 \pm 5.0$</td>
<td>$31.2 \pm 4.2^*$</td>
</tr>
<tr>
<td>Hemispheres</td>
<td>Control</td>
<td>$54.1 \pm 1.5$</td>
<td>$23.3 \pm 1.2^*$</td>
</tr>
<tr>
<td></td>
<td>MPRED</td>
<td>$48.1 \pm 2.8$</td>
<td>$25.9 \pm 1.9^*$</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Control</td>
<td>$53.0 \pm 2.3$</td>
<td>$35.3 \pm 3.3^*$</td>
</tr>
<tr>
<td></td>
<td>MPRED</td>
<td>$56.2 \pm 2.3$</td>
<td>$44.9 \pm 2.6^{***}$</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>Control</td>
<td>$39.8 \pm 3.8$</td>
<td>$20.7 \pm 1.3^*$</td>
</tr>
<tr>
<td></td>
<td>MPRED</td>
<td>$36.8 \pm 2.5$</td>
<td>$25.3 \pm 1.8^*$</td>
</tr>
<tr>
<td>Brain stem</td>
<td>Control</td>
<td>$40.1 \pm 2.3$</td>
<td>$23.9 \pm 1.9^*$</td>
</tr>
<tr>
<td></td>
<td>MPRED</td>
<td>$41.8 \pm 2.2$</td>
<td>$31.5 \pm 2.2^{***}$</td>
</tr>
<tr>
<td>Renal</td>
<td>Control</td>
<td>$134.8 \pm 7.5$</td>
<td>$89.0 \pm 7.1^*$</td>
</tr>
<tr>
<td></td>
<td>MPRED</td>
<td>$163.8 \pm 12.0$</td>
<td>$159.3 \pm 10.0^{**}$</td>
</tr>
</tbody>
</table>

$^*$The study group (MPRED) received 30 mg/kg methylprednisolone by intramuscular (i.m.) injection at 8 and 2 h before induction of anaesthesia. Control animals received 1 ml of water i.m. at the same time points. All animals underwent 60 min of deep hypothermic circulatory arrest (DHCA) at $18\degree C$ and were rewarmed and reperfused for 1 h. Cerebral blood flow (CBF) measurements were all determined at a cerebral perfusion pressure of 50 mmHg. All values in units of ml/100 g per min. $^*$Significant difference from pre-DHCA value within group, paired t-test $P < 0.05$. $^{**}$Significant difference from control value post-DHCA, unpaired t-test $P < 0.05$. $^{***}$Significant difference from pre-DHCA value within group, paired t-test $P < 0.01$. $^*$Significant difference from control value post-DHCA, unpaired t-test $P < 0.05$.
than the recovery to 58.6 ± 4.4% in the controls (P = 0.04). In contrast to the control group the CEO2 was not significantly higher in the MPRED group following DHCA (P = 0.13). Finally in the MPRED group no difference was detected in the RBF following DHCA with recovery to 99.3% of the pre DHCA level (Fig. 2).

4. Discussion

In the current study, animals were treated with two doses of MPRED (30 mg/kg), at 8 and 2 h before induction of anaesthesia. The timing of the doses was based on evidence suggesting that de novo protein synthesis is involved in the cerebroprotective effect of corticosteroids. The protective effect of dexamethasone in ischaemia induced cerebral oedema, for example, can be blocked by actinomycin D, an inhibitor of messenger RNA synthesis [16].

In control animals, following 60 min of DHCA at 18°C and 60 min rewarming, the SVR fell and the pump flow was increased to maintain a constant CPP. Throughout this study all CBF measurements were taken at a constant CPP of 50 mmHg as it has been shown that it is the arterial blood

Table 2

Global cerebral oxygen handling and cerebral vascular resistance in control and PBN groups before and following deep hypothermic circulatory arrest

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-DHCA</th>
<th>Post-DHCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDO2 (ml/100 g per min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6.62 ± 0.42</td>
<td>3.14 ± 0.02*</td>
</tr>
<tr>
<td>MPRED</td>
<td>6.25 ± 0.70</td>
<td>4.14 ± 0.53*</td>
</tr>
<tr>
<td>CMRO2 (ml/100 g per min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.89 ± 0.21</td>
<td>2.27 ± 0.18*</td>
</tr>
<tr>
<td>MPRED</td>
<td>3.77 ± 0.45</td>
<td>2.88 ± 0.39*</td>
</tr>
<tr>
<td>CEO2 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>59.5 ± 2.7</td>
<td>71.8 ± 2.7*</td>
</tr>
<tr>
<td>MPRED</td>
<td>61.0 ± 3.6</td>
<td>69.0 ± 3.0</td>
</tr>
<tr>
<td>CVR (mmHg/100 g.min/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.95 ± 0.04</td>
<td>2.14 ± 0.12*</td>
</tr>
<tr>
<td>MPRED</td>
<td>1.13 ± 0.18</td>
<td>1.82 ± 0.22*</td>
</tr>
</tbody>
</table>

* The study group (MPRED) received 30 mg/kg methylprednisolone by intramuscular (i.m.) injection at 8 and 2 h before induction of anaesthesia. Control animals received 1 ml of water i.m. at the same time points. All animals underwent 60 min of DHCA at 18°C and were rewarmed and reperfused for 1 h. CDO2, cerebral oxygen delivery; CEO2, cerebral oxygen extraction; CMRO2, cerebral metabolic rate of oxygen; CVR, cerebral vascular resistance; DHCA, deep hypothermic circulatory arrest. *Significant difference from pre-DHCA value within group, paired t-test P < 0.05.

Fig. 1. Global and regional cerebral blood flow (CBF) at 1 h of reperfusion after 60 min of deep hypothermic circulatory arrest (DHCA) at 18°C in control and MPRED groups. Data are expressed as percentage of baseline CBF before DHCA (mean ± SE of the mean). HEMI, cerebral hemispheres; CBLM, cerebellum; BG, basal ganglia; BS, brain stem. * Significantly greater percentage recovery than control group, unpaired t-test P < 0.05.

Fig. 2. Renal blood flow in control and MPRED groups at initial baseline (pre-DHCA) and at 1 h of reperfusion (post-DHCA) after 60 min of deep hypothermic circulatory arrest (DHCA) at 18°C. Data expressed as mean ± SE of the mean. * Significant difference from pre-DHCA value within group, paired t-test P < 0.05. † Significant difference from control value post-DHCA, unpaired t-test P < 0.05.

Fig. 3. Cerebral oxygen handling in the MPRED group (n = 8) at initial baseline (pre-DHCA) and at 1 h of reperfusion (post-DHCA) after 60 min of deep hypothermic circulatory arrest (DHCA) at 18°C. Data expressed as mean ± SE of the mean. CDO2, cerebral oxygen delivery; CEO2, cerebral oxygen extraction; CMRO2, cerebral metabolic rate of oxygen. * Significant difference from pre-DHCA value within group, paired t-test P < 0.05.
pressure and not the pump flow rate that determines cerebral perfusion [17]. A rise in CVR and drop in CBF followed DHCA. There was regional variation in CBF however, with recovery being greatest in the cerebellum and brainstem. As the arterial oxygen content was maintained at a constant level, the reduction in CBF was primarily responsible for the drop in CDO\textsubscript{2}. The post-DHCA CDO\textsubscript{2} in the control group was lower than the pre-DHCA CMRO\textsubscript{2}. The combination of reduced CBF and increased CEO\textsubscript{2} resulted in a fall in the CMRO\textsubscript{2}.

In the animals that received preoperative MPRED the SVR also fell following DHCA but not as much as in the control group. This suggests that the mechanism resulting in a drop in SVR in control animals was attenuated by MPRED. In contrast to the SVR, the CVR rose after DHCA. The change in CVR following DHCA in the MPRED group, however, was significantly less than in the controls. In both experimental models and clinical studies high dose MPRED has been shown to reduce the vasospasm associated with subarachnoid haemorrhage [18].

The improvement in CVR following DHCA probably contributes to the improvement in CBF seen in the MPRED group. Recovery of CBF following DHCA was significantly greater in the MPRED group both globally and in all regions studied apart from the cerebral hemispheres. The reason for the reduced recovery in the cerebral hemispheres compared to the other brain regions is not clear, however this has been a consistent finding in previous studies of DHCA in the neonatal piglet [5,6]. Although high dose MPRED appears to reduce the cerebrovascular spasm in subarachnoid haemorrhage most studies do not demonstrate an improvement in CBF with corticosteroid use. Pre-treatment with dexamethasone, for example, has been shown to prevent cerebral damage without improving CBF [19]. Furthermore, direct intracarotid injection of dexamethasone in normal baboons has been shown to have no effect on either CBF or CMRO\textsubscript{2} [20]. In a model of cerebral oedema, however, a single large dose of MPRED has been shown to reduce cortical oedema and improve local cerebral blood flow [21].

The improvement in CBF following DHCA in the MPRED group resulted in an increase in the oxygen delivery to the brain compared to the control animals. The recovery of CMRO\textsubscript{2} was also significantly better than in the control group. In contrast to the control group the cerebral oxygen extraction was not increased in the MPRED group after DHCA. Increased oxygen extraction in the control group suggests an imbalance in oxygen supply and demand and that the cerebral demands for oxygen in control animals after DHCA could only be met by an increased oxygen extraction. In the animals treated with MPRED, however, the supply of oxygen to the brain was adequate for its demands after DHCA.

In some global ischaemic models glucocorticoid administration has been shown to be detrimental [22]. This may be due to glucocorticoid neurotoxicity or occur as a secondary consequence of glucocorticoid-elevated serum glucose levels. It has been well documented that an elevated glucose and/or lactate level is detrimental to neuronal survival [23]. The situation in neonates, however, appears to be very different. Glucose supplementation during, or at the end of hypoxia has been shown to reduce infarction size in a neonatal model [24] and extreme hyperglycemia (serum glucose 35–40 mM) has been shown to offer complete protection from infarction [25].

The mechanism of action of MPRED as a neuroprotectant is fairly complex. High dose MPRED inhibits lipid peroxidation [26]. This is important because irreversible neuronal damage is related to free radical-induced lipid peroxidation. MPRED also inhibits membrane lipid hydrolysis, which includes inhibition of arachidonic acid release and the consequent formation of the vasoactive prostaglandin F\textsubscript{2}\textalpha and thromboxane A\textsubscript{2} [27]. In addition, various anti-inflammatory actions of MPRED such as inhibition of the elevation of proinflammatory cytokines could be of benefit in counteracting the inflammatory response to CPB and ischaemia. Following cerebral ischaemia the JE/MCP-1 gene, which encodes a strong monocyte chemoattractant, is expressed in the brain. High dose MPRED can reduce expression of this gene and markedly reduce macrophage accumulation in ischaemic brain [28]. This is relevant because macrophages are important sources of neurotoxic substances following ischaemia including oxygen free radicals, glutamate, nitric oxide, and lactate.

In addition to the potential for neurological protection following DHCA the use of MPRED could potentially have a beneficial effect on other organs. In the current study MPRED protected the kidney from the reduction in renal blood flow after DHCA seen in the control group. This effect would undoubtedly be beneficial in paediatric clinical practice. Additional benefit may also be seen in pulmonary function following CPB. A recent study has demonstrated that when high dose MPRED is given at 8 h and immediately before the operation, pulmonary compliance, alveolar-arterial gradient, and pulmonary vascular resistance are all improved after bypass compared with no treatment [29].

In conclusion high dose MPRED given at 2 and 8 h before CPB reduces the change in CVR and improves the CBF, CDO\textsubscript{2} and CMRO\textsubscript{2} following DHCA. The null hypothesis stated earlier can therefore be rejected. High dose MPRED given preoperatively may offer a safe and inexpensive technique for cerebral protection in children undergoing repair of congenital heart defects with the use of DHCA.

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References


Appendix A. Conference discussion

Dr. M. Turina (Zurich, Switzerland): Do you attribute increased cerebral blood flow to the improvement of cerebral protection? It could equally be argued that it might result in a higher degree of cerebral oedema later on.

Dr. Langley: The recovery of cerebral blood flow and cerebral metabolism occur together. We know that patients undergoing surgery with the use of deep hypothermic circulatory arrest have a higher incidence of neurologic problems postoperatively.

We also know that following hypothermic cardiopulmonary bypass there is a normal recovery in cerebral blood flow and in cerebral oxygen metabolism. When deep hypothermic circulatory arrest is used in conjunction with hypothermic bypass, there is a reduction in the recovery of cerebral blood flow and in cerebral oxygen metabolism after the arrest period. And that’s really been the rationale in the past for the use of CMRO2 and that’s really been the rationale in the past for the use of CMRO2 and that’s really been the rationale in the past for the use of CMRO2 and that’s really been the rationale in the past for the use of CMRO2.
oedema was actually reduced as the cerebral blood flow improved after circulatory arrest.

Dr D. DiCarlo (Rome, Italy): Children who undergo deep hypothermic circulatory arrest have a high chance of having very complex malformation and may require a long postoperative course and maybe the chest would stay open for quite a while. Aren’t you concerned that such a large doses of steroids preoperatively would increase the susceptibility to infection and mediastinitis?

Dr Langley: No, I don’t think so. With just two preoperative doses there is no evidence for that.