Anesthesiology
81:1493–1499, 1994

Intrathecal Magnesium Sulfate Protects the Spinal Cord from Ischemic Injury during Thoracic Aortic Cross-clamping

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Background: **Paraplegia is a known complication after surgery on the descending thoracic aorta. Thoracic aortic cross-clamping causes an increase in proximal aortic and cerebrospinal fluid pressures. Sodium nitroprusside, though effectively decreasing proximal aortic pressure, has been implicated in worsening the incidence of paraplegia by further increasing cerebrospinal fluid pressure and decreasing distal blood pressure, thereby reducing spinal cord perfusion pressure. Intravenous administration of magnesium sulfate has been shown to offer some spinal cord protection when used with mild hypothermia. This study investigated the effect of intrathecal magnesium on the prevention of paraplegia when sodium nitroprusside is used to control proximal hypertension during thoracic aortic cross-clamping in a dog model of spinal cord ischemia.**

Methods: **Two groups of eight dogs underwent thoracic aortic cross-clamping *via* a small thoracotomy incision for 45 min. Proximal, distal, and central venous pressures and cerebrospinal fluid pressures were monitored. Temperature was maintained at 36°C. Sodium nitroprusside was used to control proximal hypertension. The control group received no magnesium sulfate, and a second group received 3 mg/kg intrathecal magnesium sulfate before thoracic aortic cross-clamping. The dogs were neurologically evaluated 24 h later by an observer blinded to the dogs' group. Spinal cord segments were obtained for histologic examination.**

Results: **Proximal mean arterial pressure, cerebrospinal fluid pressure, spinal cord perfusion pressure, and central venous pressure were not statistically different between the two groups. Neurologic outcome, however, was statistically different between the groups. None of the eight dogs in the magnesium group had any measurable neurologic injury, in contrast to the control group, in which seven of the eight dogs had severe neurologic injury ($P < 0.005$). *Post mortem* histologic data supported these findings.**

Conclusions: **Intrathecal magnesium can prevent spinal cord injury despite markedly negative spinal cord perfusion pressure during thoracic aortic cross-clamping in a canine model of spinal cord ischemia. (Key words: Blood pressure. Ions: magnesium. Pharmacology: sodium nitroprusside. Spinal cord: ischemia.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 26A.

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Received from the Departments of Anesthesiology, Divisions of Cardiothoracic Anesthesiology, The Long Island Jewish Medical Center, New Hyde Park, New York, and The Henry K. Beecher Memorial Research Laboratories, The Massachusetts General Hospital, Boston, Massachusetts. Accepted for publication July 26, 1994.

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PARAPLEGIA continues to be a devastating complication of surgery on the descending thoracic aorta, with an estimated incidence of 3–38%.[1,2] Paraplegia is presumably a consequence of reduced spinal cord blood flow during cross-clamping of the aorta. Numerous factors—for example, the duration of cross-clamping and the collateral circulation below the cross clamp—play a role in this event. The highest possible spinal cord perfusion pressure (SCPP) is defined as the distal aortic pressure minus the cerebrospinal fluid (CSF) pressure.[3] CSF pressure is generally increased and distal aortic pressure is decreased by application of the thoracic aortic cross clamp.[4,5] Administration of sodium nitroprusside (SNP) during thoracic aortic cross-clamping decreases distal blood pressure and increases the CSF

pressure, reducing SCPP, thereby worsening ischemic injury.[3,6,7]

Intravenous administration of magnesium sulfate has been shown to add to the spinal cord protective effect of mild hypothermia in rabbits subjected to spinal cord ischemia.[8] If magnesium ion must reach the central nervous system (CNS) to be protective, then large doses may be necessary because magnesium crosses the blood brain barrier poorly.[9] Unfortunately, systemic hemodynamic side effects limit the maximum tolerable intravenous dose. Direct administration of magnesium salts into the spinal fluid could potentially avoid these limitations while achieving greater levels of magnesium within the CNS extracellular fluid compartment. This study was designed to investigate the effects of intrathecal magnesium on the prevention of paraplegia seen when SNP is used to control proximal hypertension during thoracic aortic cross-clamping in dogs.

Materials and Methods

This study was approved by the institutional animal use committee. All animals received humane care as set forth by the National Institutes of Health.**

Adult mongrel dogs weighing 15–20 kg were anesthetized with intravenous pentobarbital 30–35 mg/kg. After tracheal intubation, they were given fentanyl 10 μg/kg, pancuronium 0.1 mg/kg, and gentamycin 1 mg/kg, and their lungs were ventilated with 100% oxygen to maintain an arterial carbon dioxide tension of 25–30 mmHg, as measured by arterial blood gas analysis. All dogs were placed on warming blankets and rectal temperature was maintained at 36°C. The electrocardiogram was recorded using needle electrodes. A multigas analyzer (Datex, Helsinki, Finland) was used to measure end-tidal carbon dioxide. Femoral arterial (distal pressure), carotid arterial (proximal pressure), and external jugular central venous pressure catheters were placed surgically in sterile conditions. Pressures (systolic, diastolic, and mean) were measured by using disposable transducers (Abbott, Chicago, IL), with pressure amplifiers (Gould, Cleveland, OH) and recorded on a continuous strip-chart recorder (Gould). All data also were recorded by a computer-driven continuous data-acquisition program (Gould).

The dogs were randomly assigned to two experimental groups. One group (n = 8) received SNP without magnesium (control), and the other group (n = 8) received SNP with magnesium. Both groups had a 22-G subarachnoid needle placed in the cisterna cerebellomedullaris for CSF pressure measurement. Immediately after placement of the subarachnoid needle, CSF (0.1 ml) and simultaneous blood (1 ml) samples were drawn for determination of magnesium level. Ionized magnesium levels were measured by the use of a dye-binding Calmagite assay (Paramax, Irvine, CA). Magnesium sulfate 50% (preservative free in sterile water), 3 mg/kg, was then given (0.1–0.15 ml total volume of magnesium sulfate) in the following manner. CSF, 1.5 ml, was aspirated into a syringe containing the magnesium sulfate and then slowly reinjected into the subarachnoid space with the bevel of the needle facing caudally. This same procedure was done in the control group except that in the control group the syringe did not contain any magnesium sulfate when the CSF was aspirated in to it. A sham injection of the extra 0.1–0.2 ml sterile water into the CSF of the control group was thought not necessary because an increase in CSF volume would, if anything, be expected to worsen and not improve outcome, and sterile water would not be expected to have any effect.

Before aortic cross-clamping, blood (7 ml/kg) was removed into a citrated collection bag. Once the dog's condition was stabilized, a small left thoracotomy incision was made under sterile technique. The descending aorta was identified and after baseline CSF, proximal and distal arterial pressures and central venous pressure were measured, a thoracic aortic cross clamp was applied one cm distal to the origin of the left subclavian artery. In the group receiving intrathecal magnesium, the thoracic aortic cross clamp was applied 20 min after magnesium injection, and the clamp was maintained for 45 min in both groups. Immediately after placement of the thoracic aortic cross clamp, an infusion of SNP was started titrated to maintain a mean proximal pressure of 95–100 mmHg. Distal aortic pressure was allowed to drift. CSF pressure, proximal and distal arterial pressure, and central venous pressure were monitored throughout the clamp period and for several minutes thereafter. SCPP was calculated as mean distal arterial pressure minus CSF pressure. After 45 min of thoracic aortic cross-clamping, the SNP was discontinued, the clamp removed, the autologous blood reinfused, and bicarbonate, fluids, and phenylephrine or ephedrine given as necessary to restore pressure and

** National Institutes of Health: Guide for the Care and Use of Laboratory Animals. Publication 85-23. Revised. Bethesda, National Institutes of Health, 1985.

acid–base status to within 10% of baseline. Immediately after cross clamp removal CSF (0.1 ml) and simultaneous blood (1 ml) samples were again drawn for determination of magnesium level.

The thoracotomy incision was then closed, and appropriate intercostal blocks (0.25% bupivacaine) were placed. The muscle relaxant was antagonized with neostigmine–atropine. CSF (0.1 ml) and blood (1 ml) samples were simultaneously drawn for determination of magnesium levels. Arterial, venous, and spinal catheters and needles were removed, and when breathing spontaneously, the trachea was extubated. Twenty-four hours later all dogs were neurologically evaluated by a blinded observer using Tarlov's scale[10] (table 1).

After final neurologic evaluation, each dog was reanesthetized with pentobarbital, tracheally intubated and the lungs mechanically ventilated. The thoracotomy incision was reopened, and the left ventricle cannulated with a 14-G catheter. The right atrial appendage was then opened and 10% formalin was infused into the left ventricle until clear fluid appeared in the right atrium. Sections of cervical, thoracic and lumbar spinal cord were then removed for histopathologic examination by a veterinary pathologist who was blinded to treatment.

Statistical Analysis

Statistical analyses of measured hemodynamic data were performed by analysis of variance for repeated measures. Tarlov scores of neurologic injury and the results of the histopathologic examinations were analyzed with the nonparametric, two-group Mann–Whitney *U* test. Blood and CSF magnesium levels were compared by a factorial analysis of variance with Fisher's and Scheffé's *post hoc* tests. Differences were considered statistically significant for $P < 0.05$. All P values were two sided. All hemodynamic data are expressed as means ± SD.

Results

There was no difference between the two groups in total SNP dose, in the amount of resuscitative drugs used, or in the acid base status after cross-clamping.

Proximal mean arterial pressure, distal mean arterial pressure, CSF pressure, SCPP, and central venous pressure were not statistically different between the two groups (figs. 1A–1D). SCPP was markedly negative in both groups (fig. 1D).

Table 1. Tarlov's Scale

Grade 0	Spastic paraplegia and no movement of the lower limbs
Grade 1	Spastic paraplegia and slight movement of the lower limbs
Grade 2	Good movement of the lower limbs but unable to stand
Grade 3	Able to stand but unable to walk normally
Grade 4	Complete recovery

Neurologic outcome was very different between the groups (fig. 2). Seven of eight dogs in the control group had severe injury (six Tarlov 0 and one Tarlov 1), and only one dog in the control group had no injury (Tarlov 4). In marked contrast, none of the eight dogs in the magnesium group had any measurable neurologic injury (Tarlov 4). These differences were highly significant ($P < 0.005$).

The results of the histopathologic examinations are presented in table 2. Changes considered consistent with ischemic injury included shrunken, necrotic neurons and axonal swelling. In the control group five of eight dogs exhibited histopathologic findings consistent with ischemic injury. None of the dogs in the magnesium group exhibited histopathologic findings consistent with ischemic injury (*i.e.*, grades 2 or 3) (table 2). Differences between groups were statistically significant ($P < 0.01$).

The blood magnesium level before magnesium injection was 1.91 ± 0.24 mg/dl and after cross clamp removal was 1.94 ± 0.26 mg/dl. The difference was not statistically different. The CSF magnesium level before magnesium injection was 1.69 ± 0.55 mg/dl and after cross clamp removal was 14.03 ± 2.56 mg/dl. This difference was significant ($P < 0.001$).

Discussion

Many factors may affect the severity of the spinal cord injury after thoracic aortic cross-clamping. Decreased SCPP has been implicated by several authors as contributing to increased spinal cord injury. In this study we have shown that in a canine model of spinal cord ischemia, intrathecal magnesium sulfate prevented spinal cord ischemic injury seen with thoracic aortic cross-clamping, even in the presence of markedly negative SCPP. However, the mechanisms for this protective effect are not clear.

Cerebral and spinal cord ischemia can result in excessive excitatory amino acid neurotransmitter re-

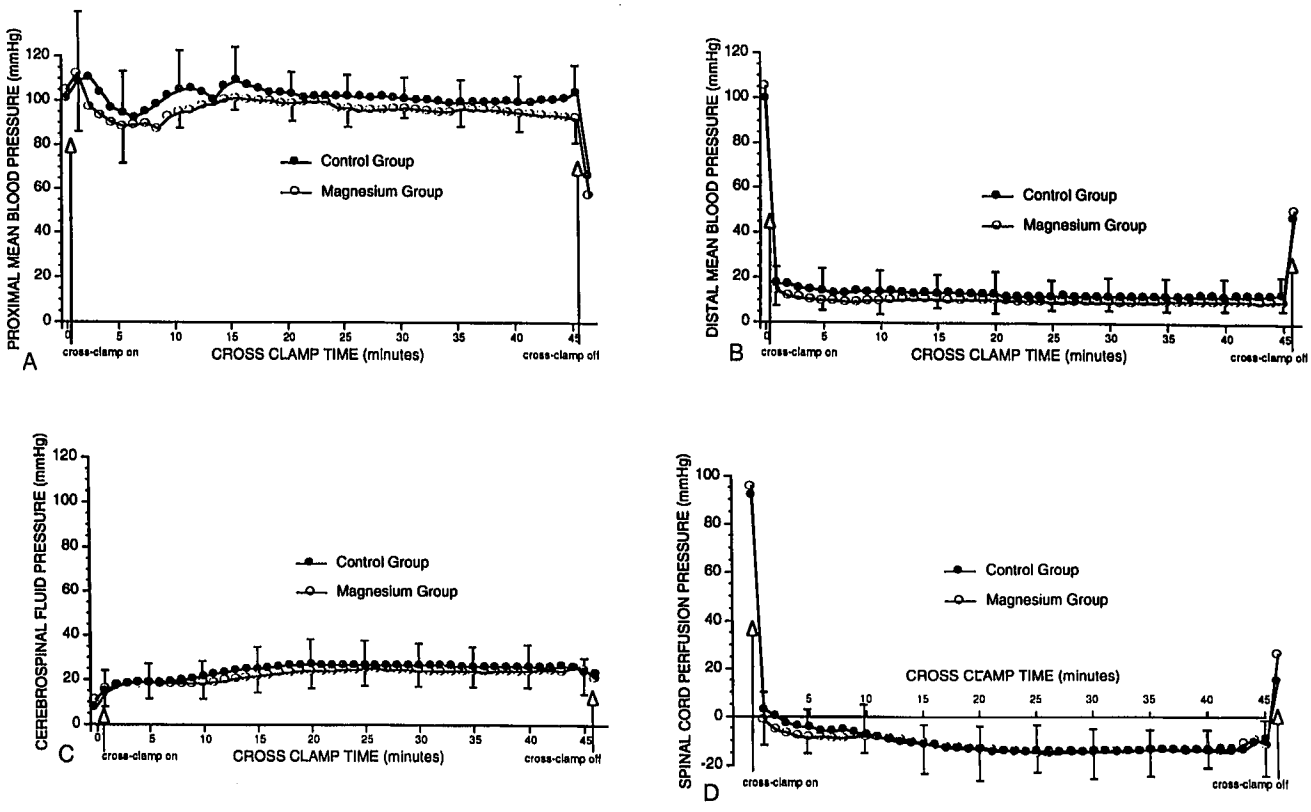

Fig. 1. (*A*) Proximal mean arterial blood pressures measured in the ascending aorta *via* the right carotid artery. (*B*) Distal mean arterial blood pressures measured in the abdominal aorta. (*C*) Cerebrospinal fluid pressure measured in the cisterna cerebellomedullaris with a 22-G spinal needle. (*D*) Spinal cord perfusion pressures calculated as the distal mean blood pressure minus the cerebrospinal fluid pressure at each minute. Filled circles = control group (n = 8); open circles = intrathecal magnesium group (n = 8). Measurements were recorded 1 min before the application of a cross clamp to the descending thoracic aorta, at 1-min intervals during the 45-min clamp time, and 1 min after cross-clamp release. There were no statistically significant differences between groups for any of these parameters.

lease.[11,12] Glutamate and aspartate are two of these excitatory amino acid neurotransmitters. They bind to various subclasses of excitatory amino acid receptors, including kainate, quisqualate, and the N-methyl-D-aspartate (NMDA) receptors which are abundant in the spinal cord.[13] Kainate and quisqualate receptors, when activated, will open monovalent cation channels that allow for the influx of sodium ions and the efflux of potassium ions from the neuron.[14] The NMDA receptor, when stimulated by these excitatory amino acid neurotransmitters, opens a nonselective divalent and monovalent cation channel that allows for the influx of calcium and sodium ions and the efflux of potassium from the neuron. Normally these channels (in the NMDA receptor) are blocked by extracellular magnesium, in a voltage-dependent manner.[15] With massive excitatory amino acid release and the resultant movement of sodium and potassium ions through the kainate and quisqualate receptors, persistent depolarization of the membrane potential may impair normal voltage dependent magnesium ion gating of the calcium channel of the NMDA receptor thereby allowing massive influx of calcium ions into the cell.[16] NMDA receptor antagonists have been shown to decrease CNS ischemic injury[17] in a rabbit model. High extracellular concentrations of magnesium markedly inhibit excitatory amino acid release. Magnesium has also been shown to antagonize the agonist activity of excitatory amino acid on the NMDA receptor, both *in vitro*[18] as well as *in vivo*,[19] and to compete with calcium for entry into the cells. One mechanism by which magnesium could protect the spinal cord during ischemia caused by thoracic aortic cross-clamping, is by facilitation of magnesium dependent inhibition of NMDA activation. This

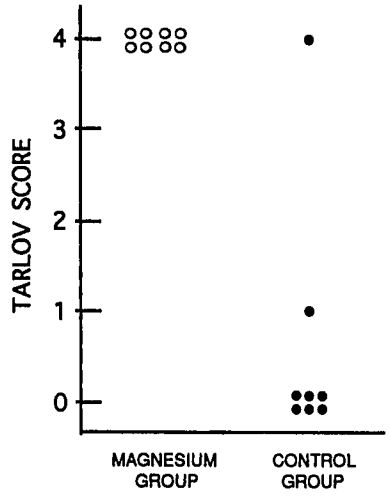

Fig. 2. Tarlov score of neurologic injury measured 24 h after aortic cross-clamp release (table 1). Filled circles = control group (n = 8); open circles = intrathecal magnesium group (n = 8). Differences between the two groups were statistically significant by the Mann–Whitney *U* test ($P < 0.001$).

may prevent initiation of the excitotoxic cascade leading to neuronal death.

Magnesium plays a key role in many aspects of cellular function, including membrane synthesis and integrity, protein synthesis, calcium transport and aerobic respiration.[20] Magnesium levels have been shown to decrease rapidly after CNS injury. Lemke *et al.* have shown that total tissue magnesium decreases after traumatic spinal cord injury.[21] Brain magnesium levels also are known to decrease after stroke.[22] This loss of magnesium seen after central nervous system injury may adversely affect the various cellular processes that depend on magnesium, thus leading to further cell injury and death. Perhaps adding external magnesium may reverse or prevent this from occurring.

Magnesium may also play a role in cerebrovascular vasospasm. Magnesium sulfate is a cerebral vasodilator.[22] Vasospasm is thought to play a role in many aspects of ischemic CNS injury. Adding exogenous magnesium into the CSF may cause vasodilatation or prevent vasospasm of vessels supplying the spinal cord and thus may be yet another mechanism for magnesium's protective effect.

In 1906, Haubold and Meltzer[23] showed that the intrathecal injection of magnesium sulfate produces spinal anesthesia that includes profound motor and sensory block without any permanent untoward effects. Some of his patients seemed to have a rostral spread of the magnesium with subsequent development of an altered state of consciousness that he called general anesthesia. This lasted only several hours with complete recovery. Lejuste[24] described a case of inadvertent intrathecal administration of magnesium sulfate. In that case the magnesium produced a motor but not a sensory block and again there was complete recovery without any untoward effects. Thus it seems that intrathecal magnesium in humans, probably does no harm although larger studies clearly need to be done to assure its safety.

High levels of plasma magnesium produces primarily peripheral effects such as hypotension, paralysis, and respiratory depression. With very high plasma magnesium levels, one may also see central effects (lethargy).[25] However, these central effects probably occur after the peripheral effects. On the other hand, magnesium applied directly to the central nervous system (*i.e.*, given intrathecally) seems to have a marked depressant effect on the CNS[26] without the corresponding peripheral effects. This difference is probably due to the poor passage of magnesium across the blood–brain barrier. Thurnau *et al.*[9] described relatively small changes of CSF magnesium levels in preeclamptic patients treated with relatively large doses of intravenous magnesium sulfate. To achieve by intravenous injection the CSF magnesium concentration that we achieved in the present study (14–15 mg/dl), the necessary dose of magnesium would undoubtedly be large enough to cause severe hemodynamic depression.

This study has several potential limitations. First, this study was not double blinded. Because 50% magnesium sulfate (in sterile water) is very viscous, aspiration of CSF into a syringe containing even very small amounts of magnesium sulfate clearly looks different than aspiration of CSF into a syringe containing sterile water, thus making it difficult to double-blind the study. Nevertheless, the dogs were randomized into the two groups, and other than the injection of magnesium sulfate into the CSF, both groups were treated the same.

Table 2. Results of Pathologic Examination of Thoracolumbar Spinal Cord

	Grade 1	Grade 2	Grade 3
Control group (n = 8)	3	1	4
Magnesium group (n = 8)*	8	0	0

Grade 1 = normal spinal cord; Grade 2 = swollen axons with occasional necrotic neurons; Grade 3 = swollen axons with many necrotic neurons.

* $P < 0.01$.

In addition, the observer performing the neurologic evaluation (Tarlov measurement) was blinded. Second, a true sham procedure—injection of 0.1–0.2 ml sterile water into the CSF of control animals—was not performed, although the CSF was aspirated and reinjected just as in the dogs receiving magnesium. As discussed earlier, it was thought that adding CSF volume to the control group would tend to worsen outcome. It also seems very unlikely that it was the sterile water (the magnesium sulfate diluent) and not the magnesium sulfate that afforded the protection seen in the magnesium group. Third, the magnesium sulfate was administered into the cisterna cerebellomedullaris, a relatively large distance from the lumbar and thoracic spinal cord. Although the total volume injected was 1.5–2.0 ml (CSF plus magnesium sulfate) with the bevel of the needle facing the thoracic cord, it is impossible for us to know the concentration of magnesium at the level of the thoracic or lumbar spinal cord. In fact, a smaller amount of magnesium may be necessary if it were injected directly in to the lumbar space. It is, however, very difficult to gain access consistently to the lumbar or thoracic CSF space in dogs because of anatomic (skeletal) considerations. Another more distant possibility is that the magnesium is in fact working at some higher CNS level although it is more difficult to postulate a mechanism for such effect.

As expected, none of the specimens from dogs that received magnesium and suffered no neurologic injury exhibited any histologic evidence of ischemic injury. However, only five of eight dogs in the control group exhibited histologic signs of injury, whereas seven of these eight dogs had clinical signs of neurologic injury (Tarlov 0 or 1). Perfusion fixation and histologic examination were both performed relatively soon after the injury (24–36 h). Perhaps insufficient time elapsed between injury and fixation for these changes to be seen with light-microscopic examination. This possibility is supported by the subtlety of many of the histologic changes seen. Nevertheless, the differences between the two groups were statistically significant.

This study used a canine model of spinal cord ischemia. In the model, we reproducibly caused irreversible ischemic injury in neural tissue, and the use of magnesium sulfate prevented this injury. Although it is not certain whether these results can be reproduced in other animal species or in humans, it is a first step that may justify further evaluation of the use of magnesium sulfate in other animal species, with another model of spinal cord ischemia.

In summary, we have shown that intrathecal magnesium sulfate can prevent spinal cord injury despite markedly negative SCPP in this canine model of spinal cord ischemia.

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