Spinal cord ischemia in thoracoabdominal aneurysm surgery: monitoring and conditioning the spinal cord

de Haan, P.

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Effect of mild hypothermia and the 21-aminosteroid U-74389G on neurologic and histopathologic outcome after transient spinal cord ischemia in the rabbit

Peter de Haan, Cor J. Kalkman, Ivo Vanicky, Michael J.H.M. Jacobs, John C. Drummond.
Abstract

Background Mild hypothermia and the 21-aminosteroids have both been neuroprotective in several models of cerebral ischemia. In this study we compared the effects of mild hypothermia and the 21-aminosteroid U-74389G, alone and in combination on neurologic and histopathologic outcome after temporary spinal cord ischemia.

Methods Forty male anesthetized New Zealand white rabbits were randomized to four groups (n=10): (1) normothermia (control); (2) U-74389G (3 mg/kg iv before aortic occlusion, 1.5 mg/kg iv and 10 mg/kg intraperitoneally after the occlusion); (3) mild hypothermia (4°C epidural temperature decrease) and (4) mild hypothermia combined with U-74389G. Spinal cord ischemia was produced by 40 min of infrarenal aortic balloon occlusion. Forty-eight h after the procedure the neurological status of the animals was assessed (Tarlov score) and the animals were sacrificed for histologic evaluation.

Results In the normothermic control group eight of ten animals became paraplegic. There was a significant reduction of the incidence of paraplegia and overall neurological deficits and a significant improved Tarlov score in the mild hypothermic group (one animal paraplegic) and in the group with both mild hypothermia and U-74389G (two animals with a mild paraparesis). The histopathologic scores showed significantly less damage in both hypothermic groups. In group 2, U-74389G administration did not improve neurologic or histopathologic outcomes.

Conclusion The results of the current study demonstrate that a slight decrease of intras ischemic spinal cord temperature significantly improved neurologic and histopathologic outcomes after experimental spinal cord ischemia. Protection by the 21-aminosteroid at normothermic conditions, or additional protection when U-74389G was added to mild hypothermia could not be demonstrated.
Spinal cord protection with mild hypothermia and the 21-aminosteroid

Introduction
Recent evidence indicates that mild hypothermia exerts a powerful neuroprotective effect in various models of cerebral ischemia.  This protective effect cannot be explained solely by the decrease of cerebral metabolic rate. Excitatory amino acids are thought to play a role in ischemic neuronal death. Mild hypothermia delays the initial release of excitatory neurotransmitter and reduces the absolute rate of excitatory neurotransmitter release during ischemia. This mechanism might be an explanation for the attenuation by mild hypothermia of excitotoxic neuronal damage.

The free radical scavenger des-methyl tirilazad, U-74389G (21-<4-(2,6-di-1-Pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl>-pregna-1,4,9(11)-triene-3,20-dione(Z)-2-butenediodate), belongs to the family of 21-aminosteroids or lazaroïds. The neuroprotective effects of the 21-aminosteroids are thought to be related to their anti-oxidant actions. In vitro, the 21-aminosteroids are potent inhibitors of iron dependent membrane lipid peroxidation. Neuroprotection by the 21-aminosteroids has been demonstrated in some but not all models of transient cerebral ischemia. In this context of inconsistent results, the precise role of lipid peroxidation in ischemia/reperfusion injury is unclear, and the exact mechanisms of action of the protective effects of the 21-aminosteroids have not been elucidated. In two investigations in a rabbit model of spinal cord ischemia, protection with an 21-aminosteroid has been demonstrated. However, in these studies spinal cord and core temperature were not reported.

This study was undertaken to compare the relative spinal cord protective effects of mild hypothermia (4°C temperature decrease) and U-74389G, alone and in combination with mild hypothermia in a model of temporary spinal cord ischemia in the rabbit.

Methods
Animal care and all procedures were performed in compliance with The National Guidelines for Care of Laboratory Animals in the Netherlands. The study protocol was approved by the Animal Research Committee of the Academic Hospital at the University of Amsterdam, the Netherlands. Forty rabbits, weight 3.2 ± 0.2 kg (SD), were randomly assigned to one of four groups: Group I; normothermia + vehicle (controls, n=10). Group II; normothermia + U-74389G (n=10). Group III; mild hypothermia (decrease of epidural temperature of 4°C) + vehicle (n=10). Group IV; mild hypothermia + U-74389G (n=10).

Anesthesia: All animals were premedicated with ketamine 50 mg/kg im and anesthetized with 1.5% halothane by mask in a mixture of 50% O₂ in air. After induction of anesthesia
an intravenous catheter (20 G) was placed in an ear vein and halothane was discontinued. From that moment anesthesia was maintained with a continuous infusion of ketamine (25 mg/kg/h) and sufentanil (5 μg/kg/h). Normal saline was infused at a rate of 4 ml/kg/h. The tracheas were intubated and the lungs were ventilated at a rate of 45 breaths/minute using an Amsterdam Infant Ventilator (Hoekloos, Amsterdam). Ventilation was adjusted to maintain end-tidal CO₂ (mainstream capnograph [Hewlett-Packard, Boeblingen, Germany]) within 4.8 to 5.3 kPa (36 to 40 mm Hg) throughout the experiment. Adequacy of ventilation was confirmed by blood gas analysis at 37°C. Intravenous cephalothin (25 mg/kg) was administered before the incision and two hours after the aortic occlusion.

Operative procedure: Fur was clipped from the left groin, and after preparation of the skin with iodine and infiltration with bupivacaine 0.5% (1 cc), a right femoral arteriotomy was performed 2 cm distal of the inguinal ligament. A 4 Fr balloon-tipped monitor catheter with pressure-monitoring ports proximal and distal to the balloon (Arrow, Reading, USA) was advanced 15 cm into the abdominal aorta. In previous experiments this position resulted in a balloon location 0.5 - 1.5 cm distal to the left renal artery, as verified by laparotomy.11,12 Immediately before catheter insertion intravenous heparin, 1000 units, was administered followed by 500 units every hour thereafter. Mean arterial pressure (MAP) both rostral and caudal to the balloon and heart rate (HR) from the ECG were recorded continuously during the study.

Spinal cord ischemia: Aortic occlusion was performed at least one hour after discontinuation of halothane. Spinal cord ischemia was induced by inflating the balloon with air until there was a loss of pulsatile distal aortic pressure (as measured with the proximal orifice of the monitor catheter). The duration of aortic occlusion was 40 min. Reperfusion was verified by the presence of a pulsatile pressure waveform via the proximal orifice of the catheter. Arterial pH, PaCO₂, PaO₂, hematocrit and plasma glucose were measured before aortic occlusion, at 30 min of aortic occlusion, and 5 minutes after balloon deflation. If MAP decreased below 60 mmHg during reperfusion, the rabbits received 2.5 mg ephedrine iv. Fifteen minutes after balloon deflation the catheter was removed and the wound was closed.

Temperature manipulations
Immediately after induction of anesthesia, baseline oesophageal and epidural temperatures were measured. Temperatures recorded in the epidural space were used to reach the target during normo-and hypothermia. The epidural temperature was measured with a flexible wire temperature probe (Malincrodt, St Louis, MO) placed through a needle in the
epidural space at the level of the 5th - 6th lumbar vertebra. Preliminary investigations in an anatomical preparation were performed to locate the percutaneous route for placing the temperature probe in the epidural space. If the intrathecal space was accidentally entered (cerebrospinal fluid from the needle) the rabbit was excluded from the study and replaced. In the normothermic groups temperature was maintained at baseline values with a pediatric warming mattress and an infrared heating device.

The target in the mild hypothermic animals (groups III and IV) was a temperature decrease of 4 °C below baseline epidural temperature. Hypothermia was induced with skin application of ethanol 70% (20 - 30 ml) on the thorax and abdomen. In a pilot experiment, we observed that the epidural temperature decreased gradually (0.5°C/hr) during aortic occlusion. In order to avoid a temperature decrease exceeding the target of 4°C below baseline, aortic occlusion was performed at an epidural temperature of 3.5°C below baseline temperature. At the end of the experiment the mild hypothermia animals were allowed to awaken when oesophageal temperature was within 2°C of baseline temperature. A rewarming period of approximately 90 min was necessary to achieve this temperature. Anesthesia was maintained in all groups of animals for an additional two hours after aortic occlusion to ensure an equal postischemic duration of anesthesia.

U-74389G administration

In groups II and IV U-74389G was dissolved in CS-4 vehicle (0.02M citric acid monohydrate, 0.0032M sodium citrate dihydrate and 0.077M HCl) and administered 15 minutes before the ischemic insult in a dose of 3.0 mg/kg, followed by 1.5 mg/kg immediately after balloon deflation. One hour after the ischemic insult 10 mg/kg U-74389G was given intraperitoneally. Groups I and III received an equal volume of vehicle.

Neurologic scoring system

The animals were scored neurologically on the 5 point scale of Tarlov 24 and 48 hours after the ischemic injury: 0 = paraplegia with no lower-extremity motor function; 1 = poor lower-extremity motor function: flicker of movement or weak antigravity movement only; 2 = some lower-extremity motor function with good antigravity strength but inability to draw legs under body and / or hop; 3 = ability to draw legs under body and hop but not normally; 4 = normal motor function.

Bladder contents were expressed twice daily with the Credé manoeuvre in paraplegic animals.
Spinal cord pathology

Forty-eight hours after the experiment the animals were anesthetized with halothane 1.5% by mask after premedication with ketamine 25 mg/kg and xylazine 5 mg/kg im. The animals were given 2500 U of heparin and were perfusion fixated with formalin 3.6%. The lumbo-sacral portion of the spinal cord was carefully removed en bloc and immersed in formalin for 10 days. The segments L3 - L5 were divided into 15 transverse blocks (3 mm thick). Each block was embedded in paraffin and two 2 μm thick sections were stained with hematoxylin-eosin (H&E). One section from each block was evaluated by an experienced histopathologist (I.V.) unaware of the experimental conditions. Histopathologic changes of the grey matter were scored on a 7 point scale as follows: 0 = no lesion observed, 1 = gray matter contained 1-5 eosinophilic neurons, 2 = gray matter contained 5-10 eosinophilic neurons, 3 = gray matter contained more than 10 eosinophilic neurons, 4 = small infarction (less than 1/3 of the gray matter area), 5 = moderate infarction (1/3-1/2 of the gray matter area), 6 = large infarction (more than 1/2 of the gray matter area). The scores from all the sections from each spinal cord were averaged to give a final score for an individual animal.

Statistical analysis

Physiological data are expressed as means ± standard deviation. The neurologic outcome and histopathologic scores are expressed as medians and 10th to 90th percentiles. Temperature, blood gases, glucose concentration and hematocrit were analyzed with repeated measures analysis of variance. Comparison of the overall incidence of neurological deficits and incidence of paraplegia in each group was performed with the Fisher exact test. The Mann Whitney U test was used to compare the histopathologic and neurologic scores. P< 0.05 was considered significant.

Results

There were no differences in weight, glucose concentration, hematocrit, pH, \( \text{PaCO}_2 \), \( \text{PaO}_2 \), MAP and heart rate before, during and after aortic occlusion and in baseline temperatures between the 4 groups of animals. Administration of U-74389G or vehicle did not result in significant hemodynamic changes. Five rabbits in the normothermic control group and 4 animals each in the other groups required ephedrine to maintain MAP after balloon deflation. After halothane was discontinued no animal exhibited signs of wakefulness during the experiment.
Table 1. Baseline oesophageal and epidural temperatures recorded at the start of the experiment, immediately after induction of anesthesia. Changes in epidural and oesophageal temperatures at the start of aortic balloon occlusion and at the end of the 40 min of occlusion in the 4 study groups, compared with baseline values. Data are expressed as means ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Normothermia (vehicle only)</th>
<th>Normothermia + U-74389G</th>
<th>Hypothermia + vehicle only</th>
<th>Hypothermia + U-74389G</th>
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<tr>
<td>Baseline epidural</td>
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<td>39.2 ± 0.5</td>
<td>39.0 ± 0.5</td>
<td>39.3 ± 0.5</td>
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<tr>
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<td>-0.5 (± 0.2)</td>
<td>-3.6 (± 0.2)</td>
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<tr>
<td>Change in oesophageal</td>
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<td>-0.2 (± 0.4)</td>
<td>-3.8 (± 0.3)</td>
<td>-3.9 (± 0.2)</td>
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<td>40 min of occlusion (°C)</td>
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<tr>
<td>Change in epidural</td>
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<td>-0.3 (± 0.2)</td>
<td>-3.4 (± 0.4)</td>
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<td>40 min of occlusion (°C)</td>
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Temperature observations

Baseline oesophageal temperature was 38.9 ± 0.4°C and baseline epidural temperature was 39.1 ± 0.5°C. At the start of aortic occlusion epidural temperatures were 35.6 ± 0.7°C in the mild hypothermia group and 35.9 ± 0.4°C in the mild hypothermia plus U-74389G group. There was a gradual decrease of epidural temperature in all experimental groups during the occlusion. After 40 min of aortic occlusion epidural temperature in the mild hypothermia group was 35.1 ± 0.6°C and 35.3 ± 0.3°C in the mild hypothermia plus U-74389G group. Table 1 shows the differences in the epidural and oesophageal temperatures at the start and after 40 min of aortic occlusion compared with baseline temperatures. The time required to rewarm the animals and reach a temperature of 2°C below baseline was 83 ± 9.9 min and 87 ± 9.5 min in the hypothermia and in the hypothermia plus U-74389G groups respectively.
Neurologic outcome

Both hypothermic groups of animals experienced a significant reduction of overall neurologic deficits, a decrease in the incidence of complete paraplegia and significantly improved Tarlov scores compared with control animals (table 2). In one animal in the mild hypothermia plus vehicle group, epidural temperature decreased to 3.0°C below baseline temperature instead of the desired target temperature decrease of 4.0°C. This animal developed a complete paraplegia after 48 hours. In both the normothermic control group and the normothermic U-74389G group, 8 and 7 animals respectively required expression of bladder contents. Two animals in both the hypothermia plus vehicle group and the hypothermia plus U-74389G group required expression of bladder contents.

Table 2: Neurologic outcomes 24 and 48 hours after the spinal cord insult in the 4 study groups. Each group consists of 10 animals. The Tarlov score is expressed as median and 10th - 90th percentiles. 0 = complete paraplegia. 1 = poor lower-extremity motor function; 2 = some lower-extremity motor function 3 = ability to draw legs under body and hop but not normally. 4 = normal motor function. \( p < 0.05 \), * = \( p < 0.01 \), \( \# p < 0.001 \) as compared with controls (normothermia and vehicle).

<table>
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<tr>
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<td>6</td>
<td>5</td>
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<tr>
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<td></td>
<td>1*</td>
<td>0*</td>
</tr>
<tr>
<td>Hypothermia + U-74389G (n=10)</td>
<td>0 #</td>
<td>2*</td>
<td>0</td>
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</table>

Histopathology

The histopathologic outcome for each group is provided as a boxplot in figure 1. The scores of the individual animals are illustrated as bargraphs in figure 2. The histopathological scores in the mild hypothermia plus vehicle group (0.9 (0.5 - 3)) and in the mild hypothermia plus U-74389G group (1 (0.3 - 1.9)) were significantly better (\( p = 0.004 \) and \( p = 0.003 \) respectively) as compared with normothermia plus vehicle animals (4.7 (2.7 - 5.9)). Addition
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Figure 1. Boxplot of the histopathological scores of each group of animals. Horizontal bars represent 90, 75, 50 (Median), 25 and 10th percentiles. * P < 0.005 as compared with normothermic controls.

of U-74389G to mild hypothermia did not alter histopathologic outcome. Histopathologic scores in the normothermic, U-74389G treated animals (5.5 (2.2 - 6.0)) were not different from normothermic controls.

Two types of injury were observed in the H&E-stained spinal cords: eosinophilic neurons in a relatively intact tissue (selective necrosis) and infarctions affecting all tissue elements. The most severe damage was observed in lower lumbar segments L4 - L5. Selective neuronal necrosis was present in the intermediate gray and in the dorsal horns, with occasional degenerate neurons in the ventral horns. Marked vacuolisation in the mass of grey matter that fills the space between individual cell bodies could be seen with small infarctions, as well as on the border zones of the large infarctions. Typically, even with the largest infarctions, there was unaffected tissue in the vicinity of the central canal, and in the most dorsal laminae of the dorsal horns. In some cases, diffuse vacuoles developed in both gray and white matter. These diffuse vacuoles occurred irregularly in some animals from all experimental groups irrespective of the type or extent of the lesion, and were not taken into consideration when scoring the injury.

Discussion

The results of the present study are consistent with the neuroprotective properties of mild hypothermia that have been observed in various models of cerebral ischemia. Mild hypothermia during spinal cord ischemia significantly improved neurological and histopathological outcomes while no protective effects of the 21-aminosteroid were observed at normothermic conditions. No conclusions could be made as to the additional protective effect of U-74389G in combination with mild hypothermia, because the substantial protective effect of mild hypothermia precluded significant additional protection.
Figure 2. Histopathologic scores for each group of animals. Each bar represents one animal. Histopathological score is on a 7 point scale; 0 (normal) to 6 (severe grey matter necrosis). * P < 0.005 as compared to normothermic control animals.

Experimental model
In the experimental model used in this study spinal cord ischemia was produced by a temporary occlusion of the abdominal aorta. In the rabbit, aortic occlusion is a highly reproducible model for the production of spinal ischemic lesions, since there is a clear relationship between the time of occlusion, histopathological changes and the resultant clinical levels of function. In a recent study, regional spinal cord cooling provided protection during temporary spinal cord ischemia in the rabbit. The authors suggested that reperfusion injury still can occur and recommended investigations of protective strategies that combine hypothermia and pharmacological agents for avoiding paraplegia completely. In order to be able to demonstrate a possible additional protective effect of the 21-aminosteroid, we opted to use a moderately severe ischemic insult, 40 minutes of ischemia, that would produce paraplegia in nearly all control animals.
Hypothermia

The protective effect of deep systemic or regional hypothermia on spinal cord ischemia is well established. Moderate hypothermia (30°C; 8°C temperature decrease) improved neurologic outcome in experiments with spinal cord ischemia in the rabbit. Two studies have described the effects of mild hypothermia on outcome after transient spinal cord ischemia. Vacanti et al. produced 25 min of spinal cord ischemia in 14 rabbits at a temperature range of 34.0 - 38.9°C, and observed that the temperature dividing good and bad recovery was 34.6°C. Marsala et al. demonstrated protection by mild hypothermia (34.0°C) in a rat model of reversible spinal cord ischemia. In this study neurological and histopathological outcome was determined after an 8 hour survival period. This post ischemic observation period may have been too short for the ischemic injury to develop, especially if the protective strategy has delayed and not prevented neuronal cell death. The present study demonstrated a significant protection of intra-ischemic mild hypothermia after a recirculation period of 48 hours.

21-aminosteroids

The 21-aminosteroids scavenge free radicals and are potent inhibitors of membrane lipid peroxidation. They lack glucocorticoid activity. The compound used in the present study, U-74389G, is a desmethyl form of tirilazad. In models of cerebral ischemia in the rat U-74389G prevented free radical formation and was able to restore levels of endogenous free radical scavengers. There are several possible explanations for the lack of protection by U-74389G in the present study. One possibility is that the timing of the administration and/or the dose of U-74389G were not optimal. The superoxide anion is produced up to two hours in the reperfusion period after ischemia. Accordingly, U-74389G was given intravenously both before and after the period of aortic occlusion and an additional dose was given intraperitoneally one hour after the beginning of the reperfusion period. There are no data available regarding the bioavailability of the 21-aminosteroids after intraperitoneal administration in rabbits. However, intraperitoneally administered desmethyl-tirilazad was effective in reducing lipid peroxidation and brain damage in the rat. Another possibility is that the ischemic period was too long to show a beneficial effect of the 21-aminosteroid. However, the duration of ischemia was not so long that mild hypothermia could not provide protection. The negative result suggests that if there is any protective potential of U-74389G in this context, it is small by comparison with that afforded by hypothermia.
In the present study all groups of animals received baseline anesthesia with ketamine, which has known NMDA receptor antagonist properties.\textsuperscript{26} In a model of incomplete cerebral ischemia in the rat, ketamine improved neurologic outcome.\textsuperscript{27} Although a possible influence of the ketamine anesthesia on the experimental outcome can not be excluded, it is not likely that ketamine prevented a potential protection of the U-74389G because the 21-aminosteroids mainly exert their action by scavenging free radicals.

In two previous investigations protection against spinal cord ischemia in rabbits by the 21-aminosteroid U-74006F (Tirilazad) was observed.\textsuperscript{9,10} In both experiments core temperature was not controlled and temperature at the site of the ischemic insult, i.e. the spinal cord was not monitored, allowing the possibility of accidental hypothermia. A temperature decrease of 2°C can significantly reduce ischemic injury.\textsuperscript{2} Various studies have emphasized that it is essential to monitor temperature at the site of the ischemic lesion during experiments involving CNS ischemia in order to rule out a possible influence of the experimental design on temperature regulation.\textsuperscript{28-30} In our study, epidural temperatures decreased gradually during the 40 minutes of aortic occlusion in all groups of animals. This effect can be attributed to a decrease in blood flow and metabolism.

The present study lacked statistical power to draw conclusions regarding a possible additional protective effect of U-74389G when combined with mild hypothermia, because mild hypothermia alone provided nearly complete neuroprotection. To demonstrate an additional pharmacological protection in this model a substantially larger study group would be required.

Comparison of protective properties
The much more effective protection by mild hypothermia compared to the 21-aminosteroid might be explained by the fact that mild hypothermia acts in the initial phase of the cascade that leads to neuronal cell death. Excessive release of excitatory amino acids (glutamate) plays a role in the initial phase of both spinal cord and cerebral ischemic injury. The glutamate neurotoxicity is believed to be mediated by a rise in intracellular calcium concentration and calcium-induced enzyme activation.\textsuperscript{31,32} Phospholipase activation leads to membrane lipolysis involving arachidonic acid formation and consequent prostaglandin, thromboxane and leukotriene formation. These eicosanoids contribute to the further evolution of the ischemic insult. The metabolism of arachidonic acid in the reperfusion phase by cyclooxygenase and lipoxygenase is a source of free radicals and free radicals can enhance the ischemic injury by means of membrane lipid peroxidation.\textsuperscript{33} Another pathway of glutamate neurotoxicity might be nitric oxide mediated.\textsuperscript{34} After N-methyl-D-aspartate receptor activation, endogenously synthetized nitric oxide leads to the formation of peroxynitrate. Peroxynitrate or its decomposition products have been suggested to initiate lipid peroxidation and cytotoxicity.\textsuperscript{35}
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Mild hypothermia exerts its action early in the cascade by slowing the release of the excitatory amino acid glutamate. The 21-aminosteroids exert their action when the ischemic cascade has run its course, by scavenging free radicals and inhibiting membrane lipid peroxidation. At that point in the injury process, the influx of calcium and sodium into the cell, cell swelling, and calcium induced enzyme activation have already occurred.

Spinal cord ischemia during thoracoabdominal aneurysm surgery

Hypothermia occurs spontaneously during thoracoabdominal aneurysm (TAAA) surgery. The results of the present study suggest that mild hypothermia might be beneficial if a period of spinal cord ischemia is likely to occur. During the resection of a TAAA, spinal cord ischemic injury might develop during aortic crossclamping. Some protective strategies attempt to maintain spinal cord perfusion by retrograde aortic bypass techniques or CSF drainage. Despite these techniques, transient spinal cord ischemia may still occur if an intercostal artery critical for spinal cord blood supply, originates between the aortic clamps. Therefore, during TAAA surgery, it would be advantageous if protective strategies were available that could improve neuronal survival following episodes of spinal cord ischemia. In the present study mild hypothermia provided substantial protection against a period of spinal cord ischemia. It is conceivable that permissive mild hypothermia might be beneficial in the context of spinal cord ischemia during TAAA surgery.

Conclusion

The results of this study suggest that the powerful neuroprotective effects of mild hypothermia observed in models of cerebral ischemia are also present during spinal cord ischemia. However, the present data do not provide evidence of protective efficacy of 21-aminosteroids in the same context.

References


Spinal cord protection with mild hypothermia and the 21-aminosteroid


