Paraplegia prevention by oral pretreatment with memantine in a rabbit model

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Objective: To evaluate the role of memantine (*N*-methyl-D-aspartate receptor antagonist) pretreatment for the prevention of spinal cord ischemia after infrarenal aortic clamping in a rabbit model.

Methods: Thirty New Zealand White rabbits were divided into 5 different groups of 6 rabbits. Groups 60-7 and 60-5 received oral memantine 60 mg once a day for 7 and 5 days, respectively, and groups 30-5 and 30-3 received oral memantine 30 mg once a day for 5 and 3 days, respectively, all before surgery. Group C (control) received normal feeds without memantine. A paraplegic model was created by clamping both the aorta and the inferior vena cava infrarenally and just proximal to their bifurcations for 45 minutes. The modified Tarlov score, motor evoked potential (MEP), serum memantine concentration, and histopathology of the spinal cord were evaluated.

Results: The mean modified Tarlov scores were 4.2 ± 1.3 , 4.3 ± 1.0 , 4.2 ± 1.3 , 4.3 ± 1.2 , and 0.8 ± 1.6 in groups 60-7, 60-5, 30-5, 30-3, and C, respectively at 6, 24, 48, and 72 hours ($P < .009$ for individual groups vs control). Percentage amplitude loss of MEP by the end of surgery was $29.5\% \pm 46.3\%$, $11.9\% \pm 28.0\%$, $30.0\% \pm 46.8\%$, $16.7\% \pm 40.8\%$, and $81.8\% \pm 40.3\%$ for the 5 groups, respectively ($P = .049$). After de-clamping, MEP reappeared in 83%, 100%, 83%, 83%, and 33% of cases in the 5 groups, respectively ($P = .073$). The serum memantine level was similar in the 4 memantine groups. Spinal cords were normal in most of the rabbits in groups 60-7, 60-5, 30-5, and 30-3, but severely ischemic in most of the rabbits in group C ($P = .041$).

Conclusions: Oral memantine pretreatment is protective against spinal cord ischemia, and can be an additional strategy for the prevention of paraplegia during thoracoabdominal aortic surgeries. (J Thorac Cardiovasc Surg 2014;148:1732-8)

Spinal cord injury is a devastating complication after thoracoabdominal aortic aneurysm (TAAA) repair. Its incidence has been reported to range from 2% to 31% depending on the series.¹⁻⁹ This seemingly large difference between series is due to the varying proportion of high-risk patients and the use of different surgical adjuncts for spinal protection, and because some studies did not have a large enough number of cases. Paraplegia after TAAA repair carries a huge burden of physical disability and is associated with decreased survival.³

Impaired cord perfusion during aortic clamping, intraoperative and perioperative hypotension, failure to reestablish

cord flow on completion of surgery, and reperfusion injury all contribute to spinal cord injury.¹⁰ A multimodality approach with several surgical adjuncts has long been adopted to help prevent paraplegia; which includes maintenance of high normal blood pressures,⁷ moderate to profound hypothermia,^{7,11} topical spinal cord hypothermia,⁷ drainage of cerebrospinal fluid (CSF),¹² left heart bypass,¹³ and reattachment of segmental intercostal or lumbar arteries.^{1,2,4} The role of pharmacologic protection has also been considered in most adjuncts, including steroids,⁷ naloxone,¹⁰ and free radical scavengers,¹⁴ among many others.

N-methyl-D-aspartate (NMDA) receptors have been shown to have an important role in mediating calcium-mediated injury in neuronal tissue after a variety of insults, including ischemic¹⁵ (Figure 1). NMDA receptors are composed of NR1, NR2, NR3A or NR3B subunits, and activation of these receptors requires dual agonists, glutamate and glycine.^{16,17} During ischemia, glutamate and glycine are coreleased by reverse operation of Na-dependent transporters, thereby leading to subsequent activation of NMDA receptors¹⁸ with subsequent injury of neuronal tissue. Ehrlich and colleagues¹⁹ showed the role of intravenous and intraarterial memantine, a noncompetitive antagonist of NMDA receptors, for the prevention of spinal cord ischemia in a rabbit model. We evaluated the neuroprotective role of

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Abbreviations and Acronyms

AMPA	= α -amino-3-hydroxy-5-methyl-4-isoxazole propionate
CSF	= cerebrospinal fluid
IVC	= inferior vena cava
MEP	= motor evoked potential
NMDA	= <i>N</i> -methyl-D-aspartate
TAAA	= thoracoabdominal aortic aneurysm

oral memantine pretreatment after infrarenal aortic clamping in a rabbit model.

METHODS

Thirty New Zealand White rabbits weighing 3.2 kg (range, 2.8–3.4 kg) were used for the experiment. Rabbits were acquired from a rabbit farm about 10 days before surgery and were allowed to adapt to the new environment in our animal laboratory, with full access to food and water and free movement inside the cage. All animals received full humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* established by the United States National Institutes of Health and the study was approved by the Animal Ethical Committee at the University of Tokyo (approval ID, P12-86). Memantine was purchased from Daiichi Sankyo Co. Ltd (Tokyo, Japan). The final food was prepared by Oriental Yeast Co. Ltd (Tokyo, Japan) to achieve a memantine concentration of 0.048% (w/w). Rabbits were then divided into 5 groups of 6. Groups 60-7 and 60-5 received oral memantine 60 mg once a day for 7 and 5 days, respectively, before surgery. Groups 30-5 and 30-3 received oral memantine 30 mg once a day for 5 and 3 days, respectively, before surgery. Group C (control) received normal feeds without memantine.

All rabbits were anesthetized with an initial dose of intramuscular ketamine 100 mg and xylazine 20 mg without endotracheal intubation. A repeat dose (ketamine 100 mg and xylazine 10 mg) was given intramuscularly 45 minutes after the initial dose. A maintenance dose of ketamine was given as a continuous intravenous infusion at 5 μ g/kg/min. Oxygen was administered via facemask at 2 L/min. Arterial and venous access was obtained using a 24-gauge cannula from the central auricular artery and marginal auricular vein, respectively. Ringer lactate solution (8 mL/kg/h) was infused as maintenance fluid intraoperatively. The core body temperature was measured using a rectal probe. Temperature was maintained as normal as possible by using a heating pad, halogen light, and an infusion of luke-warm maintenance fluid.

A midline laparotomy incision (10 cm long) was made. The bowels were reflected toward the right, and the abdominal aorta and inferior vena cava (IVC) were exposed by incising the retroperitoneum. The aorta and IVC were taped and bulldog clamps were applied to both infrarenally and just proximal to their bifurcations. Clamping was continued for 45 minutes. At the end of 45 minutes, both the aorta and IVC were declamped and the abdomen was closed in 2 layers. Bolus heparin (100 units/kg) was injected intravenously 3 minutes before aortic clamping. Activated clotting time was not measured and heparin was not reversed at the end of the procedure. The rabbits were observed for about 6 hours in the operating room, and then transferred to the cage. They were allowed free access to food, water, and mobility inside the cage.

Paraplegia was evaluated by modified Tarlov score (0, no movement of lower limbs; 1, slight movement of lower limbs; 2, sits with support; 3, sits alone; 4, weak hop; 5, normal hop) at 6, 24, 48, and 72 hours. At 72 hours, the rabbits were killed by intracardiac injection of 10 mequiv KCl. The lumbar segments of the spinal cords were harvested and stored in 10% formalin solution for 2 to 3 weeks before histopathologic examination by a neuropathologist who was blinded to the treatment model. Sections

were cut 3- μ m thick and stained with hematoxylin and eosin. In each section, we looked for normal neurons with a polygonal cell body with a cytoplasmic extension, centrally located round the nuclei with a prominent nucleolus; degenerated neurons (red neurons, ghost neurons, chromatolytic neurons, and neurons with vacuolization); and neuronal loss. Grading of the severity of necrosis was done by dividing the gray matter, excluding the posteriormost part containing sensory neurons, into 4 quadrants: right anterior, left anterior, right posterior, and left posterior. Histopathology was reported as normal if none of the 4 quadrants showed evidence of degenerated neurons or neuronal loss. Histopathology was reported as mild, moderate, or severe ischemia if only 1 quadrant, 2 quadrants, and 3 or all 4 quadrants, respectively, showed evidence of degenerated neurons or neuronal loss.

Motor evoked potentials (MEP) were monitored using a multiple electrical transcranial stimulator (Neuropack MEB-9400, Nihon Kohden, Tokyo, Japan). Stimuli consisting of a train of 5 pulses were applied to the skull with the anode placed at the frontal midline and the cathode at the central midline position. Compound action potentials were recorded from bilateral tibialis anterior by using needle electrodes. MEPs were recorded at baseline, before clamping, clamping 0 minutes, then every 2 minutes until 10 minutes, then every 5 minutes until 45 minutes, at declamping, then every 2 minutes until 5 minutes, every 5 minutes until 20 minutes, followed by every 10 minutes until 1 hour after declamping. The amplitude of the MEP, time to flat, and time to reappearance were analyzed. Flat MEP was defined as the loss of spike bilaterally after clamping. Reappearance of MEP was defined as any MEP waveform that was not flat (unilateral or bilateral) after the release of the clamp.

At the end of surgery, 5 mL of blood was centrifuged at 3000 rpm for 10 minutes to obtain serum for measurement of the memantine concentration. Serum was stored at -80°C for 2 to 3 weeks before the final analysis. Serum concentration was measured by validated liquid chromatography-tandem mass spectrometry using 4-hydroxychalcone as the internal standard. The concentrations were expressed as ng/mL of memantine free base.

Statistical Analysis

Statistical analysis was done using SPSS version 20 (SPSS Inc, Chicago, Ill). Data were expressed using the mean $\pm$ standard deviation, median, range, and percentage wherever appropriate. The Mann-Whitney *U* test, analysis of variance, and χ^2 test were used depending on the variables.

RESULTS

Baseline and Intraoperative Characteristics

The baseline and intraoperative characteristics were similar for all 5 groups (Table 1).

Evaluation of Paraplegia

Paraplegia was evaluated clinically at 6, 24, 48, and 72 hours using a modified Tarlov score. Mean modified Tarlov scores were 4.2 ± 1.3 , 4.3 ± 1.0 , 4.2 ± 1.3 , 4.3 ± 1.2 , and 0.8 ± 1.6 in groups 60-7, 60-5, 30-5, 30-3, and C, respectively, at 6, 24, 48, and 72 hours ($P < .009$ for individual groups vs control; $P = \text{NS}$ among groups 60-7, 60-5, 30-5, and 30-3) (Figure 2). Tarlov score remained the same throughout the observation period and no cases of delayed onset paraplegia were seen.

MEPs

Baseline amplitudes of MEP were 16.8 ± 8.1 , 17.9 ± 6.5 , 18.5 ± 4.7 , 16.6 ± 6.3 , and 17.5 ± 5.8 mV in groups 60-7, 60-5, 30-5, 30-3, and C, respectively ($P = .981$). Median

FIGURE 1. Apoptotic-like cell injury and death pathways triggered by excessive NMDAR activity and its prevention by memantine. The cascade includes: a, NMDAR hyperactivation; b, activation of the p38 MAPK-MEF2C (transcription factor) pathway (MEF2 is subsequently cleaved by caspases to form an endogenous dominant-interfering form that contributes to neuronal cell death); c, toxic effects of free radicals such as NO and ROS; d, activation of apoptosis-inducing enzymes including caspases and AIF; and e, blockade of NMDAR by memantine preventing Ca^{2+} influx into the neuronal cell with subsequent inhibition of steps a to d. Gly, Glycine; Glu, glutamate; NMDAR, N-methyl-D-aspartate receptor; nNOS, neuronal nitric oxide synthase; MAPK, mitogen-activated kinase; BCL2, B-cell lymphoma 2; MEF, myocyte enhancer factor; NO, nitric oxide; ROS, reactive oxygen species; AIF, apoptosis-inducing factor. (Adapted from Lipton SA. Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and beyond. *Nat Rev Drug Discov.* 2006;5:160-70; with permission from Nature Publishing Group).

time to flat MEP after clamping was 17, 15, 12, 15, and 5 minutes in groups 60-7, 60-5, 30-5, 30-3, and C, respectively ($P = .048$). After declamping, MEP reappeared in 83%, 100%, 83%, 83%, and 33% of cases in groups 60-7, 60-5, 30-5, 30-3, and C, respectively ($P = .073$). The mean values of percentage amplitude loss by the end of surgery from baseline values were $29.5\% \pm 46.3\%$, $11.9\% \pm$

28.0% , $30.0\% \pm 46.8\%$, $16.7\% \pm 40.8\%$, and $81.8\% \pm 40.3\%$ in groups 60-7, 60-5, 30-5, 30-3, and C, respectively ($P = .049$). When MEP reappeared after declamping, the median (range) time to reappearance of the MEP was 5 (2-50), 2 (2-20), 2 (2-10), 2 (2-2), and 2 (2-2) minutes in groups 60-7, 60-5, 30-5, 30-3, and C, respectively ($P = .183$).

TABLE 1. Baseline and intraoperative characteristics

Variables	Group 60-7	Group 60-5	Group 30-5	Group 30-3	Group C	P value
Baseline characteristics						
Body weight, mean ± SD (kg)	3.2 ± 0.1	3.2 ± 0.2	3.2 ± 0.1	3.1 ± 0.2	3.2 ± 0.2	.617
Systolic BP, mean ± SD (mm Hg)	86 ± 11	92 ± 3	87 ± 5	87 ± 4	92 ± 9	.383
Heart rate, mean ± SD (bpm)	158 ± 13	159 ± 11	163 ± 10	170 ± 29	151 ± 9	.372
Temperature, mean ± SD (°C)	39.2 ± 0.3	39.5 ± 0.4	39.3 ± 0.5	39.3 ± 0.7	39.2 ± 0.3	.781
Intraoperative characteristics						
Total operating time, mean ± SD (min)	86 ± 6	88 ± 4	87 ± 5	89 ± 7	96 ± 10	.132
Systolic BP, mean ± SD (mm Hg)	67 ± 17	78 ± 8	78 ± 5	69 ± 15	74 ± 9	.391
Heart rate, mean ± SD (bpm)	171 ± 13	168 ± 11	166 ± 7	169 ± 27	175 ± 18	.877
Temperature, mean ± SD (°C)	37.7 ± 0.4	38.4 ± 0.5	38.1 ± 0.7	37.9 ± 0.5	38.4 ± 0.4	.108

SD, Standard deviation; BP, blood pressure.

Serum Memantine Level

The serum memantine level was 4.0 ± 2.1, 6.4 ± 2.5, 6.8 ± 2.4, and 7.5 ± 6.3 ng/mL in groups 60-7, 60-5, 30-5, and 30-3, respectively (*P* = .421) (Figure 3, A). The serum levels ranged from 1.55 to 19.31 ng/mL, which resulted in a Tarlov score of 5 (Figure 3, B).

Histopathology

The percentages of normal cords, cords with mild, moderate, and severe ischemia were 50%, 0%, 17%, and 33%; 67%, 0%, 17%, and 17%; 67%, 0%, 33%, and 0%; 50%, 33%, 0%, and 17%; and 17%, 0%, 0%, and 83% in groups 60-7, 60-5, 30-5, 30-3, and C, respectively (*P* = .041) (Figure 4, A). Evaluation of the gray matter revealed normal neurons with polygonal cell body with a cytoplasmic extension, centrally located round nuclei with a prominent nucleolus in the memantine groups (Figure 4, B); the control group lacked these features and had degenerated neurons and neuronal loss (Figure 4, C).

DISCUSSION

Spinal cord injury after aortic surgery carries a significant risk of physical disability and increases the risk of mortality.³

Total aortic crossclamp time, the extent of the aorta repaired, aortic rupture, patient age, proximal aortic aneurysm, and history of renal dysfunction are significant predictors of paraplegia.³ The extent of the aneurysm has been consistently shown to be a major determinant of paraplegia after TAAA repair.^{3,4,7} Svensson and colleagues³ reported a 31% incidence of paraplegia after Crawford type II repairs compared with 6% after Crawford type I repairs; and the incidence increased further if accompanied by dissection. Dissection itself is a risk factor for paraplegia.¹⁰ Crossclamp time exceeding 30 minutes and emergency procedures also significantly increase the incidence of paraplegia.⁶

After so many years of basic and clinical research, thoracic vascular surgeons have been able to reduce the risk of paraplegia to outstandingly low levels, at least in expert hands⁸; however, total elimination of this complication is almost impossible because of the unavoidable interruption of spinal perfusion during the procedure. Recognition of predictors of paraplegia and implementation of various strategies including hypothermia with better understanding of Q10 for calculating the safe interval for interruption of spinal cord perfusion,¹¹ Drainage of CSF,¹² preoperative detection of the artery of Adamkiewicz by magnetic resonance angiography,^{20,21} reimplantation of critical intercostal and lumbar arteries, and the use of pharmacotherapeutic agents as adjuncts has contributed to better outcomes. In our institute, computed tomography-guided identification of the artery of Adamkiewicz by the Adamkiewicz protocol preoperatively and its reattachment during surgery; avoidance of opioids; use of mild hypothermia and partial cardiopulmonary bypass; MEP monitoring; CSF drainage, use of steroids, and naloxone in cases of noticeable MEP changes have given persistently good results for the prevention of paraplegia over the last several years. We insert a spinal drainage catheter in all patients; but institute CSF drainage at 15 mL/h maintaining CSF pressure at 10 cm H₂O only if we notice changes in MEP.

NMDA receptors have an important role in mediating ischemic neuronal injury.¹⁵ Physiologic NMDA receptor

FIGURE 2. Modified Tarlov scores at 6, 24, 48, and 72 hours. **P* < .009 compared with group C; and *P* is not significant among groups 60-7, 60-5, 30-5, and 30-3.

FIGURE 3. A, Serum level of memantine in groups 60-7, 60-5, 30-5, and 30-3. B, Scatter plot of serum memantine level versus modified Tarlov score.

activity is essential for normal neuronal function,²² and therefore must be preserved, even in the face of excessive pathologic activity in other areas of the central nervous system. However, excessive NMDA receptor activity is harmful and therefore should be prevented to maintain the integrity of the nervous system in the face of a variety of insults.¹⁵ Potential neuroprotective agents that manifest a high affinity for NMDA receptors block virtually all activity including physiologic signaling, and therefore probably have unacceptable clinical side effects.¹⁵ Memantine is unique in that it preferentially blocks excessive (pathologic) NMDA receptor activity without disrupting normal (physiologic) function.²³ Memantine does this through its action as a low-affinity, but still highly selective, uncompetitive, open-channel blocker with a relatively rapid off rate from the channel.²³ Moreover, the relatively fast off rate of memantine prevents the drug from accumulating in NMDA receptor-operated channels, so subsequent physiologic neurotransmission can proceed in a normal fashion.^{24,25} This fast off rate property contributes to the favorable profile of memantine in terms of its clinical tolerability

FIGURE 4. A, Distribution of normal cords, cords with mild, moderate, and severe ischemia in 5 different groups. B, Representative sample of a spinal cord (hematoxylin and eosin [H&E], ×20) in the memantine group showing normal neurons with polygonal cell body with a cytoplasmic extension, centrally located round the nuclei with a prominent nucleolus. C, Representative sample of a spinal cord (H&E ×20) in the control group showing degenerated neurons.

with a lower side effect profile compared with other NMDA receptor antagonists described before the discovery of memantine.^{26,27}

Memantine has already been clinically approved for the treatment of Alzheimer dementia. Bioavailability after oral administration is approximately 100%, and food does not alter its absorption.²⁸ An oral dose of 20 mg once a day as

FIGURE 5. A, Typical MEP waveforms in the memantine group (note that after clamping, MEP persisted until 15 minutes, and after declamping, MEP reappeared in 2 minutes and persisted thereafter). B, Typical MEP waveforms in the control group (note that after clamping, MEP disappeared almost immediately, and after declamping, MEP did not reappear).

used clinically results in a wide range of serum concentrations from 72 to 182 ng/mL^{29,30}; a single oral dose of 20 mg results in a serum concentration of 22.08 ng/mL.³¹ Our medical regimen results in a serum concentration ranging from 1.55 to 19.31 ng/mL, with the majority between 4 and 11 ng/mL (Figure 3, B). Although our treatment dosage (60 mg or 30 mg once a day) was higher than the dosage used clinically, we achieved serum concentrations well below the level of toxicity. Although the serum memantine level in the 4 treatment groups did not show a statistically significant difference, we noted a peculiar finding in that the group that received the highest dose of 60 mg for the longest duration

of 7 days (group 60-7) had relatively low serum levels. A modified Tarlov score of 5 was achieved with a wide range of serum concentrations from 1.55 to 19.31 ng/mL (Figure 3, B) with no specific correlation between the modified Tarlov score and the serum level. This finding demonstrates that there is no cutoff value for the serum level or a particular dosing regimen that confers spinal cord protection, thus, leaving the door open for the possibility of a further reduction in the dose and duration of treatment.

von Euler and colleagues³² reported that memantine is not protective against spinal cord injuries in a rat model. Two years later, Ehrlich and colleagues¹⁹ showed that intravenous and intraarterial memantine is protective against spinal cord ischemia after aortic clamping in a rabbit model. After a careful search of the currently available literature, we did not find any further studies on memantine for spinal cord protection beyond rabbits, despite its clinically favorable side effect profile. Since Ehrlich and colleagues¹⁹ first showed its effectiveness in late 1990s, this topic remained dormant for more than a decade. We demonstrated that oral pretreatment with memantine is effective for the prevention of paraplegia in a rabbit model. Our treatment model is important because memantine is available only in oral form in Japan and as little as 3 days of oral treatment before surgery is effective for the prevention of spinal cord injury; therefore, its easy clinical application provides huge potential.

Other NMDA receptor antagonists that have been studied in animal models and have shown effectiveness for spinal cord protection include MK-801 and CGS19755.^{33,34} However, they have clinically intolerable side effects. After ischemic insult, glutamate and aspartate not only activate NMDA receptors but also activate α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)-kainate receptor subtypes.³⁵ AMPA-kainate receptor antagonists have also shown protection against spinal cord ischemia in animal models.³⁶ However, these drugs are not yet in clinical use. Unlike AMPA-kainate receptor antagonists and other NMDA receptor antagonists, the safety profile of memantine is already proven and it is in clinical use for the treatment of Alzheimer dementia, favoring its choice over others.

MEPs have been used routinely for the detection of spinal cord ischemia during aortic surgery. In our laboratory, we have shown that in rabbits who have received memantine pretreatment, MEPs tend to persist longer after the aortic clamp is applied and reappear more frequently, although the MEP reappearance rate did not reach a level of statistical significance compared with the control group ($P = .073$). Moreover, the amplitude loss by the end of surgery compared with the baseline value was significantly higher in the control group compared with the treatment groups. When the MEP reappeared in the control group, there was no significant difference in the time to reappearance compared with the memantine groups. This is because the MEP reappeared in only 2 rabbits in the control group.

The memantine groups showed persistence of MEP for a longer period with a gradual decrease in amplitude until it finally became flat after aortic clamping; in the control group the MEP flattened abruptly immediately after or within a few minutes of aortic clamping (Figure 5).

The modified Tarlov score was significantly higher in the treatment groups compared with the control group at all observation times. The modified Tarlov score at 24, 48, and 72 hours was the same as that at 6 hours for all 5 groups, and no cases of delayed onset paraplegia were seen. Clinical evaluation closely correlated with the results of histopathology. Histopathologic grading was done by dividing the entire gray matter, excluding the posteriormost part containing sensory neurons, into 4 segments. By doing so, we were able to take even subtle changes in ischemia into consideration. Our findings open the possibility for another potential strategy in the armamentarium of TAAA repair; however, translation of these findings to large animal models or to clinical application needs to be further explored.

CONCLUSIONS

Memantine oral treatment is effective for the prevention of spinal cord injury during infrarenal aortic clamping in a rabbit model. Once daily oral pretreatment with memantine for as little as 3 days before surgery was shown to have spinal protection. As we move toward the path of excellency in aortic surgery, memantine can play its role as an additional strategy for the prevention of spinal cord injury.

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