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Mild and Moderate Hypothermia Provide Better Protection than a Burst-suppression Dose of Thiopental against Ischemic Spinal Cord Injury in Rabbits

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Abstract

Background: Controversy exists over the efficacy of different methods for protecting the spinal cord against experimental ischemic injury. Therefore, the authors compared the protective effects of thiopental with those of hypothermia (35 degrees Celsius and 32 degrees Celsius) on hindlimb motor functions and histopathology after transient spinal cord ischemia.

Methods: Twenty-seven New Zealand white rabbits were assigned to one of the four groups: a thiopental-normothermia group (burst-suppression dose of thiopental; esophageal temperature = 38 degrees Celsius; n = 7), a halothane-mild hypothermia group (halothane, 1%; esophageal temperature = 35 degrees Celsius; n = 7), a halothane-moderate hypothermia group (halothane, 1%; esophageal temperature = 32 degrees Celsius; n = 6), and a halothane-normothermia group (halothane, 1%; esophageal temperature = 38

Graphics

degrees Celsius; n = 7). The animals were then subjected to 20 min of spinal cord ischemia produced by occlusion of the aorta distal to the origin of left renal artery. Hindlimb motor function was observed for 48 h after reperfusion. Histopathology of the lumbar spinal cord also was examined.

Results: All animals in the halothane-mild hypothermia and halothane-moderate hypothermia groups were neurologically normal 48 h after ischemia. There was no statistical difference in the final neurologic status and histopathology between the thiopental-normothermia and halothane-normothermia groups. However, the final neurologic status and histopathology in both groups were worse than in the halothane-mild hypothermia or halothane-moderate hypothermia groups. There was a strong correlation between the final neurologic status and the numbers of normal neurons in the anterior spinal cord.

Conclusions: These results suggest that mild and moderate hypothermia protects against ischemic spinal cord injury in rabbits, and a burst-suppression dose of thiopental does not offer any advantage over halothane.

Key words: Anesthetics, intravenous: thiopental. Spinal cord, ischemia. Hypothermia.

Various methods have been suggested to protect against ischemic spinal cord injury, specifically barbiturates and hypothermia. However, efficacy of barbiturates is controversial. [1-3] For example, a single bolus dose of thiopental (30 mg/kg) has been reported to be protective, [1,2] whereas a burst-suppression (electroencephalogram [EEG]) dose of methohexital has been reported to not be protective. [3] There seem to be problems with the methodology of previous studies. Casual control of temperature and inconsistency in the severity of the ischemic insult may have confounded the results of these studies. Further, mild hypothermia is known to offer protection.

Therefore, by monitoring the temperature in two locations (esophagus and paravertebral muscle) and using a model in which the severity of the ischemia was rigidly controlled, we compared the effects of a burst-suppression dose of thiopental with those of mild (35 degrees Celsius) or moderate (32 degrees Celsius) hypothermia on outcome after spinal cord ischemia.

Materials and Methods

The protocol was reviewed and approved by the Animal Care Committee of the Yamaguchi University, School of Medicine. Twenty-seven New Zealand white rabbits weighing 2.2 +/- 0.2 (mean +/- SD) kg were used in this study.

Surgical Preparation

The rabbits were anesthetized in plastic box with halothane, 4%, in oxygen. An ear vein catheter was inserted. A small dose of pentobarbital (20-30 mg, intravenous) was administered to facilitate tracheal intubation. After placing a 3-mm cuffed endotracheal tube (Mallinckrodt Lo-Pro, Mallinckrodt Laboratories, Ireland), the animals' lungs were mechanically ventilated with halothane, 1%, in oxygen, and Pa sub CO_2 was maintained at 35-42 mmHg. End-tidal concentrations of

halothane and carbon dioxide were continuously measured by an infrared anesthetic analyzer (Nippon Colin, Tokyo). Intravenous infusion of lactated Ringer's solution was started at a rate of approximately 3-4 ml [center dot] kg sup -1 [center dot] h sup -1. After infiltration with bupivacaine, 0.25%, PE-60 catheters were inserted into both femoral arteries. The right side catheter was advanced 3 cm into the abdominal aorta, whereas the other was advanced 17 cm. Before catheter insertion, intravenous heparin, 400 U, was administered.

In the right lateral decubitus position, a flank skin incision (4-5 cm) parallel to the spine was made at the 12th costal level on the left side after infiltration with bupivacaine, 0.25%. The thoracolumbar fascia under the skin also was incised. After making a small incision of the major psoas muscle, the abdominal aorta at the level of left renal artery was exposed retroperitoneally. PE-60 catheter was placed around the aorta, immediately distal to the left renal artery. Then, an occluder tube (16-French rubber tube) was tunneled to the skin for later occlusion of the aorta to produce spinal cord ischemia.

Experimental Groups⬆

Animals were randomly assigned to one of the following groups: a thiopental-normothermia group (n = 7), a halothane-mild hypothermia group (n = 7), a halothane-moderate hypothermia group (n = 6), or a halothane-normothermia group (n = 7). Core temperature was monitored with a calibrated esophageal thermistor (Model MGA-III, Type 219, Nihon Kohden, Tokyo). To estimate spinal cord temperature, the paravertebral muscle (erector muscle of spine) temperature at the level of L4-L5 was monitored by a calibrated needle-type thermistor (Model PTC-201, Unique Medical, Tokyo). The esophageal temperature was controlled to 38.0 degrees Celsius with a heating lamp and warming pad throughout the study in the thiopental-normothermia and halothane-normothermia groups. In the halothane-mild hypothermia and halothane-moderate hypothermia groups, no active warming was done during surgical preparation. The animals in these two groups then were cooled to an esophageal temperature to 35.0 degrees Celsius and 32.0 degrees Celsius, respectively, after the completion of surgical preparation (see next section). Biparietal needle electrodes were placed into the scalp for continuous recording of EEG (Polygraph system, Model RM-6000, Nihon Kohden, Tokyo) in the thiopental-normothermia group.

After completion of surgery, end-tidal halothane concentration was maintained at 1% during ischemia in all groups except in the thiopental-normothermia group, in which halothane was discontinued and thiopental was administered as a bolus (20-30 mg/ kg, intravenous) and then continuously infused to maintain a burst suppression EEG until the end of the ischemic period. The halothane-mild hypothermia and halothane-moderate hypothermia groups were slowly cooled by applying ice bags to the body surface. When esophageal temperatures reached approximately 36 degrees Celsius or 33 degrees Celsius, respectively, the ice packs were removed. The esophageal temperature then was maintained at 35.0 degrees Celsius or 32.0 degrees Celsius, respectively. It required approximately 20-30 min to obtain this state. This was accomplished by activation of the heating lamp when temperature was less than 34.5 degrees Celsius or 31.5 degrees Celsius. This procedure eventually produced paravertebral muscle temperatures of [nearly equal] 34.5 degrees Celsius and [nearly equal] 31.5 degrees Celsius, respectively (see Results section). In the thiopental-normothermia and halothane-normothermia groups, esophageal temperatures were maintained at [nearly equal] 38 degrees Celsius and paravertebral muscle temperatures at [nearly equal] 37.3 degrees Celsius. Mean arterial pressure (MAP) and heart rate (HR) were recorded, and arterial blood was sampled for determination of Pa_{O_2}, Pa sub CO_2, pH, hematocrit, and plasma glucose immediately before the onset of

ischemia. These are referred to as the preischemic values.

Segmental Spinal Cord Evoked Potential Monitoring ⬆

To monitor segmental spinal cord evoked potential (SSCEP), the left sciatic nerve was exposed, and bipolar electrodes were placed around the nerve. The stimuli used were square-wave pulses of 0.1 ms duration and 0.6 mA intensity delivered at 3 Hz. Two silver needle electrodes were inserted into the midline interspinous ligament so that they were in contact with the lamina at L4-L5 and L5-L6. The SSCEPs were recorded in a monopolar fashion from the needle electrodes using Neuropack Four Mini (Model MEB-5304 Nihon Kohden, Tokyo). Fifty repetitions were averaged. SSCEPs were recorded before ischemia and every 2 min during ischemia. The typical recording of SSCEP from L4-L5 and L5-L6 demonstrates two positive waves and four negative waves (Figure 1). It is reported that the first two negative waves (N1 and N2) are presynaptic components and that the last two waves (N3 and N4) are postsynaptic ones. We measured preischemic latencies of N1 and N3 as a representative for pre- and post-synaptic component to see the effects of treatments on SSCEP. Also, amplitudes of N1 and N3 were measured before and during ischemia.
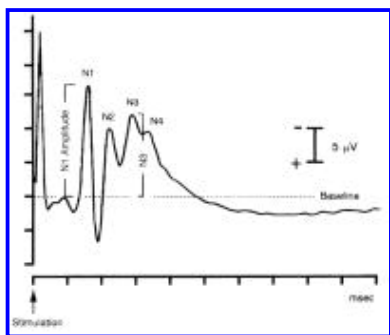

Figure 1. Segmental spinal cord evoked potential. There are four negative waves that are labeled N1-N4 in this article.

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Transient Ischemic Insult and Reperfusion ⬆

Intravenous heparin, 400 units, again was administered immediately before aortic occlusion. Spinal cord ischemia was produced by pulling the PE catheter and clamping an occluder tube for 20 min. At 10 min of ischemia, all measurements except blood gas were repeated (intraischemic values). At the end of the 20-min period of ischemia, reperfusion of the spinal cord was established by removal of the occluder tube and PE catheter with simultaneous rapid infusion of 10 ml of hydroxyethyl starch solution (9 ml of hydroxyethyl starch, 6%, and 1 ml of bicarbonate solution, 8.4%). Immediately after the declamping of the aorta, satisfactory pulsatile distal aortic pressure was observed. In the thiopental-normothermia group, thiopental infusion was discontinued at the end of the ischemic period. Halothane (0.5-1%) was administered until all wounds were sutured. Rewarming of the animals in the halothane-mild hypothermia and halothane-moderate hypothermia groups to 37.5 degrees Celsius (esophageal temperature) began immediately on reperfusion with a heating lamp and warming pad. A final set of measurements was made 10 min after reperfusion (reperfusion values). Three sets of measurements (preischemia, ischemia 10 min, and reperfusion 10 min) in the two hypothermia groups were made when rabbits were hypothermic. The values for pH, Pa_{O2}, and Pa_{CO2} were not temperature corrected.

Postischemic Care

The vascular catheters were removed, and all incisions were sutured. Anesthetic administration was discontinued, and the lungs were ventilated with 100% oxygen in the thiopental-normothermia and halothane-normothermia groups until they were extubated (134 +/- 33, 74 +/- 7 min after reperfusion, respectively). In the halothane-mild hypothermia and halothane-moderate hypothermia groups, halothane was discontinued when esophageal temperature reached 37.5 degrees Celsius, and thereafter rabbits were extubated (92 +/- 14, 139 +/- 25 min after reperfusion, respectively). Extubation of the trachea was performed when vigorous spontaneous ventilation and movement occurred. The animals were allowed to recover in a warmed plastic box that contained supplemental oxygen for 6 h. Intravenous fluid was provided until the animals began to drink. Antibiotic (cephazolin 30 mg/kg, intramuscular) was administered once daily, and bladder contents were expressed manually as required.

Neurologic Assessment

At 6, 12, 24, and 48 h after the reperfusion, the rabbits were neurologically assessed by an observer unaware of the treatment group using the 5-point grading scale proposed by Drummond et al. [4]: 4 = normal motor function, 3 = ability to draw legs under body and hop, but not normally, 2 = some lower-extremity function with good antigravity strength but inability to draw legs under body, 1 = poor lower-extremity motor function, weak antigravity movement only, 0 = paraplegic with no lower-extremity function. Paraplegia was confirmed as the absence of muscle tone or contraction.

Histologic Evaluation

After completion of the neurologic deficit scoring at 48 h, the animals were reanesthetized with halothane, 4%, in oxygen. Transcardiac perfusion and fixation were performed with 1000 ml heparinized saline followed by 500 ml phosphate-buffered formalin, 10%. The spinal cord was removed and refrigerated in phosphate-buffered formalin, 10%, for 48 h. After dehydration in graded concentrations of ethanol and butanol, the spinal cords were embedded in paraffin. Coronal sections of the spinal cord were cut at a thickness of 8 micro meter and stained with hematoxylin and eosin.

Neuronal injury was evaluated at a magnification of 400 x by an observer unaware of the treatment groups. Ischemic neurons were identified by cytoplasmic eosinophilia with loss of Nissl substance and by the presence of pyknotic homogenous nuclei. In each slice, normal neurons in the anterior spinal cord (anterior to a line drawn through the central canal perpendicular to the vertebral axis) were counted. In normal rabbits, the number of normal neurons ranged approximately from 70 to 100 in the anterior lumbar spinal cord.

Statistical Analysis

The physiologic variables were analyzed by a repeated measures analysis of variance (ANOVA). Where differences were identified, Scheffe's post hoc test for intergroup comparisons was performed. The times required from reperfusion to extubation and latencies of N1 and N3 before aortic occlusion were evaluated by one-way ANOVA with Scheffe's post hoc test. The times required for the amplitudes of N1 and N3 to decrease to 50% of the preischemic values, the hindlimb motor function, and the numbers of normal neurons in the anterior spinal cord were analyzed using a nonparametric method (Kruskal-Wallis

test) followed by the Mann-Whitney U test. The correlation of hindlimb motor function scores and numbers of normal neurons in the anterior spinal cord was analyzed by Spearman's rank correlation. P value less than 0.05 was considered statistically significant. Parametric data are presented as mean +/- SD.

Results

In the thiopental-normothermia group, animals received 86 +/- 6 mg/kg as a total dosage, and a typical interburst interval on EEG was 3-10 s. In postischemic period, it required 20-25 min to increase body temperature by 1 degree Celsius. The times required from the start of reperfusion to extubation were 134 +/- 33, 92 +/- 14, 139 +/- 25, and 74 +/- 7 min in the thiopental-normothermia, halothane-mild hypothermia, halothane-moderate hypothermia, and halothane-normothermia group, respectively. The times in the thiopental-normothermia and halothane-moderate hypothermia groups were significantly longer than in the halothane-mild hypothermia or halothane-normothermia groups.

Physiologic data are shown in Table 1. There was no significant difference among the groups for proximal and distal MAP, pH, Pa_{O2}, Pa_{CO2}, and hematocrit. HRs were significantly lower in the halothane-mild hypothermia and halothane-moderate hypothermia groups than in the thiopental-normothermia and halothane-normothermia groups. Plasma glucose was significantly higher in the halothane-moderate hypothermia group than in the thiopental-normothermia and halothane-normothermia groups.

Table 1. Physiologic Variables

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All animals survived until the final neurologic scoring (48 h after reperfusion). Animals in the halothane-mild hypothermia and halothane-moderate hypothermia groups were all neurologically normal at 48 h after reperfusion. There was no statistical difference in the final neurologic status between the thiopental-normothermia and halothane-normothermia groups. However, the final neurologic status in both groups was worse than in the halothane-mild hypothermia or halothane-moderate hypothermia groups (Figure 2).
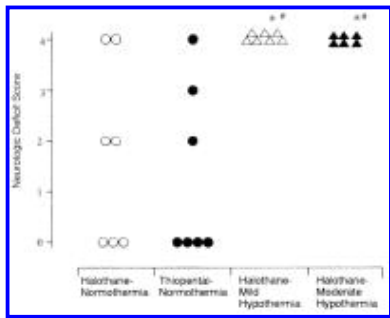
Figure 2. Neurologic score 48 h after reperfusion. Each circle or triangle represents data for one animal. Neurologic deficit scores range from 4 (normal) to 0 (paraplegia). *A significant difference (P < 0.05) from the halothane-normothermia group. #A significant difference (P <0.05) from the thiopental-normothermia group.

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Histopathology of the lumbar spinal cord was examined in 26 animals (one animal in the halothane-normothermia group was excluded because of a technical problem during perfusion-fixation). The number of normal neurons in the anterior spinal cord in the halothane-mild hypothermia or halothane-moderate hypothermia group was significantly greater than in the thiopental-normothermia or halothane-normothermia group. There was no statistical difference in the numbers of normal neurons between the thiopental-normothermia and halothane-normothermia groups (Figure 3). When data from all four groups were combined, there was a strong correlation between the final neurologic status and the numbers of normal neurons in the anterior spinal cord (r_s = 0.84; P < 0.001; Figure 4).
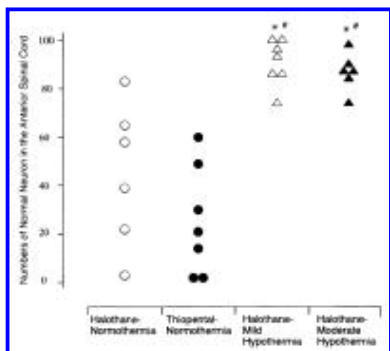

Figure 3. The numbers of normal neurons in the anterior spinal cord 48 h after reperfusion. Each circle or triangle represents data for one animal. *A significant difference (P < 0.05) from the halothane-normothermia group. #A significant difference (P < 0.05) from the thiopental-normothermia group.

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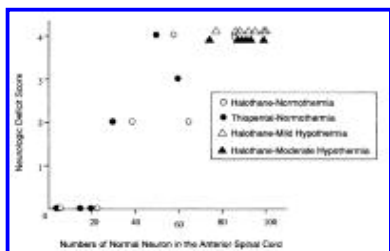Figure 4. The relation between neurologic deficit scores and the numbers of normal neurons in the anterior spinal cord (r_s = 0.84; P < 0.001).

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In SSCEP, N1 and N3 amplitude decreased progressively during ischemia. The time required for N1 wave to decrease by 50%

was significantly longer in the halothane-mild hypothermia group than in the thiopental-normothermia and halothane-normothermia groups (Table 2). In the halothane-moderate hypothermia group, N1 wave in four animals and N3 wave in two animals did not decrease to 50% of the preischemic values.

Table 2. Segmental Spinal Cord Evoked Potential during Ischemia

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Discussion

A feared complication after thoracoabdominal aortic aneurysm surgery is paraplegia caused by spinal cord ischemia during aortic occlusion. To protect the spinal cord against ischemic injury, various therapeutic strategies have been proposed, including hypothermia, [5,6] elevation of spinal cord perfusion pressure by cerebrospinal fluid drainage, [7] and pharmacologic manipulation. [1,8,9]

We confirmed in this study that mild (35 degrees Celsius) and moderate (32 degrees Celsius) hypothermia protect against ischemic injury as observed by hindlimb motor function and histopathology. Significant attenuation of the decrease in amplitude of N1 in SSCEP supported the protective effect of hypothermia. These results are consistent with the previous investigations. [1,2,5,6,10] Moderate hypothermia (rectal temperature 30 degrees Celsius) has been demonstrated to provide significant protective properties by several studies. [1,2,10] A temperature reduction of 3 degrees Celsius during ischemia has been reported to double the duration of ischemia tolerated. [5] Provided that hypothermia reduces cerebral metabolic rate (CMR) and spinal cord metabolic rate (SCMR) for oxygen equally at a rate of approximately 5% per degree centigrade, [11] the SCMR reductions attributable to mild hypothermia (35 degrees Celsius) and moderate hypothermia (32 degrees Celsius) in this study may have been 15% and 30%, respectively. In contrast, the reduction with barbiturate in the glucose utilization in the spinal cord gray matter is almost the half of the brain. [12] Because burst-suppression dose of thiopental is reported to reduce CMR by 40-50%, [13] SCMR reduction with thiopental in this study is calculated to be 20-25%. Therefore, our results suggest that metabolic depression cannot be the sole explanation for the spinal cord protection by hypothermia. The present study does not provide the mechanism for protection by hypothermia. The modulation of the release of excitatory amino acids may be a mechanism for protection. [14] It is unlikely that plasma glucose elevation in the moderate hypothermia group is the cause of protection because hyperglycemia itself is known to aggravate ischemic damage. [4]

Perhaps the most extensively investigated pharmacologic manipulation to provide spinal cord protection during ischemia resides with the barbiturates. However, the present study demonstrated that an EEG burst-suppression dose of thiopental did not offer any advantage over halothane in those with spinal cord ischemia. The results are consistent with a recent study examining the effect of methohexital in dogs. [3] Variable results with barbiturates reported in the literatures [1,2,3,15] may deserve consideration with respect to temperature monitoring, residual blood flow during ischemia, and timing of neurologic scoring.

Oldfield et al. [15] demonstrated beneficial effects of thiopental in transient spinal cord ischemia (25 min) produced by occlusion of the infrarenal aorta in rabbits. However, they did not measure body temperature in their study. Importance of temperature is now widely recognized as a crucial variable. Small differences in central nervous system temperature (only 1 degree Celsius) can have a substantial impact on outcome after experimental ischemia. [16] In our study, there was no difference in either esophageal or paravertebral muscle temperature between the thiopental-normothermia and the halothane-normothermia groups.

Robertson et al. [1,2] demonstrated that thiopental (30 mg/kg given intravenously 30 min before ischemia) or hypothermia (30 degrees Celsius) had protective properties in transient spinal cord ischemia in rabbits anesthetized with ketamine. However, a critical examination of their studies presents some points for concern. They occluded the infrarenal aorta by inflating an intraaortic balloon. This procedure is easy and less invasive. However, it is difficult to verify the position and totality of aortic occlusion. The incidence of incomplete occlusion was 10% in the control group as demonstrated by no change in the SSCEP during ischemia. [2] These are possibly related to the residual blood flow during ischemia. Aortic occlusion with a snare catheter placed under direct vision, as used in the present study, is simple and more complete, although it is invasive. [17]

Naslund [10] demonstrated that animals treated with thiopental (25 mg/kg intravenously given 3 min before aortic occlusion) had a lower incidence of paraplegia with acute onset after 21 min of spinal cord ischemia than animals treated with halothane. However, when acute and delayed onset of paraplegia were combined, no difference was evident. Therefore, it seems difficult to conclude that thiopental has any beneficial effect on the ultimate outcome.

The dose of thiopental in the previous studies that demonstrated protective effects is smaller than in our study. [1,2,15] From a hemodynamic standpoint, the systemic arterial pressure in the present study was well maintained with large dose of thiopental (86 +/- 6 mg/kg) even during aortic clamp. Thus, the failure of protection in our study cannot be attributed to the decrease in spinal cord perfusion pressure by the administration of large dose of thiopental.

In summary, mild and moderate hypothermia (3-6 degrees Celsius reduction) protected against ischemic spinal cord injury. In contrast, a burst-suppression dose of thiopental did not offer any advantage over halothane on hindlimb motor functions or histologic damage after transient spinal cord ischemia. These results, if applicable in humans, support the induction of mild-to-moderate hypothermia for protection of the spinal cord but do not support the use of thiopental during surgical procedures that may result in transient ischemia of the spinal cord.

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