J Anesth (2010) 24:234–239
DOI 10.1007/s00540-010-0876-7

ORIGINAL ARTICLE

Low-dose but not high-dose prostaglandin E_1 improves the histological outcome of severe forebrain ischemia in rats

Yoshihide Miura · Kaoru Kanazawa · Noriko Yokoo · Kazue Iizawa · Masayuki Okada · Shinya Oda · Masaki Nakane

Received: 11 September 2009 / Accepted: 25 November 2009 / Published online: 18 February 2010

Abstract
Purpose Prostaglandin E_1 (PGE_1) has been shown to provide short-term neuroprotection against various types of brain ischemia in a dose-dependent manner in mice. However, these findings were obtained from experiments performed without any control over physiological parameters. We performed an outcome study where physiological parameters were controlled in an attempt to confirm the dose-dependant neuroprotective effects of PGE_1.
Methods A rat model of severe forebrain ischemia was used. Two doses of PGE_1 were administered during the pre-ischemic period, a low dose (LowPG group) and a high dose (HighPG group). Normotension was maintained in the LowPG group, while hypotension was induced in the HighPG group. In separate groups, normal saline (Control) or sodium nitroprusside (SNP) were infused to compare outcomes under similar blood pressure conditions. Histological outcomes in the hippocampal CA1 and entorhinal cortex were evaluated 5 days post-ischemia.
Results HighPG resulted in hyperglycemia. The percentage of dead neurons in the hippocampal CA1 and entorhinal cortex were similar in the Control, SNP, and HighPG groups, the percentage being significantly attenuated in the LowPG group (CA1: Control = 92.8 ± 2.4%, LowPG = 85.0 ± 8.5%, HighPG = 95.3 ± 2.4%, and SNP = 96.4 ± 0.7%, $P < 0.01$; entorhinal cortex: Control = 73.8 ± 4.0%, LowPG = 53.2 ± 12.3%, HighPG = 72.1 ± 12.6%, and SNP = 76.5 ± 4.1%, $P < 0.01$).
Conclusion Pre-ischemic administration of low-dose PGE_1 in rats provided neuroprotection against severe forebrain ischemia. A dose dependency was not observed with PGE_1 dose and outcome.

Keywords Prostaglandin E_1 · Sodium nitroprusside · Hypotensive anesthesia · Brain ischemia · Rat

Introduction

It has been reported that prostaglandin E_1 (PGE_1) exerts neuroprotective effects against various types of ischemia/anoxia in mice [1]. If this neuroprotective effect of PGE_1 is robust enough, it may be of help when selecting the hypotensive agent for hypotensive anesthesia during neurosurgical procedures, which may present a risk for cerebral ischemia [2, 3]. In their study, Masuda et al. observed a dose-dependent prolongation of survival time with the subcutaneous administration of 0.1–3.0 mg kg^{-1} of PGE_1 against normobaric hypoxia, hypobaric hypoxia, and histotoxic anoxia upon the administration of KCN [1]. A dose-dependently prolonged gasping time after decapitation was also observed [1]. However, the study did not control any physiological parameters known to affect outcome [4], such as blood pressure, blood glucose, arterial blood gas, and brain temperature. In particular, high-dose PGE_1 may have significantly affected blood pressure and thus influenced outcome in their study. The neuroprotective effect of PGE_1 needs to be re-examined using a chronic experimental model with regulated physiological parameters. This study thus evaluated the effects of two doses of PGE_1 on rats with experimentally induced severely ischemic

Y. Miura (✉) · K. Kanazawa
Department of Dental Anesthesiology,
Health Sciences University of Hokkaido,
Hokkaido 061-0293, Japan
e-mail: ymiura@hoku-iryo-u.ac.jp

N. Yokoo · K. Iizawa · M. Okada · S. Oda · M. Nakane
Department of Anesthesiology,
Yamagata University School of Medicine, Yamagata, Japan

forebrain while measuring and controlling all of the other parameters known to affect outcome. Two doses of PGE_1 were administered before ischemia to observe dose-dependent effects on outcome: a high dose to simulate hypotensive anesthesia (HighPG), and a low dose to maintain normotension (LowPG). To compare the effect of HighPG and LowPG on outcome under similar MAP conditions, sodium nitroprusside and normal saline were administered in separate groups as SNP and Control, respectively. Histological outcomes in the hippocampal CA1 and entorhinal cortex regions were evaluated 5 days post-ischemia. We hypothesized that both HighPG and LowPG would produce an improved outcome compared to SNP and Control. Between the PGE_1 treatment groups, better outcomes were expected with LowPG because of the maintenance of MAP.

Methods

The Yamagata University Animal Care and Use Committee approved this study. PGE_1 (500 μg $vial^{-1}$) was donated by Ono Pharmaceutical Co., Ltd., Japan. The hypotensive agent sodium nitroprusside was purchased from Maruishi Pharmaceutical Co., Japan. Male Sprague–Dawley rats (8–11 weeks of age, Kumagai Shigeyasu, Co., Ltd., Sendai, Japan) were fasted for 12–18 h but allowed free access to water before the experiment.

With the animal in a Plexiglas box, anesthesia was induced with 5% halothane in oxygen. After orotracheal intubation, inspired halothane concentration was reduced to 1.5–2.0%, and the lungs were mechanically ventilated with 50% O_2 in N_2. End-tidal medical gas concentrations were continuously monitored during the experiment (Narcotica, model HC-510A, Fukuda Denshi, Inc., Sendai, Japan). Minute ventilation was adjusted to maintain Pa_{CO_2} at between 36 and 42 mmHg. A bilateral cortical electroencephalogram (EEG) was continuously monitored from active subdermal electrodes positioned over the parietal cortex, a reference electrode placed on the nasion, and a ground lead positioned in the hind paw. A 22-gauge needle thermistor (Unique Medical Co., Ltd., Tokyo, Japan) was percutaneously placed adjacent to the skull beneath the temporalis muscle. Pericranial temperature was servoregulated at 37.0 ± 0.1°C by surface heating and cooling from the start of surgery until the return of righting reflexes after anesthesia. Surgery was performed with aseptic techniques, and all surgical fields were infiltrated with 1% lidocaine. The tail artery was cannulated to monitor blood pressure and sample arterial blood. Normal saline, 4 ml kg^{-1} h^{-1}, was continuously infused as maintenance fluid through the tail artery catheter. Via a ventral neck incision, the right jugular vein was cannulated with a silicone catheter for drug infusion and blood withdrawal. The common carotid arteries were encircled with sutures. The vagus nerves and cervical sympathetic plexus were left intact. Muscle paralysis was provided by a 1-mg intra-arterial bolus of succinylcholine, repeated as necessary to allow control of ventilation. Heparin 50 IU was given intravenously.

A pilot study was performed with 6 rats to determine the PGE_1 and sodium nitroprusside doses required to achieve hypotension. Target MAP was set at 60 mmHg. PGE_1 and sodium nitroprusside were dissolved in normal saline. The doses needed to achieve the target MAP varied from 4 to 10 μg kg^{-1} min^{-1} and 0.4–0.8 μg kg^{-1} min^{-1} for PGE_1 and sodium nitroprusside, respectively. These doses were applied to HighPG and SNP, respectively. The dose for LowPG was determined as 0.1 μg kg^{-1} min^{-1} taking into account the dose required to induce and maintain hypotension in humans (0.05–0.2 μg kg^{-1} min^{-1}). It was confirmed that the blood pressure was unaffected by this dose. To realize the same infusion volume for each group, ~1 ml h^{-1}, PGE_1 was prepared at concentrations of 100 and 2 μg ml^{-1} for HighPG and LowPG, respectively. SNP was prepared at a concentration of 30 μg ml^{-1}. The total infusion volume was adjusted to 4 ml kg^{-1} h^{-1} by changing the maintenance fluid volume.

After surgical preparation, the halothane concentration was reduced to 1% and a 30 min interval was allowed for physiological stabilization at an F_{IO_2} of 0.3. At 20 min after stabilization, baseline values of mean arterial pressure (MAP), blood glucose and hematocrit were obtained. Rats with hyperglycemia (>180 mg dl^{-1}) and anemia (Hct < 38%) were excluded from the study. Animals were then randomly assigned to one of four groups ($n = 8$ or 9): Control, LowPG, High PG, and SNP. Each drug was administered for 40 min via a PE10 catheter through the jugular catheter. MAP decreased to 60 mmHg in HighPG and SNP groups within 5 min, after which the doses of these drugs were adjusted to maintain a MAP of 60 mmHg. At 30 min, measurements of MAP, blood glucose, hematocrit, and arterial blood gas sampling were repeated.

At 40 min, drug administration was terminated and the PE10 catheter was removed. The rate of maintenance fluid administration was increased back to 4 ml kg^{-1} min^{-1}. Ischemia was induced by reducing MAP to 30 mmHg by withdrawing blood from the jugular catheter, followed by bilateral carotid occlusion using temporary aneurysm clips. Ischemia was maintained for 10 min. To terminate ischemia, the withdrawn blood was reinfused and the carotid arteries were deoccluded. An aliquot of $NaHCO_3$ (0.1 mEq IV) was given to minimize systemic acidosis. Rats exhibiting any EEG activity during ischemia were excluded from the experiment.

Anesthesia was maintained for an additional 2 h with 1% halothane. MAP and arterial blood gases were

measured at 10 and 60 min post-ischemia. The wounds were closed after the last blood sampling. At 2 h after recirculation, halothane administration was terminated and the rats were allowed to awaken. Mechanical ventilation was continued after recovery of the righting reflex until the rats exhibited escape movements. The rats were placed in an oxygen-enriched recovery chamber (F_{IO_2}= 0.3–0.4) for several hours. The animals were allowed to extubate themselves and then returned to their home cage with free access to water and food for 5 days.

On the fifth postoperative day, the rats were once again anesthetized with halothane, and in situ brain fixation by intracardiac injection of buffered 4% formalin was performed. After overnight stabilization, the brains were removed and stored in 4% formalin. Paraffin-embedded brain sections were serially cut (into 5-μm thick sections) and stained with hematoxylin and eosin. Using light microscopy, investigators blinded to group assignment evaluated the ischemia-induced injuries in the hippocampal CA1 and entorhinal cortex regions at bregma −4.0 mm. Viable and nonviable neurons were manually counted and the percentage of nonviable neurons was calculated (% of dead neurons in CA1 and % of dead neurons in the entorhinal cortex). By convention, values from the hemisphere with more severe damage were used for the final analysis.

Statistical analysis

Statistical analysis was performed with the JMP 6.0 software package (SAS International Japan, Japan). Physiological values, % CA1 dead neurons and % dead entorhinal cortex were compared using a one-way analysis of variance. When indicated by a significant F ratio, post hoc comparisons were performed with Scheffe's correction for multiple comparisons. Statistical significance was assumed when $P < 0.05$.

Results

Each group included 8–9 animals. One rat in the HighPG and two rats in the SNP group died postoperatively for unknown reasons, and these animals were excluded from the experiment.

Physiological values of survivors are reported in Table 1. Pericranial temperature was regulated as intended in all animals. During drug administration, a similar decrease in hematocrit was observed in all groups. Target MAP was achieved in both the HighPG and SNP groups. High-dose PGE_1 administration was associated with significantly elevated pre-ischemic blood glucose levels. During ischemia, all rats exhibited isoelectrical EEG. The amount of blood withdrawn was not significantly different among the groups. At 10 min post-ischemia, MAP was significantly increased from stabilization values in the Control, LowPG and SNP groups, with a lower MAP in the LowPG and HighPG groups compared to the Control group. At 60 min post-ischemia, MAP in the HighPG group was significantly lower than in the other groups. Time to righting reflex was significantly delayed in the HighPG group.

Histological outcomes are shown in Fig. 1. The percentages of CA1 dead neurons were 92.8 ± 2.4, 85.0 ± 8.5, 95.3 ± 2.4, and 96.4 ± 0.7%, and the percentages of entorhinal cortex dead neurons were 73.8 ± 4.0, 53.2 ± 12.3, 72.1 ± 12.6, and 76.5 ± 4.1% in the Control, LowPG, HighPG, and SNP groups, respectively. LowPG resulted in a significantly lower percentage of CA1 dead neurons ($P = 0.0002$) and entorhinal cortex dead neurons ($P = 0.0001$) as compared to the other groups.

Discussion

Due to concerns over poor neurological outcome attributable to intraoperative hypotension, the practice of hypotensive anesthesia during neurosurgical procedures is now performed less frequently [5]. Although controversy exists as to whether hypotensive anesthesia affects neurological outcome [3, 6], anesthesiologists may still be requested by neurosurgeons to induce hypotension during dissection of and clip application to aneurysms, in order to reduce the transmural pressure gradient and thus reduce the risk of intraoperative aneurysm rupture [2].

A vast selection of hypotensive agents are available, such as high-dose volatile anesthetics, sodium nitroprusside, nitroglycerin, Ca^{2+} channel blockers, β-blockers, and PGE_1. It is generally believed that the mechanism of hypotensive action does not affect the choice of hypotensive agent as long as MAP is maintained above the lower limit of autoregulation (LLA) [7]. However, high-dose isoflurane has been shown to worsen both neurological and histological outcomes in the rat model of severe forebrain ischemia [8]. Among the hypotensive agents available, PGE_1 has advantageous properties for neurosurgical procedures. Cerebral blood flow is maintained and CO_2 reactivity is preserved during PGE_1-induced hypotension in neurosurgical patients [9]. PGE_1 is also reported to have cytoprotective effects on major organs, such as the lung [10], liver [11, 12], kidneys [13], and brain [1]. However, the study that examined PGE_1-mediated neuroprotection had methodological flaws in that physiological parameters that independently affect neurological outcome were not controlled.

Table 1 Physiological values

	Control ($n = 8$)	Low PG ($n = 8$)	High PG ($n = 8$)	SNP ($n = 7$)
Body weight (g)	290 ± 39	285 ± 31	290 ± 35	289 ± 29
Stabilization				
MAP (mmHg)	88 ± 7	87 ± 6	87 ± 3	89 ± 5
Glucose (mg/dl)	108 ± 18	122 ± 18	112 ± 22	119 ± 19
Hematocrit (%)	41 ± 3	41 ± 2	42 ± 4	41 ± 3
Arterial pH	7.40 ± 0.03	7.39 ± 0.02	7.41 ± 0.02	7.41 ± 0.02
$PaCO_2$ (mmHg)	39 ± 2	39 ± 4	40 ± 3	41 ± 2
PaO_2 (mmHg)	111 ± 13	122 ± 15	118 ± 15	120 ± 4
10 min pre-ischemia				
MAP (mmHg)	90 ± 9	87 ± 9	60 ± 2*,#	61 ± 1*,#
Glucose (mg/dl)	108 ± 18	128 ± 13	174 ± 42*	133 ± 27
Hematocrit (%)	38 ± 2#	38 ± 2#	37 ± 2#	38 ± 2#
Arterial pH	7.40 ± 0.03	7.39 ± 0.02	7.41 ± 0.02	7.41 ± 0.02
$PaCO_2$ (mmHg)	39 ± 2	38 ± 2	40 ± 2	38 ± 3
PaO_2 (mmHg)	111 ± 18	124 ± 21	108 ± 16	113 ± 11
Blood withdrawal (ml/kg)	23 ± 4	19 ± 4	24 ± 7	27 ± 4
10 min post-ischemia				
MAP (mmHg)	118 ± 6#	105 ± 13*,#	94 ± 10*	111 ± 7#
Arterial pH	7.37 ± 0.06	7.41 ± 0.05	7.38 ± 0.08	7.39 ± 0.03
$PaCO_2$ (mmHg)	38 ± 3	40 ± 5	41 ± 5	43 ± 6
PaO_2 (mmHg)	114 ± 12	119 ± 11	113 ± 23	110 ± 13
60 min post-ischemia				
MAP (mmHg)	99 ± 8	89 ± 7	85 ± 9*	95 ± 12
Arterial pH	7.40 ± 0.02	7.42 ± 0.04	7.42 ± 0.04	7.43 ± 0.03
$PaCO_2$ (mmHg)	39 ± 4	37 ± 3	38 ± 3	39 ± 4
PaO_2 (mmHg)	112 ± 22	127 ± 17	117 ± 16	121 ± 15
Time to righting reflex (min)	23 ± 10	27 ± 18	52 ± 22*	40 ± 22

Values mentioned are mean ± SD

* Significant difference among groups ($P < 0.05$)

Significant difference from stabilization values ($P < 0.05$)

In this study, the target MAP of 60 mmHg in the HighPG and SNP groups was chosen for two reasons. First, this is the value clinically accepted as being above the LLA of cerebral perfusion during hypotensive anesthesia [14]. Second, a previous report showed that CBF remains unchanged until the MAP range of 45–54 mmHg when hypotension is induced by hemorrhage in rats [15]. The dose of SNP required to achieve a MAP of 60 mmHg in rats was comparable to that in humans. However, a 10–100 times larger human dose of PGE_1 was required to induce hypotension in rats, which may be attributable to a species difference (as per a personal communication with the pharmaceutical company). A slight but significantly lower MAP was observed in the LowPG and HighPG groups 10 min post-ischemia and in the HighPG group 60 min post-ischemia, which may suggest residual vasodilatory effects of PGE_1. Since it has been shown that severe and prolonged hypotension itself, with a MAP of 25 mmHg for 20 min, does not influence histological outcome in rats [16], it is unlikely that the slight post-ischemic decrease in MAP affected outcomes in our study.

Lowering blood pressure to a MAP of 60 mmHg with either high-dose PGE_1 or SNP resulted in similar histological outcomes in the CA1 and entorhinal cortex regions as in the control group, suggesting that both high-dose PGE_1 and SNP did not have any distinct effects on outcome after severe forebrain ischemia. LowPG with normotension attenuated the outcome relative to the other groups. Contrary to the report of Masuda et al. [1], PGE_1 did not show dose-dependent neuroprotection against cerebral ischemia. Considering the equivalent pre-ischemic MAP between the Control and LowPG groups, these results indicate that administration of low-dose PGE_1 provides neuroprotection. However, the mechanism(s) of PGE_1-mediated neuroprotection are speculative, as the current experiment examined only outcome. We surmise that the mechanisms proposed for PGE_1-mediated cytoprotection, namely platelet anti-aggregation [17], release of anti-inflammatory cytokines

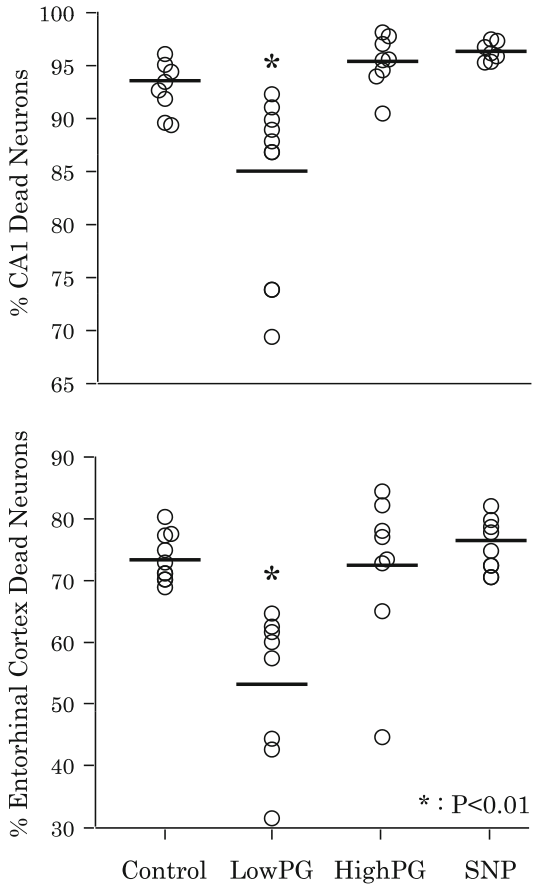

Fig. 1 Histological outcome. *Circles* depict percentages of dead neurons in the hippocampal CA1 (*upper*) and entorhinal cortex (*lower*) regions determined 5 days after severe forebrain ischemia in individual rats. *Horizontal bars* depict mean values. HighPG and SNP had similar outcomes to controls in both the CA1 and entorhinal cortex regions, while LowPG produced a significantly attenuated outcome. $*P < 0.01$, compared to Control, HighPG and SNP

[10] and improvement of endothelial function [18], may have contributed to reduced ischemia–reperfusion injury.

Unexpectedly, high-dose PGE_1 administration caused hyperglycemia in the HighPG group. Direct PGE_1 injection into the third cerebral ventricle has been reported to produce hyperglycemia in rats [19]. Because PGE_1 is transported across the blood–brain barrier [20], there is a possibility that the high dose of PGE_1 administered in this study resulted in an elevated brain PGE_1 concentration, leading to hyperglycemia. Hyperglycemia is known to be an independent factor contributing to a poor outcome after cerebral ischemia [21]. We therefore propose that hyperglycemia in the HighPG group nullified the beneficial effects of PGE_1. Furthermore, the significantly prolonged time to recovery of righting reflex in the HighPG group may have been the result of hyperglycemia-induced brain edema [22].

In conclusion, we investigated the neuroprotective effect of PGE_1 using a rat model of severe forebrain ischemia, while controlling other physiological parameters known to affect neurological outcome. High-dose PGE_1 and SNP that was used to produce pre-ischemic hypotension resulted in a similar histological outcome to that observed in the controls. Low-dose PGE_1 with normotension resulted in an attenuated outcome. It was thus confirmed that a low dose of PGE_1 exerts neuroprotective effects during cerebral ischemia, while maintaining normotension.

Acknowledgments This work was supported by a research fund of the Department of Anesthesiology, Yamagata University School of Medicine, and by Ono Pharmaceutical Co., Ltd., Osaka, Japan. Ono Pharmaceutical Co. kindly provided free samples of PGE_1 (prostandin). The authors are grateful to the late Professor Emeritus Hideo Horikawa for his instruction in performing the study. We also wish to thank Mr. Tadayoshi Karube and Mrs. Michiko Sakai for their expert technical assistance.

References

1. Masuda Y, Ochi Y, Ochi Y, Karasawa T, Hatano N, Kadokawa T, Shimizu M. Protective effect of prostaglandins D_2, E_1 and I_2 against cerebral hypoxia/anoxia in mice. Naunyn Schmiedebergs Arch Pharmacol. 1986;334:282–9.
2. Drummond JC, Patel PM. Neurosurgical anesthesia. In: Miller RD, editor. Miller's anesthesia. 6th ed. Philadelphia: Churchill Livingstone; 2005. p. 2127–73.
3. Chang HS, Hongo K, Nakagawa H. Adverse effects of limited hypotensive anesthesia on the outcome of patients with subarachnoid hemorrhage. J Neurosurg. 2000;92:971–5.
4. Miura Y, Grocott HP, Bart RD, Pearlstein RD, Dexter F, Warner DS. Differential effects of anesthetic agents on outcome from near-complete but not incomplete global ischemia in the rat. Anesthesiology. 1998;89:391–400.
5. Priebe HJ. Aneurysmal subarachnoid haemorrhage and the anaesthetist. Br J Anaesth. 2007;99:102–18.
6. Hoff RG, Vand GW, Mettes S, Verweij BH, Algra A, Rinkel GJ, Kalkman CJ. Hypotension in anaesthetized patients during aneurysm clipping: not as bad as expected? Acta Anaesthesiol Scand. 2008;52:1006–11.
7. Gogarten W, Aken HV. Induced hypotension. In: Newfield P, Cottrell JE, editors. Handbook of neuroanesthesia. 3rd ed. Philadelphia: Lippincott Willams & Wilkins; 1999. p. 53–73.
8. Nasu I, Yokoo N, Takaoka S, Takata K, Hoshikawa T, Okada M, Miura Y. The dose-dependent effects of isoflurane on outcome from severe forebrain ischemia in the rat. Anesth Analg. 2006;103:413–8.
9. Abe K, Nishimura M, Yoshiya I. Local cerebral blood flow and CO_2 reactivity during prostaglandin E_1-induced hypotension in patients undergoing cerebral aneurysm surgery. Eur J Anaesthesiol. 1992;9:485–91.
10. de Perrot M, Fischer S, Liu M, Jin R, Bai XH, Waddell TK, Keshavjee S. Prostaglandin E_1 protects lung transplants from ischemia–reperfusion injury: a shift from pro- to anti-inflammatory cytokines. Transplantation. 2001;72:1505–12.
11. Henley KS, Lucey MR, Normolle DP, Merion RM, McLaren ID, Crider BA, Mackie DS, Shieck VL, Nostrant TT, Brown KA. A double-blind, randomized, placebo-controlled trial of prostaglandin E_1 in liver transplantation. Hepatology. 1995;21:366–72.
12. Miura Y, Nunokawa H, Iizawa K, Tanaka H, Shinzawa H. Perioperative administration of prostaglandin E_1 inhibits post-

operative serum bilirubin increase and preserves prothrombin time in patients with hepatocellular carcinoma and cirrhosis after laparoscopic microwave coagulation therapy (in Japanese with English abstract). Masui (Jpn J Anesthesiol). 2007;56:671–6.
13. Nakayama Y, Nonoguchi H, Kiyama S, Kohda Y, Inoue T, Tomita K. Long-term renoprotective effect of combination therapy with prostaglandin E_1 and angiotensin-converting enzyme inhibitor in patients with chronic renal failure. Hypertens Res. 2005;28:733–9.
14. Gogarten W, Aken HV. Handbok of neuroanesthesia. In: Newfield P, Cottrell JE, editors. Induced hypotension. 3rd ed. Philadelphia: Lippincott Willams & Wilkins; 1999. p. 299–309.
15. Verhaegen MJ, Todd MM, Hindman BJ, Warner DS. Cerebral autoregulation during moderate hypothermia in rats. Stroke. 1993;24:407–14.
16. Warner DS, Reasoner DK, Todd MM, McAllister A. Secondary hypotensive insults in a rat forebrain ischemia model. Brain Res. 1990;536:176–82.
17. Koga T, Az-ma T, Yuge O. Prostaglandin E_1 at clinically relevant concentrations inhibits aggregation of platelets under synergic interaction with endothelial cells. Acta Anaesthesiol Scand. 2002;46:987–93.
18. Marchesi S, Pasqualini L, Lombardini R, Vaudo G, Lupattelli G, Pirro M, Schillaci G, Mannarino E. Prostaglandin E_1 improves endothelial function in critical limb ischemia. J Cardiovasc Pharmacol. 2003;41:249–53.
19. Yatomi A, Iguchi A, Yanagisawa S, Matsunaga H, Niki I, Sakamoto N. Prostaglandins affect the central nervous system to produce hyperglycemia in rats. Endocrinology. 1987;121:36–41.
20. Taogoshi T, Nomura A, Murakami T, Nagai J, Takano M. Transport of prostaglandin E_1 across the blood–brain barrier in rats. J Pharm Pharmacol. 2005;57:61–6.
21. Li PA, Shuaib A, Miyashita H, He QP, Siesjo BK, Warner DS. Hyperglycemia enhances extracellular glutamate accumulation in rats subjected to forebrain ischemia. Stroke. 2000;31:183–92.
22. Morimoto Y, Morimoto Y, Warner DS, Pearlstein RD. Acute changes in intracranial pressure and pressure–volume index after forebrain ischemia in normoglycemic and hyperglycemic rats. Stroke. 1996;27:1405–9.