Kazuo Abe MD, Akira Demizu MD,
 Kitaro Kamada MD, Tetsuya Morimoto MD,
 Toshiyuki Sakaki MD, Ikuto Yoshiya MD

Local cerebral blood flow with prostaglandin E₁ or trimethaphan during cerebral aneurysm clip ligation

This study was performed to examine changes in local cerebral blood flow during hypotensive anaesthesia with either prostaglandin E₁ (PGE₁) or trimethaphan (TMP). Local cerebral blood flow (LCBF), mean blood pressure (MBP), heart rate (HR), and hourly urine output (UO) were studied in 51 patients undergoing cerebral aneurysm surgery with neuroleptanalgesia (NLA). The incidence of vasospasm after aneurysm surgery, and outcome (Glasgow Outcome Scale) at discharge were evaluated. Measurements of LCBF were made using a thermal gradient blood flow meter. The dose of PGE₁ or TMP was adjusted to maintain MBP at about 70 mmHg, and LCBF was studied during and after PGE₁ or TMP administration. Hypotensive drugs were discontinued at the completion of aneurysm clipping. After starting PGE₁ or TMP, MBP decreased immediately, but HR did not change in either group. The LCBF decreased 30 min after the start of TMP administration and increased immediately after its discontinuation, whereas PGE₁ did not affect LCBF. Urine output increased during PGE₁ administration but was unchanged during TMP. Neither drug affected surgical outcome or the incidence of vasospasm. These results suggest that PGE₁ may be preferable to trimethaphan for hypotensive anaesthesia in cerebral aneurysm surgery because LCBF is maintained.

Key words

ANAESTHETIC TECHNIQUES: hypotensive anaesthesia;
 BLOOD PRESSURE: hypotension;
 BRAIN: blood flow;
 HORMONES: prostaglandin E₁;
 SYMPATHETIC NERVOUS SYSTEM: pharmacology,
 trimethaphan.

From the Department of Anaesthesiology, Osaka University Medical School.

Address correspondence to: Dr. Kazuo Abe, Department of Anaesthesiology, Osaka Police Hospital, 10-31 Kitayamacho Tennoujiku Osaka 543, Japan.

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Cette étude a été faite afin d'examiner les changements dans le flot sanguin cérébral local lors d'une anesthésie sous hypotension avec soit de la prostaglandine E₁ (PGE₁) ou du triméthaphan (TMP). Le flot sanguin cérébral local (LCBF), la pression artérielle moyenne (MBP), la fréquence cardiaque (HR), et l'excrétion urinaire horaire (UO) ont été étudiés chez 51 patients subissant une chirurgie pour anévrisme cérébral sous neuroleptanalgesie (NLA). L'incidence de vasospasme après chirurgie, et l'issue (Glasgow Outcome Scale) lors du congé furent évaluées. Les mesures du LCBF furent faites utilisant un appareil qui mesure le gradient de température du flot sanguin. La dose de PGE₁ ou de TMP fut ajustée afin de maintenir une MBP à environ 70 mmHg, et le LCBF fut étudié durant et après l'administration de PGE₁ ou de TMP. Les médicaments hypotenseurs furent cessés à la fin du clampage de l'anévrisme. Après le début du PGE₁ ou du TMP, la MBP diminua immédiatement mais le HR n'a pas changé dans aucun des groupes. Le LCBV a diminué 30 minutes après le début de l'administration de TMP et augmenta immédiatement après son arrêt alors que la PGE₁ n'a pas affecté le LCBF. Le débit urinaire augmenta durant l'administration de PGE₁ mais demeura inchangé durant l'administration de TMP. Aucune des drogues n'a affecté l'issue chirurgicale ou l'incidence de vasospasme. Ces résultats suggèrent que la PGE₁ pourrait être préférable au triméthaphan pour l'anesthésie hypotensive lors de la chirurgie de l'anévrisme cérébral à cause du maintien du LCBF.

Deliberate hypotension is frequently employed to decrease blood loss during surgery and to diminish the need for and the risk of blood transfusion.^{1,2} The characteristics of an ideal hypotensive drug include easy administration, predictability, a rapid onset of action, rapid elimination, compatibility with anaesthetic agents, lack of toxic side-effects, maintenance of adequate perfusion to the vital organs at low blood pressure, and absence of rebound hypertension and tachyphylaxis. A wide variety of intravenous drugs such as trimethaphan (TMP), nitroglycerin, adenosine triphosphate and sodium nitroprus-

side have been used. All these drugs are suitable for deliberate hypotension, but may demonstrate side-effects including increased intracranial pressure, bronchospasm, and cyanide toxicity. In 1959, Bergstrom³ administered prostaglandin E₁ (PGE₁) to patients and reported an antihypertensive effect on systolic and diastolic blood pressure. Although there have been some clinical trials using this drug,⁴⁻⁶ little information is available about its influence on local cerebral blood flow (LCBF). To evaluate PCE₁, the effect of this drug on the LCBF was compared with that of TMP during hypotensive anaesthesia for neurosurgical procedures.

Methods

The protocol was approved by the subcommittee on human studies at the Osaka Police Hospital and informed consent was obtained from each patient or their relatives. Fifty-one patients undergoing craniotomy for cerebral aneurysm clip ligation were studied. Thirty-two patients were given PGE₁ (Group A) and 19 were given TMP (Group B). Subarachnoid haemorrhage (SAH) was documented in all cases by bloody spinal tap and CT scanning. Conventional angiography was performed a few hours to a few days after SAH to confirm the presence of an aneurysm. Patients with SAH were graded neurologically using the scale of Hunt and Kosnik.⁷ Neurological status was recorded at the time of admission. As premedication, 0.5 mg atropine and 100 mg phenobarbitone were administered *im* one hour before surgery. Anaesthesia was induced with 4 mg·kg⁻¹ thiopentone and 0.1 mg·kg⁻¹ pancuronium bromide was given to facilitate tracheal intubation. Ventilation was maintained mechanically with 70% nitrous oxide in oxygen. Anaesthesia was maintained with fentanyl (2 µg·kg⁻¹·hr⁻¹) and droperidol (0.1 mg·kg⁻¹). Continuous blood pressure recordings and intermittent arterial blood samples were obtained via a cannula in the radial artery. The end tidal carbon dioxide tension (PETCO₂) was monitored continuously using an Ohmeda 5200 capnometer (BOC Health Care Co. Ltd.). The ventilator was adjusted to maintain PETCO₂ between 30–40 mmHg. A venous cannula was inserted into the femoral vein for the infusion of PGE₁ or TMP. After the dura mater was opened, the probe of a thermal gradient blood flow meter (Biomedical Science Co, Ltd.) was placed on the middle frontal gyrus, 3–4 cm from the nearest point of intended brain retraction. Control measurements were made before the start of PGE₁ or TMP administration. Initially, either PGE₁ 0.1 µg·kg⁻¹·min⁻¹ or TMP 20 µg·kg⁻¹·min⁻¹ was administered and the dose was adjusted to maintain mean blood pressure (MBP) at about 70 mmHg. The LCBF, MBP, HR, and UO were measured. Urine samples were collected hourly. Infusion of PGE₁ or TMP was discontinued at the end of cerebral aneurysm clipping. The LCBF, MBP

and HR were measured at 10, 30, 60 and 120 min after the start of the PGE₁ or TMP infusion and at 10, 30, 60 min after its discontinuation.

Vasospasm after surgery was evaluated by cerebral angiography. Outcome of patients at discharge was graded by Glasgow Outcome Scale.⁸

Statistical analysis

Values are given as mean ± SD unless otherwise stated. Statistical analysis of age between groups was performed with an unpaired Student's *t* test. Statistical analysis of neurological status and outcome was tested with the Chi-square test. Analysis of variance and Bonferroni procedure were used to define differences within and between groups. A *P* < 0.05 was regarded as statistically significant.

Results

The demographic data of the study patients are shown in Table I. There were no differences between groups in neurological status, or after surgery.

Cerebral vasospasm after aneurysm surgery was seen in 16 patients in the PGE₁ group and in ten after TMP. After the start of PGE₁ or TMP, MBP decreased immediately in both groups and remained low for about one hour after discontinuation of PGE₁. The HR did not change in either group. Urine output increased after the start of PGE₁ but did not change during TMP administration, and increased after its discontinuation. The LCBF did not change compared with baseline values in the PGE₁ group. During TMP, LCBF decreased after 30 min but increased to the pretreatment level immediately after its discontinuation (Table II). The LCBF was less in the TMP than in the PGE₁ group at 30, 60 and 120 min after the start of administration (Figure). There were no differences in MBP or HR between groups.

Discussion

In this study there was no change in local cerebral blood flow during PGE₁ administration, but it decreased 30 min after the start of the administration of TMP. The drugs were discontinued at the completion of the clipping procedure, but the hypotensive effect of PGE₁ continued for at least one hour.

This study was designed to examine CBF during hypotensive anaesthesia with PGE₁. Comparisons were made with patients given TMP because TMP is a ganglionic blocker and the hypotensive agent which is most frequently used during anaesthesia in Japan. The patients in each group were similar although the allocation to PGE₁ or TMP was not randomized. An autonomic ganglionic blocker was chosen because there is some doubt whether cerebral vessels possess intrinsic regulatory tone from the autonomic nervous system. It has been

TABLE I Patients' backgrounds

No.	Age	Sex	Aneurysm location	Neurological status	Outcome scale	Spasm
<i>PGE₁</i>						
1	59	F	l. AchA	II	I	—
2	48	M	r. MCA	III	III	+
3	78	F	A comA	IV	IV	+
4	60	F	A comA	II	I	+
5	81	F	A comA	II	I	—
6	43	M	A com	III	II	+
7	73	F	l. MCA	IV	IV	+
8	26	F	l. MCA	II	I	—
9	41	F	l. IC-Bif	III	I	—
10	41	F	r. MCA	IV	IV	—
11	47	F	r. MCA	II	I	+
12	76	F	A comA	III	I	—
13	50	F	A comA	III	I	—
14	26	F	A comA	II	V	+
15	55	M	l. AchA	I	I	+
16	80	M	A comA	II	I	—
17	55	M	r. MCA	I	I	—
18	68	F	l. IC-PC	I	I	—
19	48	M	l. AchA	II	III	+
20	21	M	A comA	II	II	+
21	44	M	r. AchA	I	I	—
22	55	F	l. Ophthal	I	I	—
23	44	F	l. IC-PC	II	II	+
24	41	F	r. AchA	I	I	—
25	56	M	r. MCA	I	I	—
26	50	M	l. MCA	I	I	—
27	40	M	r. MCA	IV	V	+
28	68	F	r. IC-PC	IV	III	+
29	53	M	A comA	I	I	—
30	50	F	l. IC-PC	IV	III	+
31	50	M	r. MCA	I	I	—
32	60	M	r. IC-PC	II	III	+
mean	50.5					
SD	16					
<i>TMP</i>						
1	60	F	A comA	II	I	+
2	57	M	A comA	III	III	+
3	72	M	r. AchA	II	II	—
4	67	F	l. IC-PC	I	I	—
5	72	F	A comA	II	I	—
6	58	M	A comA	I	I	—
7	68	F	l. AchA	I	I	—
8	60	F	l. IC-PC	III	III	+
9	49	F	l. MCA	II	I	—
10	54	M	r. MCA	II	I	—
11	65	F	A comA	III	III	+
12	70	F	r. AchA	IV	IV	+
13	76	F	l. IC-PC	II	II	+
14	64	M	A comA	I	I	+
15	43	M	A comA	I	I	—
16	78	F	l. IC-PC	I	I	—
17	54	F	A comA	I	I	—
18	51	F	l. IC-PC	II	III	+
19	30	F	r. IC-PC	III	IV	+
mean	60.6					
SD	11.1					

A comA: anterior communicating artery, IC-PC: junction of the internal carotid and posterior communicating arteries, MCA: middle cerebral artery, AchA: anterior choroidal artery, Ophthal: ophthalmic artery, IC-Bif: internal carotid artery bifurcation.

Neurological status was graded by Hunt and Kosnik scale. Outcome was graded by Glasgow Outcome Scale. Statistical analysis of neurological status and outcome scale was performed with chi-square test.

Glasgow Outcome Scale: I—good recovery; II—moderate disability; III—severe disability; IV—persistent vegetative state; V—death.

TABLE II Changes in time course

		Infusion				Post-infusion		
	Pre-drug	10 min	30 min	60 min	120 min	10 min	30 min	60 min
MBP								
- PGE ₁	109.7 ±13.7	90.0 ±16 **	76.1 ±10.5 **	74.5 ±8.4 **	73.6 ±8.8 **	89.8 ±14.3 **	95.1 ±10.2 **	6.9 ±12.9 **
- TMP	110.3 ±14.9	81.2 ±13.1 **	70.0 ±12.5 **	69.7 ±12.1 **	69.6 ±10.9 **	84.8 ±12.6 **	93.3 ±12.2 **	102.3 ±10.1 NS
HR								
- PGE ₁	82.9 ±11.6	84.2 ±12.7	85.3 ±16.2	85.8 ±15.1	86.2 ±8.3	83.5 ±11.5	83.6 ±11.1	81.8 ±9.2
- TMP	84.1 ±18.1	89.1 ±17.3	90.3 ±14.4	88.5 ±13.1	89.4 ±12.8	87.3 ±11.6	82.2 ±21.7	88.5 ±11.4
LCBF								
- PGE ₁	56.8 ±9.9	56.9 ±11.1	56.8 ±11.8 **	56.0 ±12 **	53.9 ±1 **	54.9 ±11.8	56.1 ±13.2	53.6 ±11.1
- TMP	54.8 ±8.9	50.2 ±10.3	44.8 ±9.6	43.3 ±7.8	44.2 ±7.5	51.8 ±10.5	52.6 ±9.7	52.9 ±8.4
UO								
- PGE ₁	74.4 ±49.7		122.3 ± 60.4**			177.5 ± 87.0**		
- TMP	65.7 ±32.1		48.3 ± 28.9			112.5 ± 47.1**		

Comparison with pre-drug values: **: $P < 0.01$; *: $P < 0.05$.

MBP: mean blood pressure (mmHg), HR: heart rate (min^{-1}),

LCBF: local cerebral blood flow ($\text{mL} \cdot \text{min}^{-1}$, 100 g^{-1}),

UO: urine output ($\text{mL} \cdot \text{hr}^{-1}$)

reported that autoregulation of cerebral blood flow is a myogenic mechanism triggered by intraluminal⁹ or cerebral tissue pressure¹⁰ and is under metabolic but not neurogenic influence. However, it has also been reported that the nerves around the intracerebral arterioles receive adrenergic fibres to a varying extent in different brain regions.¹¹

Goto *et al.*¹² reported prolongation of the hypotensive effect of PGE₁ during general anaesthesia, although the blood concentration of PGE₁ decreased to the pre-administration level about ten minutes after the end of its administration. The reason for prolonged hypotensive effect of PGE₁ has not been explained.

Local cerebral blood flow was measured using a thermogradient blood flow meter. The principles of measurement are based on changes in heat conductivity of the tissue which varies according to tissue blood flow. Stimulation of the probe produces a heat gradient, which shows its maximum value at zero blood flow (V_0). As cortical blood flow increases, the temperature difference

decreases in proportion to flow. The tissue blood flow (ψ) is calculated by the following formula using the electromotive force (V) of the thermocouple generated by temperature changes: $\psi = k(1/V - 1/V_0)$, in which k is constant. From this formula, tissue blood flow (ψ) is obtained.^{13,14} After incision of the dura mater, the probe was attached to the cerebral cortex away from surface vessels for continuous measurement of the tissue blood flow.

Blood flow values remain stable as long as the probe remains in position. There are several methods available to measure cerebral blood flow including ¹³³Xenon inhalation, ¹³³Xenon clearance, single photon emission computed tomography, positron emission tomography, or Xenon computed tomographic blood flow mapping. The apparatus used for these methods is expensive and complex whereas our method is simple, atraumatic and lacks radioactive hazard. The major advantage is the ability to measure change in LCBF rapidly and continuously.

Decrease in blood pressure induces peripheral vasodi-

FIGURE Changes in LCBF between groups.

lation. The most important problems are disturbance of autoregulation of blood flow to major organs and a decrease in cerebral perfusion pressure.¹⁵ PGE₁ reduces blood pressure by relaxing the vascular smooth muscle, mainly by dilatation of resistance vessels, but it also dilates capacitance vessels at higher doses.¹⁶ At the doses employed in this study, it is likely that PGE₁ dilated resistance vessels and, as a result, cerebral blood flow remained constant despite a reduction in mean arterial pressure or in cerebral perfusion pressure.

Moyer *et al.*¹⁷ reduced cerebral perfusion pressure by 40% in 19 normal volunteers using hypotensive drugs. Cerebral blood flow decreased by 10–20%, but was reduced to a considerable extent only with trimethaphan. When mean arterial pressure was reduced 40–50% with trimethaphan in 12 patients with nephrosclerosis, cerebral blood flow decreased acutely, but returned to control level by 60 min.¹⁸ Trimethaphan may produce cerebral vasoconstriction, although it has direct arteriolar vasodilating effects in some vascular beds.¹⁹ The control of blood pressure by TMP is easy because of its short plasma half-life, but histamine release has been reported to cause bronchospasm²⁰ and potential increases in intracranial pressure.²¹ In addition, TMP reduces cardiac output and consequently reduces the blood supply to vital organs.²² In this study, TMP caused a decrease in the LCBF after 30 min of continuous administration. However, withdrawal of the medication resulted in an increase in the blood flow to the pretreatment level.

Steiner *et al.*²³ found that PGE₁ had no effect on cerebral blood flow and cerebral arterial diameter in patients with SAH and cerebral vasospasm. Olsen *et al.*²⁴ studied the effect of intracarotid PGE₁ on regional

cerebral blood flow in man and found a mild increase in blood flow during the PGE₁ infusion. Their study seems to have been carried out under physiological conditions without anaesthesia and premedication. In our study, anaesthesia was maintained with neuroleptanalgesic drugs which may have same advantages during intracranial surgery. It is reported that a combination of droperidol and fentanyl does not reduce cerebral blood flow.²⁵

Patients with ruptured cerebral aneurysms have a poor outcome in spite of modern anaesthetic methods and microsurgical techniques;²⁶ PGE₁ or TMP did not affect the outcome of these patients.

In conclusion, LCBF was not changed by PGE₁ administration, which indicates that PGE₁ may maintain normal local cerebral blood flow at doses that produce hypotension during general anaesthesia. Thus PGE₁ may be superior to TMP in maintaining local cerebral blood flow, but neither improves the outcome of patients with ruptured cerebral aneurysms.

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