Intra-aortic injection of propofol prevents spinal cord injury during aortic surgery

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Abstract

Objective: We investigated whether propofol, a widely used anesthetic, injected into clamped aortic segments quickly attenuated transcranial spinal motor-evoked potential (MEP) amplitudes and protected against spinal cord injury during thoracoabdominal aortic surgery. Methods: Eighteen beagle dogs were divided into three groups (n = 6, each group): group 1 (20 ml of saline, intra-aortic injection), group 2 (1.5 mg/kg of propofol, intravenous injection), and group 3 (1.5 mg/kg of propofol, intra-aortic injection). Aortic cross-clamping was performed for 30 min. In each group, MEP amplitudes were recorded before, during, and after aortic cross-clamping. Tarlov score and histopathological examination were used to evaluate the protective effects of intra-aortic propofol injections. Results: MEP amplitudes in group 3 attenuated to a value that was 60% of the control in just a minute after aortic cross-clamping, but maintained 40% of the control value during aortic cross-clamping. However, MEP amplitudes in groups 1 and 2 gradually attenuated and almost disappeared. Groups 1 and 2 amplitudes were lower than those in group 3, 30 min after aortic cross-clamping (p < 0.001). Twenty-four hours after ischemia, the Tarlov score in group 3 was 3.5 ± 0.5 and was higher than scores from groups 1 and 2, which were 0.5 ± 0.5 and 1.3 ± 1.2 (mean ± SD, p < 0.001, and p < 0.001, respectively). Histopathologically, normal spinal cord motor neurons in group 3 were preserved to a significantly greater extent than in groups 1 and 2 (p = 0.0031, and p = 0.0282, respectively). There was a strong correlation between Tarlov scores at 24 h and the number of normal motor neurons in the anterior horns of spinal cords (r = 0.897; p < 0.001). Conclusions: Intra-aortic propofol injections produce the quick suppression of MEP amplitudes and protect spinal cords from ischemia during aortic cross-clamping.

Keywords: Propofol; Motor-evoked potentials; Spinal cord protection; Aortic surgery

1. Introduction

Protection against iatrogenic neurological deficits resulting from spinal cord ischemia is the most important issue in thoracoabdominal aortic aneurysm (TAAA) surgeries. Paraplegia has been reported at incidences ranging from 4.6 to 21% following TAAA repair [1–4]. Despite various refinements in surgical techniques and developments in adjunctive measures such as cerebrospinal fluid drainage, distal aortic perfusion, and spinal cord cooling [5–7], paraplegia remains a serious threat.

Transcranial spinal motor-evoked potentials (MEPs) enable an evaluation of spinal cord function during general anesthesia and an early diagnosis of spinal cord ischemia during TAAA surgery [8–10]. We monitored the attenuation of MEP amplitudes in the current practice of TAAA repair to determine whether intercostal or lumbar arteries in clamped segments of aortas should be reconstructed [8].

Propofol, a widely used anesthetic and sedative agent, is reported to suppress neural excitability in both brain and spinal cords with dose-dependence on evoked potentials upon intravenous injection [11,12]. Propofol also protects brain neurons [13,14]. During TAAA surgeries, propofol may potentially shorten the time for diagnosis of spinal cord ischemia and protect the spinal cord from ischemia. Thus, the selective injection of propofol into the aortic segment may be useful for confirming whether critical arteries are involved in the segment.

In the current study, we examined whether an injection of propofol into a clamped aortic segment quickly attenuates MEP amplitudes and protects the spinal cord against ischemia during aortic cross-clamping in a canine model.
2. Materials and methods

2.1. Animal preparations

Animals received humane care in compliance with ‘Principles of Laboratory Animal Care’ formulated by the Institute of Laboratory Animal Resources and the ‘Guide for the Care and Use of Laboratory Animals’ prepared by the Institute of Laboratory Animal Resources and published by the National Institute of Health. The study protocol was approved by Guiding Principles on Animal Experiments in Research Facilities for Laboratory Animal Science, School of Medicine, Hiroshima University.

2.2. Anesthesia

Eighteen adult beagle dogs weighing 9.0–11.0 kg were studied. Anesthesia was induced with intramuscular injections of ketamine hydrochloride (0.3 ml/kg) and atropine sulfate (0.5 mg). After endotracheal intubation with an intravenous injection of thiamyl sodium (15 mg/kg) and pancuronium bromide (0.05 mg/kg), general anesthesia was maintained with isoflurane (1.5–2.0%) carried by O2 (2 l/min) mixed with nitrous oxide (4 l/min). Pancuronium bromide was given at a rate of 0.02 mg/kg/h to eliminate electromyograms from MEP recordings. The rectal temperature was kept at around 37 °C using a warm blanket.

2.3. Surgical procedures

After a thoracotomy at the fifth intercostal space and laparotomy on the right decubitus position, the aorta was encircled just distal to the left subclavian artery, at the aortic hiatus, and proximal to the bifurcation, and every visceral branch was encircled. Proximal and distal arterial pressures (PAP and DAP) were monitored at the right forelimb and the right femoral artery, respectively. The PAP was stabilized at 85 ± 5 mmHg during aortic cross-clamping as previously reported [15]. Siliconized plastic catheters placed in the left subclavian artery and left common carotid vein were connected to a siliconized reservoir, which was placed at a level 108 cm above the dog, so that blood freely moved between the dog and the reservoir. Our previous study showed that all six dogs subjected to this procedure exhibited a significant reduction in MEP amplitudes within 30 min after aortic cross-clamping, and were all paraplegic 48 h after ischemia, whereas two of six dogs which were not subjected to the previously described system showed complete functional recoveries with intact MEP findings [15]. After systemic heparinization (100 unit/kg, intravenously), blood was withdrawn and the systolic PAP was reduced to 80 mmHg.

Spinal cord ischemia was induced for 30 min by cross-clamping at the above three levels and every visceral branch except the intercostal and lumbar artery was clamped. After aortic declamping, blood was returned to the left common carotid vein using a roller-type pump (50–100 ml/min). Once the chest and abdomen were closed and all catheters were drawn, the dog was extubated.

2.4. Measurements of electrically evoked spinal cord potentials

MEP amplitudes were measured as spinal cord potentials evoked by electrical transcranial stimulation of motor cortices for 45 min in each group. Stimulations (intensity, 0.1 A; pulse duration, 0.5 ms; pulse rate, 4.0 Hz; and single-pulse) were applied to bilateral temporal scalps using two needle type electrodes. After the laminectomy, amplitudes were recorded by an electrode, which was placed in the lumbar epidural space (L5) as established by previous studies [7, 15]. MEP amplitudes were averaged for 50 impulses per recording using a Nicolet Viking Quest system ( Nicolet Biomedical, Inc., Madison, WI, USA). MEP amplitudes were recorded 1 min prior to aortic cross-clamping and 1, 4, 7, 10, 15, 20, 25, and 30 min after aortic cross-clamping. Potentials were also recorded at 5, 10, and 15 min after aortic declamping. MEP amplitudes 1 min prior to aortic cross-clamping were defined as controls. MEP amplitude data were expressed as the percent-change of corresponding control values. The concentration of isoflurane was fixed at 1.5% during MEP monitoring to avoid changes in the amplitudes caused by fluctuating concentrations.

2.5. Drug injections

A 16-French plastic catheter was inserted into the clamped segment of the abdominal aorta for drug injection. Dogs were divided into three groups (n = 6, each group): group 1 (20 ml of saline, intra-aortic injection), group 2 (1.5 mg/kg of propofol, intravenous injection), and group 3 (1.5 mg/kg of propofol in 20 ml of blood, intra-aortic injection). Drugs were injected into the aorta (groups 1 and 3) in 30 s and intravenously (group 2) as a bolus. The dose of propofol was lower than that in the clinical use. A preliminary study showed that this dose of propofol given intravenously did not produce a significant suppression of MEPs, which was measured for 15 min without aortic cross-clamping. This result indicates that 1.5 mg/kg propofol does not significantly affect the brain and spinal cord.

2.6. Neurological assessments

Neurological function was assessed in every group at 6, 12, and 24 h after ischemia by an observer unaware of the treatment group. Hindlimb motor functions were graded using Tarlov scores, in which 0 indicates no movement of hindlimbs, 1 indicates perceptible movements of hindlimb joints, 2 indicates good joint movement but an inability to stand, 3 indicates the ability to stand and walk, and 4 indicates a complete recovery.

2.7. Histopathological studies

Spinal cords in all groups were excised for histopathological examinations after the completion of 24-h neurological evaluations. Sectioned specimens at lumbar spinal cords (L5) were stained with hematoxylin and eosin. Normal motor neurons in the anterior horns of spinal cords (anterior to a transverse line drawn through the central canal) were counted at ×400 magnification in two sections for each
animal and averaged. Ischemic feature changes of motor neurons were identified by shrunken cellular bodies, a disappearance of Nissl granules, an intensely eosinophilic cytoplasm and triangular and pyknotic nuclei.

2.8. Statistical analyses

Data were expressed as mean ± standard deviation. To adjust for multiple comparisons when analysis of variance (ANOVA) showed a significant difference between groups \((p < 0.05)\), Fisher’s protected least significant difference post hoc test was used to identify which group differences accounted for the significant \(p\)-value. Correlations of hindlimb motor function scores and numbers of normal motor neurons in anterior horns of spinal cords were analyzed using Spearman’s rank correlation tests. A \(p\)-value < 0.05 was considered statistically significant.

3. Results

3.1. Changes in hemodynamics and MEP amplitudes

There was little change in blood pressure among the groups during aortic cross-clamping, indicating that pressure control with a reservoir worked adequately. Heart rates did not change between groups as compared with preischemic levels.

During aortic cross-clamping, MEP amplitudes attenuated gradually and finally disappeared in group 1 (Fig. 1). They also attenuated in group 2 to about 10% of the control value at 30 min but remained significantly higher than those in group 1 \((p = 0.0372)\). In group 3, MEP amplitudes attenuated to 40% of the control value within 4 min but remained during aortic cross-clamping. At either 1 or 4 min following the propofol injection, MEP amplitudes in group 3 were significantly lower than those in group 1 \((p = 0.0012\) and \(p = 0.0046\), respectively) and 2 \((p = 0.0114\) and \(p = 0.0067\), respectively). Thirty minutes after the injection, on the contrary, MEP amplitudes in group 3 were significantly higher than those in groups 1 and 2 \((p < 0.001\) and \(p < 0.001\), respectively). After reperfusion, MEP amplitudes approximated control values in group 3, whereas those in groups 1 and 2 recovered to a value that was only 40 and 70% of the control value, respectively. In groups 2 and 3, there were significant differences at each time after reperfusion compared with group 1. Recovered MEP amplitudes in group 3 were higher than those in group 2, although there was no significant difference.

Morphological changes in MEP waveforms in the three groups are shown in Fig. 2. Group 1 is the intra-aortic saline injection group. Group 2 is the intravenous propofol injection group. Group 3 is the intra-aortic propofol injection group. Arrows show changes in waveforms. One minute after injection, a significant attenuation was recognized only in group 3. The other groups did not change in 1 min. MEP: transcranial motor-evoked potentials.

2. (\(p < 0.001\) and \(p = 0.0010\), respectively). After reperfusion, MEP amplitudes approximated control values in group 3, whereas those in groups 1 and 2 recovered to a value that was only 40 and 70% of the control value, respectively. In groups 2 and 3, there were significant differences at each time after reperfusion compared with group 1. Recovered MEP amplitudes in group 3 were higher than those in group 2, although there was no significant difference.

3.2. Neurological outcomes

Fig. 3 shows changes in Tarlov scores. Tarlov scores in group 3 were significantly higher than those in group 1 \((p = 0.0127,\ p < 0.001,\ and\ p < 0.001,\ respectively)\) and
group 2 ($p = 0.0127$, $p = 0.0037$, and $p < 0.001$, respectively) at each time point after ischemia. There was no significant difference between groups 1 and 2.

3.3. Histopathological assessments

Typical histopathological findings of lumbar spinal cords (L5) in group 3 with a Tarlov score of 4 and those in group 1 with a Tarlov score of 0 are shown in Fig. 4. There were little ischemic changes in the former, while neurons exhibited ischemic cellular changes in the latter. Normal motor neurons were preserved in significantly greater numbers in group 3 than in group 1 ($p = 0.0031$). There was a significant correlation between Tarlov scores at 24 h and the number of normal motor neurons in the anterior horns of spinal cords ($r = 0.849, p < 0.001$; Fig. 5).

4. Discussion

This study demonstrated that (1) an intra-aortic injection of propofol produces a quick and reversible attenuation of MEP amplitudes; and (2) propofol injected into the aortic segment protects spinal cords against ischemia based on both neurological and histopathological assessments.

Propofol has been reported to enhance neural suppression by several mechanisms, mainly presynaptic, extrasynaptic, and axonal GABA$_\text{A}$ receptors, which exist in the central nervous system and the spinal cord, by mediating inhibition among them [16,17]. Propofol also provides neuroprotective effects and improvements of motor function in cerebral ischemia by suppressing neurotransmitter release, oxygen consumption, metabolic rate, and direct antioxidant activity [13,18–20]. MEPS represent the function of anterior and lateral corticospinal tracts and mainly assess motor neurons [21,22]. When the spinal cord is exposed to a hypometabolic state, the electrical activity of the spinal cord is suppressed and MEP amplitude is attenuated. Attenuation of MEP amplitudes to 50% of the control value in spinal cord ischemia indicates a critical state of spinal cords.

In group 3, MEP amplitudes quickly attenuated but MEP amplitudes and Tarlov scores were significantly preserved. The aforementioned results indicate that propofol selectively affected the spinal cord by suppressing the spinal motor neuron, but not by ischemia [11,12,17,19]. The protective effect of propofol was apparent by the restoration of MEP amplitudes and Tarlov scores in group 3. Tarlov scores in group 3 even improved at 12 and 24 h after declamping. Since there was no difference in surgical procedures among the three groups, improvements may be caused by recovery from surgical insult or by the protective effect of propofol.

As group 2 was compared to group 1, MEP amplitudes in the former remained significantly higher during aortic cross-clamping and after reperfusion. Tarlov scores in group 1 gradually dropped by 24 h, whereas those in group 2 remained unchanged. The previous results suggest that intravenously injected propofol also provides spinal cords with a mild protective effect against ischemia.

Intra-aortic injections of propofol produced quick changes in MEP amplitudes. In clinical settings, the detection of MEP changes after aortic cross-clamping often necessitates more than 15 min [9,10,23], as seen group 1. The ischemic injury in the spinal cord progresses during the diagnostic process.
Although the suppressive effect of propofol has been considered to be a disadvantage for spinal cord monitoring, this effect is rather advantageous, because it enables a quick identification of the critical artery, which needs to be reconstructed.

Myogenic MEP monitoring is currently popular in TAAA surgeries [24]. However, MEP monitoring is affected by muscle relaxants and lower limb ischemia. In this model, neurogenic MEP monitoring was used because lower limbs became ischemic during aortic cross-clamping, and we used neurogenic MEPs in the clinical practice [8].

There are several limitations in this study. First, the clamping of every visceral branch and the absence of distal perfusion are unusual in a clinical setting. However, the aforementioned maneuver was necessary in the experimental design to eliminate collateral perfusion and constantly reproduce spinal cord ischemia. Second, the follow-up period was only 24 h following surgery. The prognosis during late phase recovery was not assessed in the current study. Third, the intravenously injection of propofol in high doses may have produced better results in MEP amplitudes and Tarlov scores. This study demonstrated that only a similar dose of propofol is adequate in intra-aortic injection for obtaining a better result. However, it is necessary to establish the safety and tolerability of propofol in humans as we aim towards its use in clinical applications.

In conclusion, intra-aortic propofol injections produce the quick suppression of MEP amplitudes and protect spinal cords from ischemia during aortic cross-clamping. The combination of MEP monitoring and the intra-aortic injection of propofol can be an effective method for identifying the critical artery and protect spinal cords during TAAA surgeries.

References


Appendix A. Conference discussion

Dr C. Rokkas (Athens, Greece): The first question is, why do you choose propofol versus another anesthetic agent? What’s the mode of action of this drug on the spinal cord? How does this protect the spinal cord?

The second question is on your choice of the animal model. We know that the dog is a very burly model for spinal cord ischemia because it does not produce consistent results due to the blood supply to the spinal cord, and the pig or other animals are better models. Why do you choose the dog over pig or something else?

And a third comment is that in your model you did not use distal perfusion, you just used proximal perfusion, and that’s not how aortic surgery/thoracoabdominal surgery is done these days.

Dr Kumagai: We chose propofol because propofol has already been reported to suppress neuroactivity. This is a disadvantage of propofol. But we changed this disadvantage to an advantage. And, propofol reported that it provided neuroprotective effects in several ischemia models. So we choose propofol.

And second question, you mentioned some pig model is good. But we chose the dog. And dog has rich collateral perfusion to the spinal cord, and so we made this model using a blood reservoir. Using blood reservoir, we controlled the...
proximal blood pressure as we like and reduced collateral perfusion. And we could keep the proximal blood pressure at about 85 mmHg.

Dr J. Vøge (Oslo, Norway): I missed something about the mechanistic aspects in this. What is the mechanism of the protective effect of the propofol?

Dr Kumagai: I think propofol provides neuroprotective effects by suppression of the neurotransmitter release and oxygen consumption and metabolic rate and direct antioxidant activity. So, when propofol acted on spinal cords, spinal cords were protected from ischemia.