Evaluation of spinal cord protective threshold of serum memantine, an NMDA receptor antagonist, in a rabbit model of paraplegia

Nirmal Panthee¹ · Minoru Ono¹ · Takehito Yamamoto² · Masako Ikemura³ · Tsuruhito Tanaka¹ · Yoshifumi Itoda¹ · Hiroshi Suzuki²

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Abstract

Purpose To evaluate the threshold of serum memantine for prevention of spinal cord injury (SCI) in a rabbit paraplegic model. **Methods** Forty-two New Zealand white rabbits were divided into 7 groups. Preoperatively, oral memantine was given starting from 60 mg OD for 7 days in the initial group, then reducing the dose and/or duration to 60 mg OD for 5 days, 30 mg OD for 5 days, 30 mg OD for 3 days, 15 mg OD for 3 days, 30 mg single dose, and 60 mg single dose, in subsequent 6 groups. A paraplegic model was created by clamping both infrarenal aorta and inferior vena cava (IVC) for 45 min. Motor evoked potentials (MEPs), modified Tarlov score (0–5), serum memantine concentration, and histopathology of the spinal cord were evaluated. **Results** Half of all rabbits (21/42) showed spinal protection. Receiver operating characteristic (ROC) curve analysis showed serum level of 4.5 ng/ml as a cutoff value for spinal protection (sensitivity 86%, specificity 62%, area under the curve (AUC) 0.785, $P = .002$). Sixteen rabbits had serum level ≥ 4.5 ng/ml (group A), with 26 rabbits having < 4.5 ng/ml (group B). Further comparison was done between groups A and B. The mean modified Tarlov score at 6, 24, 48, and 72 h was 4.5 ± 0.9 and 2.4 ± 1.6 , in groups A and B, respectively ($P < .001$). The modified Tarlov score showed positive correlation with serum memantine level (Spearman's $\rho = 0.618$, $P = .01$). Results of MEP and histopathology were significantly better for group A. **Conclusions** We showed that memantine is protective against SCI at serum levels ≥ 4.5 ng/ml in a rabbit model; thus, it can be a potential adjunct for spinal protection during thoracic/thoracoabdominal aortic surgeries.

Keywords Spinal cord injury · Memantine · Serum level · Thoracic/thoracoabdominal aortic surgeries

Introduction

Spinal cord injury (paraplegia/paraparesis) following thoracoabdominal aortic aneurysm (TAAA) repair is a grave complication, with reported incidence ranging from 2 to 32% [1–8]. The higher incidence corresponds to complex repairs (Crawford I and II) in high-risk patients [3]. Compromised

spinal cord perfusion during aortic clamping is unavoidable, therefore, posing a risk of spinal cord injury during TAAA surgery. Other contributing factors for spinal cord injury include failure to reestablish cord flow on completion of the surgery and reperfusion injury [9]. Emphasis has been given for adapting a multimodal approach to combat this serious consequence, ranging from reattachment of significant intercostal or lumbar arteries [4], use of hypothermia [9, 10], institution of cerebrospinal fluid (CSF) drainage [11] to use of pharmacological adjuncts, which include use of free radical scavengers, naloxone, and steroids [9, 12]. The roles of CNB-001, a novel curcumin-based compound, and Q-VD-OPh, a pancaspase inhibitor, have also been studied in animal models in the quest for search of novel adjuncts [13, 14].

Pharmacological agents are always adjuncts, and none of those offers a panacea for cord protection in isolation. The role of *N*-methyl-D-aspartate receptors (NMDAR) in prevention of neuronal tissue injury has already been described [15].

✉ Minoru Ono
ono-tho@h.u-tokyo.ac.jp

¹ Department of Cardiac Surgery, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

² Department of Pharmacy, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

³ Department of Neuropathology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

NMDARs are heteromeric ligand-gated ion channels composed of four subunits, NR1, NR2, NR3A, or NR3B [16–18]. NMDARs require occupation by two types of agonists for channel activation: a glutamate site agonist at NR2 subunits and a glycine site agonist at NR1 subunits [16]. Any ischemic insult to neuronal cells leads to co-release of glutamate and glycine, thereby leading to subsequent activation of NMDARs [19]. Once the NMDARs are activated, they lead to Ca^{2+} influx through NMDARs, activating an array of intracellular signaling pathways with diverse potential consequences, including apoptotic-like neuronal death [16]. Memantine is a non-competitive antagonist of NMDAR, which has already been in clinical use for treatment of Alzheimer's dementia, and its potential other clinical applications are constantly being explored. The role of memantine in the prevention of spinal cord injury has already been described by our group and others [13, 14, 20, 21]. Our group has previously described the efficacy of different treatment regimens of oral memantine [20]. In this study, we aim to evaluate the serum threshold of memantine which offers spinal protection in a rabbit model of paraplegia. The primary objective of this study is to identify the cutoff value of serum memantine level and the secondary objective is to identify the correlation between total memantine dose and modified Tarlov score.

Materials and methods

Forty-two New Zealand white rabbits weighing 3.2 kg (range, 2.7–3.5 kg) were acquired from a rabbit farm about 10 days prior to the experiment and were allowed to adapt to the new environment of our animal laboratory, with full access to food, water, and 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 US 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. Final memantine food was prepared by Oriental Yeast Co. Ltd., Tokyo, Japan, to achieve a concentration of 0.048% (w/w). Rabbits were then divided into 7 groups of 6 each. Preoperatively, oral memantine was given starting from 60 mg OD for 7 days in the initial group, then reducing the dose and/or duration to 60 mg OD for 5 days, 30 mg OD for 5 days, 30 mg OD for 3 days, 15 mg OD for 3 days, 30 mg single dose, and 60 mg single dose, in subsequent 6 groups.

Our experimental protocol has been described earlier [20]. Briefly, a paraplegic model was created by clamping both aorta and inferior vena cava (IVC) for 45 min at infrarenal position and just proximal to their bifurcations. Motor evoked potentials (MEPs) were monitored by using a multiple electrical transcranial stimulator (Neuropack MEB-9400, Nihon

Kohden, Tokyo, Japan). Amplitude, time to flat, and time to reappearance of the waveforms were analyzed. At the end of surgery, 5 ml of blood was centrifuged at 3000 rpm for 10 min to obtain serum for measurement of memantine concentration. Serum was stored at -80°C for 2–3 weeks before final analysis. Measurement of serum concentration was done by validated liquid chromatography-tandem mass spectrometry using 4-hydroxychalcone as the internal standard. We conducted multiple readings from the same sample and took an average of those multiple readings. The concentrations were expressed as nanograms per milliliter of memantine free base. Paraplegia was evaluated by the 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 h. At the time of secondary analysis, spinal protection was defined as a Tarlov score of 4 or 5, while Tarlov score of 0–3 was defined as having no spinal protection. Tarlov score of 4 was included in the spinal protection group, because of all the 42 rabbits, only 2 rabbits had Tarlov score of 4 and both of these rabbits had normal spinal cords on histopathology. At 72 h, rabbits were sacrificed and lumbar segments of spinal cords were harvested for histopathological examination using hematoxylin and eosin (H&E) stain.

Statistical analysis

Statistical analysis was done using SPSS version 26 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). Data were expressed using mean $\pm$ SD, range, and percentage wherever appropriate. The Mann-Whitney *U* test, independent samples *t* test, Kruskal-Wallis *H* test, analysis of variance (ANOVA), Fisher's exact test, and chi-square tests were utilized depending on the variables. Spearman's rho was utilized as a test of correlation. Receiver operating characteristic (ROC) curve was plotted to find out cutoff values of serum levels yielding spinal protection. During ROC curve creation, paraplegia was entered as a state variable and serum memantine was entered as a test variable. Final analysis included the comparison between two groups (group A and group B), where group A had serum level equal to or above the cutoff value, and group B had serum level below the cutoff value. The level of significance was fixed at a *P* value of $< .05$.

Results

Results of all 7 different treatment groups have been summarized in Table 1. Because the aim of this study is to find out the serum threshold for spinal protection, results have been further presented in two groups based on the serum drug level. Spinal protection was achieved in 50% (21/42) rabbits. ROC curve analysis showed serum level of 4.5 ng/ml as a cutoff point for spinal protection. Sixteen rabbits had serum level ≥ 4.5 ng/ml

Table 1 Results of all 7 different groups taken together

Parameters	M 60 mg 7 d	M 60 mg 5 d	M 30 mg 5 d	M 30 mg 3 d	M 15 mg 3 d	M 30 mg 1 d	M 60 mg 1 d	P value
Modified Tarlov score at 6, 24, 48, 72 h, mean $\pm$ SD	4.2 $\pm$ 1.3	4.3 $\pm$ 1.0	4.2 $\pm$ 1.3	4.3 $\pm$ 1.2	2.0 $\pm$ 2.0	1.3 $\pm$ 0.8	2.2 $\pm$ 1.5	.002
Serum memantine level, mean $\pm$ SD (ng/ml)	4.0 $\pm$ 2.1	6.4 $\pm$ 2.5	6.8 $\pm$ 2.4	7.5 $\pm$ 6.3	2.0 $\pm$ 1.3	1.2 $\pm$ 1.4	2.3 $\pm$ 1.6	.001
MEP, baseline amplitude, mean $\pm$ SD (mV)	16.8 $\pm$ 8.1	17.9 $\pm$ 6.5	18.5 $\pm$ 4.7	16.6 $\pm$ 6.3	13.0 $\pm$ 1.8	16.9 $\pm$ 8.0	12.6 $\pm$ 3.3	.497
MEP % amplitude loss from baseline value by the end of surgery, mean $\pm$ SD	29.5 $\pm$ 46.3	11.9 $\pm$ 28.0	30.0 $\pm$ 46.8	16.7 $\pm$ 40.8	62.5 $\pm$ 48.8	79.1 $\pm$ 17.4	66.5 $\pm$ 48.0	.132
Time to flat MEP after aortic clamp, mean $\pm$ SD (min)	15.7 $\pm$ 11.7	12.8 $\pm$ 5.3	10.2 $\pm$ 5.9	13.3 $\pm$ 4.9	10.6 $\pm$ 7.9	8.7 $\pm$ 6.0	3.8 $\pm$ 5.7	.454
Reappearance of MEP after aortic declamp (%)	83.3%	100%	83.3%	83.3%	66.7%	66.7%	50%	.512
Time to reappearance of MEP after aortic declamp, mean $\pm$ SD (min)	20.8 $\pm$ 24.5	5.0 $\pm$ 7.3	4.0 $\pm$ 3.5	2.0 $\pm$ 0.0	18.5 $\pm$ 25.1	4.7 $\pm$ 3.8	18.0 $\pm$ 27.7	.325
Spinal cords with moderate and severe ischemia (%)	50%	33.3%	33.3%	16.7%	66.7%	100%	66.7%	.128

d day(s), M memantine, mV millivolt, MEP motor evoked potential, SD standard deviation

(group A), and the remaining 26 rabbits had serum level < 4.5 ng/ml (group B).

Baseline and intraoperative characteristics

Baseline and intraoperative characteristics of both groups A and B were similar (Table 2). Trends of intraoperative blood pressure, rectal temperature, and heart rate were also similar (Fig. 1).

Evaluation of paraplegia

Paraplegia was evaluated clinically at 6, 24, 48, and 72 h by using the modified Tarlov score. The mean modified Tarlov scores were 4.5 ± 0.9 and 2.4 ± 1.6 , in groups A and B, respectively, at 6, 24, 48, and 72 h ($P < .001$) (Fig. 2). The Tarlov score remained the same throughout the observation period and we did not see any case of delayed deterioration of the Tarlov score.

Clinical spinal cord injury was noted in 18.8% (3/16) cases in group A and in 69.2% (18/26) cases in group B ($P = .001$).

Serum memantine level and total memantine dose

The mean value of serum memantine for all rabbits was 4.3 ± 3.6 ng/ml (range, 0.3–19.3 ng/ml). ROC curve was plotted to calculate a cutoff value for spinal protection (Fig. 3a). The area under the curve (AUC) of the ROC curve was 0.785 ($P = .002$; CI 0.648–0.921). Serum level of 4.5 ng/ml showed a sensitivity of 85.6%, with a specificity of 61.9%. The mean value of serum levels in group A was 7.8 ± 3.6 ng/ml, while in group B was 2.2 ± 1.3 ng/ml ($P < .001$). Total dose of memantine received by group A and B animals was 214 ± 119 mg and 121 ± 141 mg, respectively ($P = .034$). The modified Tarlov score showed positive correlation of 0.6 with serum memantine (Spearman's $\rho = 0.618$, $P = .01$) (Fig. 3b). We also looked for any correlation between total

Table 2 Baseline and intraoperative characteristics

Variables	Group A (n = 16)	Group B (n = 26)	P value
Baseline characteristics			
Body weight, mean $\pm$ SD (kg)	3.2 $\pm$ 0.2	3.2 $\pm$ 0.1	.651
Systolic BP, mean $\pm$ SD (mmHg)	87 $\pm$ 7	85 $\pm$ 9	.463
Heart rate, mean $\pm$ SD (bpm)	164 $\pm$ 17	159 $\pm$ 27	.523
Temperature, mean $\pm$ SD ($^{\circ}$ C)	39.2 $\pm$ 0.5	39.2 $\pm$ 0.6	.808
Intraoperative characteristics			
Total operating time, mean $\pm$ SD (min)	85 $\pm$ 6	87 $\pm$ 7	.295
Systolic BP, mean $\pm$ SD (mmHg)	75 $\pm$ 10	70 $\pm$ 12	.241
Heart rate, mean $\pm$ SD (bpm)	165 $\pm$ 15	171 $\pm$ 18	.243
Temperature, mean $\pm$ SD ($^{\circ}$ C)	38.0 $\pm$ 0.6	37.9 $\pm$ 0.6	.764

BP blood pressure, SD standard deviation

Fig. 1 Intraoperative trends of vital signs. **a** Systolic blood pressure. **b** Heart rate. **c** Rectal temperature. Decl=declamp

memantine dose and modified Tarlov score and found to have a positive correlation of 0.6, which means there exists moderate positive correlation between total memantine dose and modified Tarlov score (Spearman's $\rho = 0.636$, $P = .01$) (Fig. 4a). Total memantine dose and serum drug level also showed a positive correlation of 0.6 (Spearman's $\rho = 0.591$, $P = .01$) (Fig. 4b).

Fig. 2 Modified Tarlov scores at 6, 24, 48, and 72 h. The difference between groups A and B is statistically significant ($P < .001$)

Motor evoked potentials

Group A animals revealed significantly longer duration of persistence of MEP waveforms after aortic clamping, had significantly less amplitude loss by the end of surgery, and had significantly higher rate of reappearance of MEP after aortic

Fig. 3 **a** Receiver operating characteristic (ROC) curve to calculate a cutoff value for spinal protection. Area under the curve (AUC) of the ROC curve was 0.785 ($P=.002$; CI 0.648–0.921). **b** Correlation between modified Tarlov score and serum memantine (Spearman's $\rho=0.618$, $P=.01$)

declamping, compared with their respective counterparts in group B (Table 3). MEPs showed gradual decrease in amplitude before getting flat, and early reappearance after aortic declamping in majority of group A, as opposed to immediate flattening of MEPs after aortic clamping, and no reappearance after declamping in majority of group B animals (Fig. 5).

Histopathology

The percentages of normal cords and cords with mild, moderate, and severe ischemia were 68.8, 6.2, 18.8, and 6.2% and 26.9, 3.8, 34.6, and 34.6% in groups A and B, respectively ($P=.039$) (Fig. 6a). Majority of cords in group A revealed gray matter with normal neurons having a polygonal cell body with cytoplasmic extension, centrally located round nuclei with prominent nucleolus (Fig. 6b), while these features were

lacking in majority of cords in group B (Fig. 6c). Out of four quadrants in each cord segment, the mean number of quadrants with evidence of ischemia was 0.7 ± 1.2 and 2.0 ± 1.5 in groups A and B, respectively ($P=.005$).

Discussion

We have previously described the protective role of memantine in spinal cord injury in four different treatment groups of a rabbit model. We started with a higher dose of memantine and kept on further reducing the dose. We were surprised to see that reducing the dose further resulted in numerically higher levels of serum drug level, although statistically not significant [20]. This led to the genesis of our current

Fig. 4 **a** Correlation between total memantine dose and modified Tarlov score. Spearman's rho = 0.636, $P = .01$. **b** Correlation between total memantine dose and serum memantine level. Spearman's rho = 0.591, $P = .01$

work by further reducing the dose to find out a cutoff value for spinal cord protection.

Neuroprotective strategies for spinal cord injury following aortic surgery have been studied in various animal models. A group from California [13] has been working on the effects of [4-((1E)-2-(5-(4-hydroxy-3-methoxystyryl)-1-phenyl-1H-pyrazol-3-yl)vinyl)-2-methoxy-phenol] (CNB-001), a novel curcumin-based compound, in a rabbit spinal cord injury model. CNB-001 is known to inhibit human 5-lipoxygenase and 15-lipoxygenase and reduce the ischemia-induced inflammatory response, thereby potentially being useful for spinal protection after TAAA repairs. In their study, they used memantine as a positive control to demonstrate that CNB-001 was effective to prevent spinal cord injury. The spinal protection results of memantine and CNB-001 were similar.

Most of the experimental studies using new drugs focus on the neuronal damage by two major mechanisms: necrosis and apoptosis. Caspases are the key regulator of apoptosis. Q-VD-

Oph is a wide-spectrum irreversible inhibitor of pancaspases. A Turkish group [14] looked into the role of Q-VD-Oph either alone or in combination with memantine in the prevention of spinal cord injury in a rat model. They concluded that memantine was found to be effective in the prevention of necrosis and Q-VD-Oph was found to be effective in the prevention of apoptosis following spinal cord injury by using terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining. Combination of memantine and Q-VD-Oph resulted in better outcomes in their study.

While excessive NMDAR activation is harmful, physiological NMDAR is essential for normal neuronal function [22]. Neuroprotective agents like MK-801 and CGS19755 have been shown to have spinal protection in animal models; however, they have a high affinity for NMDARs, blocking virtually all activity across the receptor including physiological signaling, thereby having severe clinical side effects [15, 23, 24]. Memantine is different from all other NMDAR antagonists by virtue of its preferential blockade of excessive

Table 3 Motor evoked potentials during surgery

MEP parameters	Group A ($n = 16$)	Group B ($n = 26$)	P value
Baseline amplitude, mean $\pm$ SD (mV)	17.2 $\pm$ 5.5	15.3 $\pm$ 6.1	.318
% amplitude loss from baseline value by the end of surgery, mean $\pm$ SD	10.1 $\pm$ 25.3	62.1 $\pm$ 43.8	.002
Time to flat after aortic clamp, mean $\pm$ SD (min)	14.2 $\pm$ 7.3	8.5 $\pm$ 6.8	.029
Reappearance of MEP after aortic declamp, yes, % (n/n)	100 (16/16)	61.5 (16/26)	.004
Time to reappearance after aortic declamp, mean $\pm$ SD (min)	6.4 $\pm$ 11.3	13.0 $\pm$ 19.5	.254

MEP motor evoked potential, SD standard deviation

Fig. 5 **a** Typical MEP waveforms in rabbits of group A showing gradual decrease in amplitude after aortic clamping and immediate reappearance after declamping (this rabbit had serum memantine level of 5.56 ng/ml). **b**

Typical MEP waveforms in rabbits of group B showing abrupt flattening after aortic clamping, without reappearance after declamping (this rabbit had serum memantine level of 3.99 ng/ml)

NMDAR activity, without disrupting physiological function [25]. This unique property can be utilized for further exploration of its therapeutic potentials, including spinal cord protection during TAAA repairs.

Oral bioavailability of memantine is almost 100% and its absorption is not altered by food [26]. Because our methodology included feeding rabbits memantine food containing fixed preparation of 0.048% memantine (w/w), we believe the bioavailability of the drug should have been assured. After oral intake in humans, it has a half-life of 60–80 h [26], and plasma steady state is reached in 4–5 half-lives (almost 10 days of oral treatment). However, it has a much shorter half-life in rats, ranging from 3 to 5 h [27]. We did not find any study addressing its half-life after oral intake in rabbits. Clinically used oral doses of 20 mg OD result in a wide range of serum level measuring 72–182 ng/ml [28, 29]. Our treatment regimens resulted in serum concentration ranging between 0.3 and 19.31 ng/ml. There was only one case with serum level of 19.31 ng/ml (possibly an outlier), while majority of the readings fell between 2 and 10 ng/ml. Despite the fact that 6 out of our 7 treatment groups received a treatment regimen with higher dose compared with clinically used regimen of 20 mg OD, each of these groups attained a serum concentration well below the level of toxicity. The remaining one group receiving 15 mg OD for 3 days also had a serum level well below the level of toxicity, as expected.

We started treatment with a higher dose and longer duration in the initial group and gradually tapered the dose and/or duration in subsequent groups. The initial 2 groups receiving 60 mg memantine for 7 or 5 days and the subsequent 2 groups receiving 30 mg memantine for 5 or 3 days all showed spinal protection. Importantly, all these four

groups had similar levels of serum memantine and similar values of modified Tarlov scores. This finding encouraged us to further reduce the dose and/or duration. Subsequent 3 groups received oral memantine 15 mg for 3 days, 30 mg single dose, and 60 mg single dose before surgery. The serum level of memantine in the latter 3 groups was significantly lower compared with the preceding 4 groups, and these 3 groups failed to show spinal protection. Analysis of all the 7 groups together helped us define the threshold of serum concentration which confers spinal protection. We also looked for any correlation between total oral dose received and serum level of memantine, which showed a positive correlation of 0.6 (Spearman's rho = 0.6, $P = .01$). At least in this animal model, we were not able to show that increased total dose would necessarily result in increased serum levels in a proportionate way. We do not know the reason behind this finding, but we speculate that it might be related to the pharmacokinetic property of memantine in rabbits.

Measurement of CSF concentration of memantine would have been the best way to define its role in spinal protection. However, obtaining CSF sample in this small animal model was technically challenging; therefore, we chose to measure the serum level as a surrogate of the CSF level. Previous studies have shown CSF levels of memantine to be highly correlated with serum levels with mean CSF/serum level ratio of 0.5 [30, 31]. Therefore, we believe that CSF concentration of almost half of the serum concentration would have been achieved in our treatment model had we measured CSF concentration. Even in clinical settings, measurement of the serum level is very convenient which avoids invasive lumbar puncture to obtain CSF sample.

Fig. 6 **a** Bar diagram showing the distribution of normal cords and cords with mild, moderate, or severe ischemia in the two groups. **b** Representative slide of the spinal cord (H&E $\times 40$) in group A showing normal neurons with a polygonal cell body and centrally located round nucleus with a prominent nucleolus (this rabbit had serum memantine level of 5.97 ng/ml). **c** Representative slide of the spinal cord (H&E $\times 40$) in group B showing vacuolization and degenerated neurons (this rabbit had serum memantine level of 3.22 ng/ml). Bar measures 100 μ

Maintenance of high normal blood pressure intraoperatively is a routine practice during TAAA repairs in the clinical settings, as is routine monitoring of MEPs and institution of CSF drainage. In our experimental model, we tried to maintain blood pressure to as normal as

possible, although both groups A and B had similar levels of decrease in blood pressure. We monitored MEPs and maintained core body temperature as normal as possible to nullify the role of hypothermia as a confounding factor for spinal protection.

In the quest of finding adjuncts to prevent spinal cord ischemic injury, a Japanese group has shown that CSF oxygenation with artificial CSF, using nanobubble technology, prevents spinal cord injury in a rabbit model [32]. A Korean group has shown the spinal cord protective effect of histidine-tryptophan-ketoglutarate (HTK) solution in a rat model [33]. Our group A animals showed higher degree of spinal protection as evidenced by clinical Tarlov scores, MEP parameters, and histopathology. Our findings suggest that memantine could play its potential role as a new adjunct in the currently available adjuncts for spinal protection during TAAA repairs at appropriate serum concentrations. Encouraged by the findings of our laboratory, we have already started clinical studies using oral memantine pretreatment in our high-risk TAAA patients, and hopefully we will be able to report those data in coming years. We believe that the oral dose-serum concentration relationship for spinal protection could potentially be different in humans, compared with this rabbit model, and it needs to be explored further.

Limitations

We did not calculate the required sample size and did not look for power of the study, and utilized our conventional wisdom to select the number of animals in each group. Our histopathological examination included staining with H&E only; however, we believe that looking for the evidence of apoptosis by TUNEL assay and genetic studies for hypoxia-inducible factors (HIF) would have further reinforced our histopathological findings. Due to the design of the study, Tarlov score was monitored by the researcher, who was not blinded to the treatment groups, thereby having a theoretical risk of bias; however, histopathological evaluation and serum memantine level measurement were done by researchers who were blinded to the treatment protocol. Large animal models, like canine or porcine models, would be warranted to obtain further insights before clinical application.

Conclusions

By utilizing different oral treatment regimens (dose and duration) in 7 different groups, we showed that memantine is protective against SCI at serum levels ≥ 4.5 ng/ml in a rabbit model. Oral memantine treatment, achieving an appropriate serum drug level, thus, can be a potential adjunct for spinal protection during thoracic and thoracoabdominal aortic surgeries.

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Compliance with ethical standards

Informed consent Not applicable

Ethics committee approval The study was approved by the Animal Ethical Committee at the University of Tokyo (approval ID: P12-86).

Conflict of interest H Suzuki received some grant support from Daiichi Sankyo Co. Ltd. for measurement of serum level of memantine.

Human and animal rights statement All animals received full humane care in compliance with the “Guide for the Care and Use of Laboratory Animals” established by the US National Institutes of Health.

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