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Neuroprotective Effect of Low-dose Lidocaine in a Rat Model of Transient Focal Cerebral Ischemia

Baiping Lei, M.D., Ph.D., James E. Cottrell, M.D.,† Ira S. Kass, Ph.D.‡*

Background: **A low concentration of lidocaine (10 μM) has been shown to reduce anoxic damage *in vitro*. The current study examined the effect of low-dose lidocaine on infarct size in rats when administered before transient focal cerebral ischemia.**

Methods: **Male Wistar rats (weight, 280–340 g) were anesthetized with isoflurane, intubated, and mechanically ventilated. After surgical preparation, animals were assigned to lidocaine 2-day (n = 10), vehicle 2-day (n = 12), lidocaine 7-day (n = 13), and vehicle 7-day (n = 14) groups. A 1.5-mg/kg bolus dose of lidocaine was injected intravenously 30 min before ischemia in the lidocaine 2-day and 7-day groups. Thereafter, an infusion was initiated at a rate of 2 mg · kg^{-1} · h^{-1} until 60 min of reperfusion after ischemia. Rats were subjected to 90 min of focal cerebral ischemia using the intraluminal suture method. Infarct size was determined by image analysis of 2,3,5-triphenyltetrazolium chloride–stained sections at 48 h or hematoxylin and eosin–stained sections 7 days after reperfusion. Neurologic outcome and body weight loss were also evaluated.**

Results: **The infarct size was significantly smaller in the lidocaine 2-day group (185.0 ± 43.7 mm^3) than in the vehicle 2-day group (261.3 ± 45.8 mm^3, $P < 0.01$). The reduction in the size of the infarct in the lidocaine 7-day group (130.4 ± 62.9 mm^3) was also significant compared with the vehicle 7-day group (216.6 ± 73.6 mm^3, $P < 0.01$). After 7 days of reperfusion, the rats in the lidocaine group demonstrated better neurologic outcomes and less weight loss.**

Conclusions: **The current study demonstrated that a clinical antiarrhythmic dose of lidocaine, when given before and during transient focal cerebral ischemia, significantly reduced infarct size, improved neurologic outcome, and inhibited postischemic weight loss.**

CEREBRAL ischemia is a frequent consequence during cardiac and neurologic surgery. Many surgical procedures such as coronary artery bypass graft, carotid endarterectomy, aneurysmectomy, and resection of arteriovenous malformations, are associated with a substantial risk of focal cerebral ischemia.

Prophylactic pharmacologic neuroprotective interventions could be of great benefit in patients undergoing these procedures. However, there are currently no safe and efficacious agents available to protect the brain from ischemia. Although some agents, such as anesthetics, competitive and noncompetitive *N*-methyl-D-aspartate (NMDA) antagonists, and glycine site antagonists, have been shown to protect against ischemic brain injury *in vivo*,[1,2] they are effective only at the high concentrations. The neurotoxic and systemic side effects of these agents at high concentrations have limited their use as intraoperative neuroprotective agents.

Previous studies in our laboratory found that a low concentration of lidocaine (10 μM) could reduce anoxic damage *in vitro* without affecting electrophysiologic activity.[3] This concentration of lidocaine has little systemic toxicity and is used widely as an antiarrhythmic agent. Therefore, we conducted the present study to examine the effect of low-dose lidocaine on infarct size in rats when administered before transient focal cerebral ischemia.

Materials and Methods

Animals and Surgical Preparation

This study was approved by the Institutional Animal Care and Use Committee of the State University of New York–Health Science Center at Brooklyn. Male Wistar rats (weight, 280–340 g) were used in the experiments. Animals were allowed free access to food and water before surgery. Rats were placed in a plexiglas box and anesthetized by inhalation of a gas mixture of isoflurane (3%), oxygen (40%), and nitrogen (remainder). After tracheal intubation was completed, the lungs were mechanically ventilated. The isoflurane concentration was reduced to between 2 and 2.2%. The end-tidal carbon dioxide concentration, the inspiratory oxygen concentration, and the inspiratory isoflurane concentration were monitored continuously using an airway gas monitor (DATEX Intrumentarium Co., Helsinki, Finland). Ventilation was adjusted to maintain normocapnia. Temperature probes were inserted into each animal's rectum and left-side temporalis muscle. Rectal and pericranial temperatures were kept constant at 38.0°C ± 0.2°C by surface heating or cooling using a temperature-controlled heating pad (Harvard Apparatus Ltd., Edenbridge, Kent, UK) and a temperature controller (Physitemp, Clifton, NJ) throughout the surgical procedure. The tail artery was catheterized for continuous blood pressure monitoring and periodic blood sampling for arterial gas level, pH, and blood glucose level (10 min before ischemia, at 45 min of ischemia, and 60 min after reperfusion). Mean arterial blood pressure was recorded continuously with a Macintosh type of computer (Power

* Research Assistant Professor, † Professor and Chairman, Department of Anesthesiology, ‡ Professor, Departments of Anesthesiology and Physiology and Pharmacology.

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Address reprint requests to Dr. Kass: Department of Anesthesiology, Box 6, State University of New York Health Science Center at Brooklyn, 450 Clarkson Avenue, Brooklyn, New York 11203. Address electronic mail to: ikass@netmail.hscbklyn.edu.

Computing Corp., Round Rock, TX) using a MacLab/4e analog-to-digital converter (AD Instruments Pty Ltd., Castle Hill, Australia). The right-side femoral vein was cannulated for drug administration. Then animals were prepared for middle cerebral artery (MCA) occlusion according to the method of Koizumi *et al.*[4] An incision was made in the midline of the neck, and the right-side carotid bifurcation was exposed. The right-side external carotid artery (ECA) and the internal carotid artery (ICA) were dissected.

After completion of the surgical preparation, the isoflurane concentration was reduced to 1.7%. The animals were randomly allocated to one of four experimental groups: the vehicle 2-day group (n = 12), the lidocaine 2-day group (n = 10), the vehicle 7-day group (n = 14), or the lidocaine 7-day group (n = 13). In the lidocaine 2-day and 7-day groups, a 1.5-mg/kg (1 mg/ml in saline) bolus dose of lidocaine was administered intravenously over a period of 2 min. Thereafter, a continuous infusion of lidocaine was initiated at a rate of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ and continued until 60 min after reperfusion. This is a standard antiarrhythmic dose and is expected to produce a plasma concentration of 2–5 μg/ml during the period of infusion.[5] Actual plasma lidocaine concentrations were measured in rats not subjected to ischemia (described later in this section). In the vehicle 2-day and 7-day groups, the animals were given the same volume of saline.

Transient Focal Ischemia

After 30 min of lidocaine or saline administration, the right-side common carotid artery and the ECA were ligated and the blood flow of the ICA was transiently interrupted. An arterial incision was made on the carotid bifurcation near the ICA. A 19-mm length of silicone-coated 4-0 nylon suture was inserted into the lumen of the ICA until it blocked the origin of the MCA. After 90 min of ischemia, reperfusion was accomplished by withdrawal of the suture. The neck incision was closed with sutures. After 180 min of reperfusion, temperature probes and catheters were removed. The trachea was extubated and the animal was allowed to survive for either 2 or 7 days. The animal's body weight was measured before the experiment and at 24 and 48 h and 7 days after reperfusion.

Neurologic Evaluation

A neurologic examination, as described by Longa *et al.*,[6] was performed 30 min after recovery from anesthesia and at 48 h and 7 days after reperfusion. A standard scoring scale was used: 0, normal; 1, fails to extend the left forepaw; 2, circles to the left; 3, falls to the left; and 4, does not walk spontaneously and exhibits a consciousness disturbance. Neurologic tests were performed by an observer who was blinded to the experimental groups. Rats that exhibited convulsion, sustained consciousness disturbance, or were without neurologic deficit 30 min after recovery from anesthesia were excluded from the study.

Measurement of Infarct Size

In the vehicle and lidocaine 2-day groups, the animals were anesthetized and decapitated 48 h after reperfusion. The brains were removed rapidly and kept in saline solution (0–4°C) for 2 minutes. Each brain was cut into seven 2-mm-thick coronal slices using a rat brain matrix. Slices were immediately incubated at 37°C for 30 min in 2,3,5-triphenyltetrazolium chloride (TTC), 2%. The stained slices were fixed in 10% buffered formalin solution for 2 h. Video images of slices were captured with a charge-coupled device camera (Pixera Corp., Los Gatos, CA), and the areas traced using an image analysis system (NIH Image 1.60; National Institutes of Health, Bethesda, MD). Infarct volumes in cubic millimeters were calculated using the slice thickness and the measured areas of lesion. To correct for the effect of brain edema, infarct volumes were adjusted by the ratio of the volumes of both cerebral hemispheres (left over right). The extent of infarction was also expressed as the percentage of lesion to the contralateral hemisphere.

In the vehicle and lidocaine 7-day groups, the brains were removed 7 days after reperfusion. Unlike at 48 h after reperfusion, TTC staining could not adequately differentiate the infarcted area from the area that was not infarcted, 7 days after reperfusion. Therefore, we used the hematoxylin and eosin staining method to detect infarct size. Each brain was cut into seven 2-mm-thick coronal blocks. The blocks were immediately fixed in 10% buffered formalin solution and embedded in molds with embedding compound (Sakura Finetek U.S.A., Inc., Torrance, CA) and dry ice. Coronal sections (20 μm) approximately 1 mm from the anterior surface of each block were cut on a cryostat. The sections were dried and stained with hematoxylin and eosin. Video images of individual sections were obtained with a CCD camera, equipped with a macro lens. Brain areas were traced and measured with an image analysis system (NIH Image 1.60). The volume of infarction was calculated as the integrated product of the cross-sectioned area for all sections and the distance between sections. To avoid errors associated with processing of the tissue for histologic analysis, the infarct size was also expressed as the percentage of lesion to the contralateral hemisphere.

Measurement of Lidocaine Concentration

An additional five rats were used to measure plasma lidocaine concentrations. These rats were prepared as described earlier in this section, except that the MCA was not occluded. The dosage regimen of the lidocaine administration was the same as for the lidocaine groups. Blood was obtained during the lidocaine infusion 75 min after the initial bolus of lidocaine. This time point was

Table 1. Physiologic Variables in the Four Experimental Groups

	Vehicle 2-day	Lidocaine 2-day	Vehicle 7-day	Lidocaine 7-day
Number	10	8	9	11
Body weight (g)	315 ± 17	310 ± 19	310 ± 18	312 ± 14
Before ischemia				
MABP (mmHg)	91 ± 7	92 ± 8	96 ± 6	93 ± 6
Arterial pH	7.42 ± 0.01	7.43 ± 0.02	7.42 ± 0.02	7.43 ± 0.02
Pa_{O_2} (mmHg)	143 ± 28	134 ± 22	130 ± 22	133 ± 16
Pa_{CO_2} (mmHg)	41 ± 3	40 ± 1	43 ± 2	41 ± 2
Glucose (mg/dl)	182 ± 36	179 ± 26	187 ± 15	187 ± 20
During ischemia				
MABP (mmHg)	98 ± 9	99 ± 7	106 ± 7	107 ± 6
Arterial pH	7.42 ± 0.02	7.41 ± 0.01	7.43 ± 0.02	7.42 ± 0.02
Pa_{O_2} (mmHg)	135 ± 21	143 ± 26	133 ± 23	140 ± 21
Pa_{CO_2} (mmHg)	41 ± 4	42 ± 2	41 ± 3	42 ± 2
Glucose (mg/dl)	172 ± 27	173 ± 18	182 ± 20	188 ± 21
After reperfusion				
MABP (mmHg)	97 ± 7	94 ± 7	93 ± 4	95 ± 8
Arterial pH	7.43 ± 0.02	7.43 ± 0.02	7.42 ± 0.02	7.42 ± 0.02
Pa_{O_2} (mmHg)	136 ± 15	133 ± 23	131 ± 23	138 ± 17
Pa_{CO_2} (mmHg)	39 ± 3	38 ± 3	41 ± 2	42 ± 2
Glucose (mg/dl)	177 ± 26	171 ± 21	184 ± 21	188 ± 18

Data are mean ± SD. Before ischemia, values were measured 10 min before ischemia. During ischemia, values were measured 45 min after the onset of ischemia. After reperfusion, values were measured 60 min after the onset of reperfusion.

2-day = 2 days, 7-day = 7 days of reperfusion after middle cerebral artery occlusion; MABP = mean arterial blood pressure; Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension.

equivalent to 45 min after the onset of ischemia. Lidocaine concentrations were determined by high-performance liquid chromatography with an ultraviolet spectrometer using a ESA Model 580 pump (ESA, Inc., Chelmsford, MA) and UVIS-205 absorbance detector (Linear Instruments Corp., Reno, NV). Plasma samples were extracted with diethyl ether and sulfuric acid according to the method of Klein *et al.*[7] Chloroprocaine was used as an internal standard. The analytic conditions were as follows: the column, Inertsil ODS-3 (4.6 × 250 mm; Restek Corp., Bellefonte, PA); the mobile phase, 0.05 M KH_2PO_4 (pH 5.2)–acetonitrile (80/20, vol/vol); and the flow rate, 1 ml/min.

Statistical Analysis

All values, except for neurologic score, are presented as mean ± SD. Infarct size, body weight, and physiological variables were analyzed with the unpaired *t* test. Neurologic scores are reported as the median (quartile deviation). Neurologic scores were compared by the use of the two-tailed Mann–Whitney U test. A value of $P < 0.05$ was considered significant.

Results

One animal from the vehicle 2-day group, two from the lidocaine 2-day group, two from the vehicle 7-day group, and one from the lidocaine 7-day group were excluded from the study because of subarachnoid hemorrhage. One animal from the vehicle 2-day group and one from the lidocaine 7-day group were discarded from the study because of unsuccessful MCA occlusion resulting in no neurologic disturbance 30 min after recovery from anesthesia. Three additional animals in the vehicle 7-day group died on the fifth and sixth days after reperfusion and were discarded from the study, although they did not die of subarachnoid hemorrhage. This may have underestimated the efficacy of lidocaine as a neuroprotective agent.

Physiologic variables in the four experimental groups are given in table 1. Mean arterial blood pressure, arterial oxygen tension (Pa_{O_2}), arterial carbon dioxide tension (Pa_{CO_2}), arterial pH, and blood glucose level did not differ significantly between vehicle and lidocaine groups. During the period of ischemia there was a slight increase in mean arterial blood pressure in all groups. Moderate hyperglycemia was also noted in all groups, but there was no difference between vehicle and lidocaine groups. The plasma lidocaine concentration 75 min after the initial bolus administration of lidocaine with our dosage regimen was 1.2 ± 0.4 μg/ml (n = 5).

All animals in the study lost weight at 24 and 48 h of reperfusion when compared with values before MCA occlusion (fig. 1). The weight differences at 24 and 48 h between the animals in the vehicle groups and the lidocaine groups were not statistically different. However, animals from the vehicle 7-day group continued to lose weight. At 7 days after reperfusion, the lidocaine 7-day group of rats exhibited significantly greater weight than the vehicle 7-day group of rats ($P < 0.01$).

The neurologic scores 30 min after recovery from anesthesia were not significantly different between vehicle and lidocaine groups (vehicle 2-day, 2 [range, 2–2.5] *vs.* lidocaine 2-day, 2 [range, 2–2.5], P = not

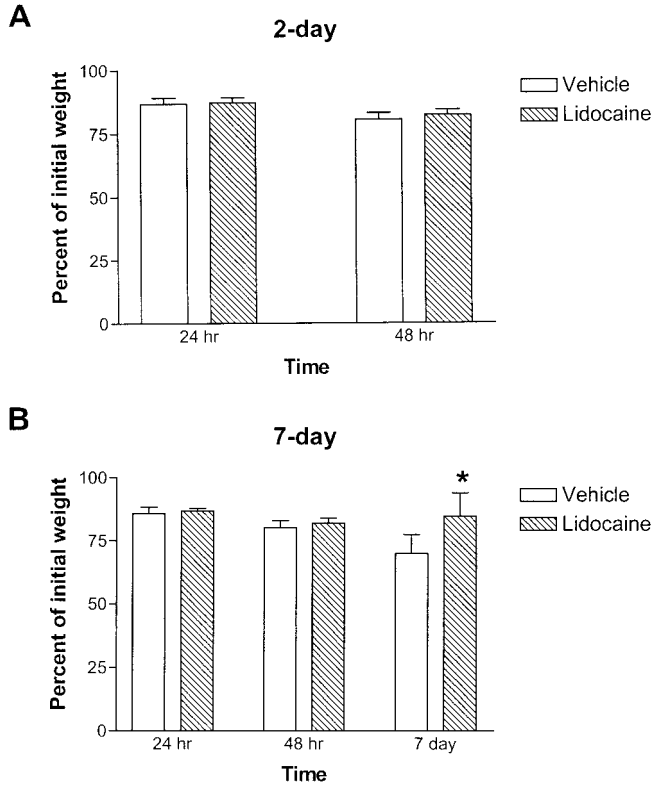

Fig. 1. Changes in weight after middle cerebral artery occlusion and reperfusion in the 2-day (*A*) and the 7-day (*B*) groups. *$P < 0.01$ compared with the vehicle 7-day group.

significant [NS]; vehicle 7-day, 2 [range, 2–2] *vs.* lidocaine 7-day, 2 [range, 2–2], P = NS). At 2 days after reperfusion, neurologic scores were slightly better in the lidocaine group compared with the vehicle group, but the differences were not statistically significant ($P = 0.17$; fig. 2A). At 7 days after reperfusion, the neurologic scores were significantly better in the lidocaine 7-day group than in the vehicle 7-day group ($P < 0.05$; fig. 2B).

The infarct size was significantly smaller in the lidocaine 2-day group (185.0 ± 43.7 mm^3) than in the vehicle 2-day group (261.3 ± 45.8 mm^3; $P < 0.01$; fig. 3). The reduction in the size of the infarct in the lidocaine 7-day group (130.4 ± 62.9 mm^3) was also statistically significant compared with the vehicle 7-day group (216.6 ± 73.6 mm^3; $P < 0.01$; fig. 4).

Discussion

Our study demonstrates that intravenous administration of low-dose lidocaine (a clinical antiarrhythmic dose) significantly reduces infarct size in a rat model of transient focal cerebral ischemia when administration begins 30 min before MCA occlusion. Pretreatment with lidocaine also improves neurologic outcome and postischemic body weight loss.

Lidocaine, which is commonly used as a local anesthetic and antiarrhythmic agent, has also been investigated as a potential neuroprotective agent.[8–16] However, the use of lidocaine for cerebral protection during ischemia has produced conflicting results. The inconsistent results might well reflect a divergence in animal models, lidocaine dosage regimen, or techniques for evaluating the effect of lidocaine. When high-dose lidocaine (resulting in burst suppression and isoelectric electroencephalogram) and severe cerebral ischemia models were used, several studies failed to show the protective effect of lidocaine.[9,12] In contrast, a lower dose of lidocaine has been shown to have protective effect after mild cerebral ischemia.[11,14] Indeed, at high concentrations lidocaine is neurotoxic.[17,18] Low concentrations of lidocaine have significant effects on other excitable tissue.[5] Thus, the effect of lidocaine on neurons may depend on its concentration; the concentration necessary to produce neuroprotective effects may be within the range of lower concentrations. Recently, Mitchell *et al.*[19] reported that prophylactic infusion of an antiarrhythmic dose of lidocaine could improve neurologic outcome after cardiac operations, suggesting that this dose of lidocaine is neuroprotective.

Neuroprotective mechanisms of lidocaine have been postulated to include one or more of the following pharmacologic effects of this drug: (1) deceleration of ischemic transmembrane ion shifts and inhibition of anoxic depolarization,[3,20] (2) reduction in cerebral metabolic rate,[21] (3) reduction in the release of excitatory amino acids,[22–24] (4) modulation of leukocyte activity,[25] (5) increase in cerebral blood flow,[15,16] (6) scavenging of oxygen free radicals,[26] or (7) reduction in the intracranial pressure.[27] However, the exact mechanism for the neuroprotective effect of lidocaine, especially low-

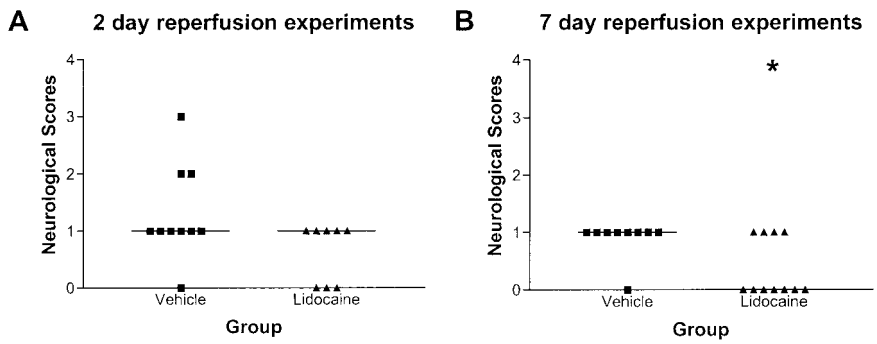

Fig. 2. Neurologic scores at 2 days (*A*) and 7 days (*B*) after reperfusion. The following standard scoring scale was used: 0, normal; 1, fails to extend the left forepaw; 2, circles to the left; 3, falls to the left; and 4, does not walk spontaneously and exhibits a consciousness disturbance. Each point depicts the value for a single rat. Horizontal bars depict median values for each group. *$P < 0.05$ *versus* the vehicle 7-day group.

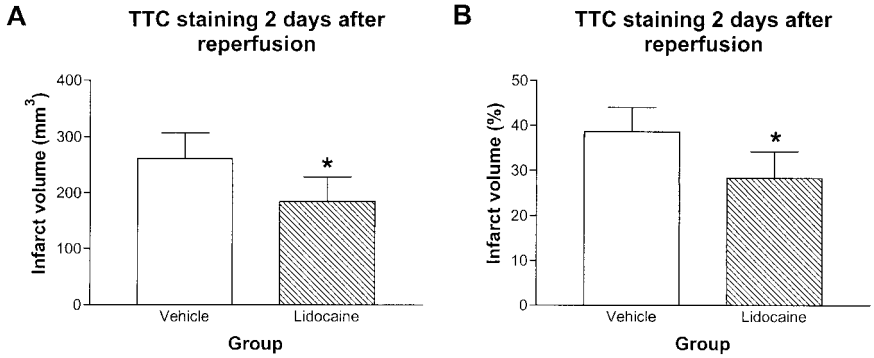

Fig. 3. Infarct size 2 days after reperfusion. (*A*) Infarct volume (cubic millimeters, mean ± SD). (*B*) Percentage of the contralateral hemisphere (mean ± SD). Infarct volumes were measured from 2,3,5-triphenyltetrazolium chloride (TTC)–stained sections and corrected for the effect of brain edema (see Materials and Methods). *$P < 0.01$ compared with the vehicle group.

dose lidocaine, is not known. In a previous study from our laboratory, a low concentration of lidocaine (10 μM) significantly improved recovery of the evoked population spike recorded from the CA1 pyramidal cell layer after anoxia.[3] This concentration of lidocaine had no significant effect on potassium levels or calcium influx during anoxia but reduced cellular sodium levels and preserved adenosine triphosphate (ATP) levels during anoxia. The protective action of low-dose lidocaine observed in the current study may be related to deceleration of ischemic transmembrane ion shifts and reduction in neuronal ATP consumption.

Because most episodes of cerebral ischemia during surgical procedures are focal in nature, we chose a rat model of transient focal cerebral ischemia. It has become increasingly clear that focal cerebral ischemia produces a densely ischemic core and a perifocal area with a moderate reduction of blood flow.[28–30] The latter, often referred to as the ischemic penumbra, has received a great deal of attention because the neuronal injury in this area is essentially reversible and may be salvageable by pharmacologic agents.[30] It has been reported that the volume of the ischemic penumbra is greater than the volume of the densely ischemic core soon after the onset of focal ischemia.[31] However, the ischemic penumbra disappears because of progressive metabolic deterioration in the first hours following MCA occlusion and becomes a part of the irreversibly damaged infarct core. Periinfarct depolarizations have been suggested to play an important role in the progression of the ischemic penumbra into the infarct core.[28] Glutamate efflux or the release of K^+ from the deteriorating ischemic core produce repetitive waves of anoxic depolarization in cells in the ischemic penumbra.[28,30] Repetitive depolarizations are harmful to the energetically stressed cells in the penumbra. Inhibition of periinfarct depolarizations has been shown to reduce the infarct size.[32–35] It is possible that low-dose lidocaine may increase the tolerance of cells in the ischemic penumbra to repetitive depolarizations by attenuating ATP depletion.[3] In addition, lidocaine may also reduce periinfarct depolarizations by blocking Na influx[3] or inhibiting the release of glutamate[22–24]; this may limit the expansion of the infarction.

Shokunbi *et al.*[15] found that a continuous infusion of lidocaine preserved the blood flow in the ischemic zone in a feline model of transient focal cerebral ischemia. Muir and Ellis[36] also found that lidocaine infusion improved posttraumatic blood flow. Although the doses of lidocaine used in those studies are different from that of the present study, it is possible that the neuroprotective effect observed in the present study may be a result of an intraischemic blood flow improvement in the infarct and periinfarct areas. Because the cerebral blood flow was not measured in the present study, we do not know whether the neuroprotective effect of lidocaine is at a cellular level or by preserving the cerebral blood flow. It is necessary to clarify the effect of low-dose lidocaine on cerebral blood flow in this rat model of transient focal cerebral ischemia.

Isoflurane was used in this study. Isoflurane has been shown to have neuroprotective effects in a model of

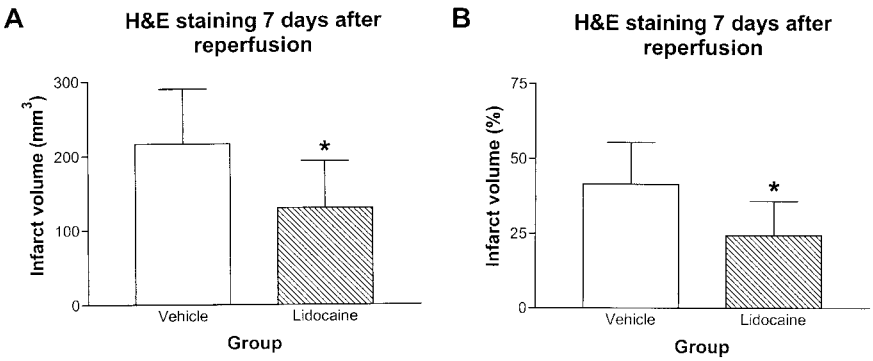

Fig. 4. Infarct size 7 days after reperfusion. (*A*) Infarct volume (cubic millimeters, mean ± SD). (*B*) Percentage of the contralateral hemisphere (mean ± SD). Infarct volumes were measured from hematoxylin and eosin (H&E)–stained sections. *$P < 0.01$ compared with the vehicle group.

focal cerebral ischemia in the rat similar to that used in the present study.[37] It has been reported that isoflurane can inhibit the release of glutamate,[38] reduce the frequency of NMDA receptor channel opening, the mean open time of the channel in response to stimulation of NMDA[39] and NMDA toxicity.[40] In addition, isoflurane may reduce the degree of ischemia, particularly in the ischemic penumbra, because of the effects of its metabolic suppression.[41] Although both control and experimental groups were subjected to the same concentration of isoflurane, it is possible that lidocaine may exert synergistic effects.

The neurologic scores at 30 min after recovery from anesthesia were similar in the vehicle and the lidocaine groups. The neurologic outcome improved in both the vehicle and the lidocaine groups over time. However, there was a better neurologic outcome in the lidocaine group after 7 days of reperfusion. It has been proposed that, initially, the neurologic deficits reflect injury to the core as well as the penumbra.[30] Thus, neurologic deficits do not necessarily reflect a structural lesion. The similar neurologic deficits at the early stage of reperfusion do not indicate that the size of the densely ischemic core was the same in vehicle and lidocaine groups. Because the size of the infarct in the densely ischemic core is not modified by pharmacologic interventions, we postulate that there may be a greater ischemic penumbra area and a smaller densely ischemic core in the lidocaine groups than in the vehicle groups or that a larger part of the ischemic penumbra in the lidocaine groups may be salvaged and not progress into infarction.

In conclusion, we have demonstrated that intravenous administration of a clinical antiarrhythmic dose of lidocaine starting 30 min before transient focal cerebral ischemia significantly reduces infarct size, improves neurologic outcome, and inhibits postischemic weight loss.

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