Intracerebral Hemorrhage in the Rat
Effects of Hematoma Aspiration

Mensura Altumbabic, MD; James Peeling, PhD; Marc R. Del Bigio, MD, PhD

Background and Purpose—Deep intracerebral hemorrhage is associated with considerable mortality and morbidity, but the value of surgical therapy is debatable. The purpose of this study was to evaluate whether aspiration of the hematoma in a rodent model of intracerebral hemorrhage could improve final neurological outcome.

Methods—Intracerebral hemorrhage was induced in 2 groups of rats by injection of bacterial collagenase into the caudate nucleus. In 1 group of rats, streptokinase was used to lyse the hematoma 4 hours after hemorrhage induction, and the clot was then aspirated. Behavioral function was evaluated repeatedly until the rats were killed 7 weeks after collagenase injection. Histology was used to assess neuronal loss, astroglial proliferation, and overall brain morphology. In a second experiment, brain water was measured at 24 hours.

Results—The treated rats performed significantly better than controls on a motor-behavior evaluation on days 1, 2, and 28 after aspiration. Skilled forelimb testing performed for 3 weeks after the global behavior evaluations showed a significant deficit of contralateral forelimb function in both groups, but there was no significant difference between the 2 groups. Neuronal loss in the perihematoma striatum was significantly greater in untreated compared with treated rats. In most rats, structural damage extended into the internal capsule and thalamus.

Conclusions—Aspiration of the hematoma after collagenase-induced hemorrhage slightly improved acute functional outcome and reduced neuronal loss from the striatum. Further studies are required to delineate the mechanism of the effect. (Stroke. 1998;29:1917-1923.)

Key Words: behavior, animal ● hematoma ● stroke, hemorrhagic ● rat ● surgery

Hemorrhagic stroke occurs when a blood vessel or vascular anomaly ruptures, releasing blood into the surrounding brain tissue. Spontaneous intracerebral hemorrhage (ICH) represents one of the most devastating types of stroke, occurring annually in 12 to 35 persons per 100 000 population, and accounting for 8% to 14% of all strokes. Most clinical cases are associated with hypertension, and the most common sites of ICH are striatum, cerebellum, and pons. The 30-day mortality rate is 43% to 51%, and most survivors are left with a neurological disability.

Current management of ICH includes control of systemic hypertension and treatment or prevention of raised intracranial pressure. While most agree that cerebellar and superficial lobar hematomas should be removed, there is controversy concerning the use of surgery for deep hematomas in the basal ganglia. Different forms of surgical management, for example, open craniotomy, stereotactic injection of thrombolytic agents to facilitate clot lysis and removal, or the use of endoscopy, have been described as treatments for ICH. A meta-analysis of randomized clinical studies in 1997 suggested that immediate surgical removal of hematomas might improve outcome in noncomatose patients <60 years of age with a hematoma volume of <50 mL. The authors emphasized that the problem needs to be studied in a randomized trial.

Materials and Methods
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All experimental procedures were done in accordance with the guidelines of the Canadian Council on Animal Care. Protocols were approved by the local experimental ethics committee. Sixty-six young adult male Sprague-Dawley rats weighing 175 to 250 g were used. Forty-four rats were underwent behavior testing followed by pathological exam 7 weeks after hemorrhage. Fourteen rats were killed 24 hours after ICH for brain-water determinations. Eight rats were used for assessment of streptokinase injection. For induction of
hemorrhage, each rat was anesthetized with pentobarbital (50 mg/kg IP) and placed in a stereotactic frame (David Kopf Instruments). Through a hole drilled in the skull, a 30-gauge needle was introduced into the caudate nucleus (3 mm lateral to midline, 0.02 mm anterior to coronal suture, depth 6 mm below the surface of the skull), and 1.4 μL of saline containing 0.3 U collagenase (Type IV, Sigma Chemical Co) was infused over 7 minutes. After the infusion, the needle was left in the place for 3 minutes and then removed. Physiological parameters were not monitored during the procedure. The bone hole was sealed with bone wax, the scalp wound was sutured, and the animal was placed in a box with free access to food and water. Every second rat with collagenase injection was selected for aspiration of the hematoma. Four hours after collagenase injection, the rat was reanesthetized with pentobarbital (50 mg/kg IP) and again placed in the stereotactic frame. Using the same stereotactic coordinates, streptokinase (3 μL; 1000 U/μL, Sigma) was injected by a 27-gauge needle into the hematoma center. One hour later, aspiration was accomplished by application of gentle suction with a syringe attached to a 25-gauge needle placed at the same stereotactic coordinates. Physiological parameters were not monitored in this experiment. The volume of aspirated blood was measured. Eight rats with ICH were matched with the same quantity of streptokinase in 1 side and an equal volume of saline in the contralateral striatum and were killed 1, 3, 7, or 11 days later for histological assessment.

Behavioral Testing
All testing was done by a single observer without knowledge of the treatment group. Motor behavior was evaluated using 4 tests in each rat 1, 3, 5, 7, 11, 14, 17, 21, and 28 days after collagenase injection. The specific tests included (1) observation of spontaneous ipsilateral circling, graded from 0 (no circling) to 3 (continuous circling); (2) contralateral hindlimb retraction, which measured the ability of the animal to replace the hindlimb after it was displaced laterally by 2 to 3 cm, graded from 0 (immediate replacement) to 3 (replacement after minutes or no replacement); (3) beam walking ability, graded from 0 for a rat that readily traverses a 2.4-cm-wide, 80-cm-long beam to 3 for a rat unable to stay on the beam for 10 seconds; and (4) bilateral forepaw grasp, which measures the ability to hold onto a 2-mm-diameter steel rod, graded from 0 for a rat with normal forepaw grasping behavior to 3 for a rat unable to grasp with the forepaws. The scores from all 4 tests, which were done over a period of about 15 minutes on each assessment day, were added to give a motor deficit score (maximum possible score, 12).

Skilled forelimb function was also tested using a staircase feeding apparatus. This required pretraining before induction of ICH. Rats had free access to food and water during first 2 days after arrival from the supplier. The rats were housed in pairs in standard plastic boxes with a 12-hour day/night cycle. During the following 7 days, the rats were fed 8 to 15 g/d of standard laboratory chow to reduce their body weight to 85% to 90% of the initial weight. Hunger was the incentive to perform in the testing apparatus. The staircase pretraining was performed twice per day, with a time interval of at least 4 hours between trials. The rat was placed in a clear plastic box with a food-baited staircase on either side. Each staircase had 7 steps, each with a well containing 3 45-mg pellets (P.J. Noyes Co Inc). The number of food pellets reached and eaten in 20 minutes was counted. When a plateau was reached, the top well was no longer baited with pellets, because these can be reached with the tongue. An additional 4 to 6 trials were used to calculate mean pretraining number of pellets eaten from each side. If the side-to-side difference was >4 on the final trials, the side on which rat collected more pellets was designated its “preferred” side. ICH was induced in the dominant brain hemisphere in rats with a preferred side. After pretraining, the rats were allowed free access to food for 2 days before surgery and during the 4 weeks after ICH. Beginning 28 days after ICH, the rats were fed 10 to 12 g/d standard laboratory chow to decrease the body weight to 90% of the free feeding level. They were then evaluated daily in the staircase apparatus for 3 weeks. The top well of the staircase apparatus was not baited. The number of food pellets eaten in 20 minutes on each side was counted (maximum possible 18 per side).

Histological Examination
Seven weeks after collagenase injection, each rat was reanesthetized and perfused through the heart with 300 mL cold 4% paraformaldehyde in 0.1 mol/L phosphate-buffered saline. The brain was removed and stored in the same fixative. Fixed brains were cut coronally through the needle entry site (identifiable on the brain surface), as well as 2 mm anterior and 2 mm posterior to that plane. Brain slices were dehydrated and embedded in paraffin. Sections (5 μm) were cut, and each 10th section from the rostral to the caudal portion of the residual hematoma cavity was stained with hematoxylin and eosin.

All sections were inspected macroscopically and microscopically to determine anatomical structures involved in the hematoma site. According to the part of striatum involved, hematomas were classified as being medial, lateral, or whole striatum location. Extension of the hematoma into the internal capsule was semiquantitatively graded: 0, no extension; 1, extension in anterior limb; and 2, extension into posterior limb. Extension of the hematoma into the thalamus was similarly graded: 0, no extension; 1, focal calcium deposition and cell loss; and 2, residual cavity.

A “camera lucida” was used to assess the overall brain morphology on the coronal slice with the maximum hematoma diameter. The ipsilateral cortical injection site lesion, hematoma cavity, residual striatum, and ventricle were traced onto a sheet of paper, as were the contralateral striatum and ventricle. Computerized planimetry was used to measure the traced areas. Side-to-side differences were compared. Striatal area loss was calculated as the percentage difference between contralateral and ipsilateral striatum.

Medium-size striatal neurons were quantified at the coronal level of the maximum hematoma diameter as previously described. With a square ocular graticule and ×250 ocular magnification (objective magnification ×20), neurons were counted in three fields (each area 400×400 μm) immediately adjacent to the hematoma site; areas with large blood vessels were avoided. Three anatomically comparable fields in the contralateral caudate nucleus were assessed in the same manner. The difference between the sums from each side was used as an index of relative neuronal depletion in striatal tissue adjacent to the hematoma.

GFAP immunohistochemical labeling was performed on sections at the coronal level of the maximum hematoma diameter. Sections were incubated with 20% goat serum for 30 minutes, then the primary polyclonal GFAP antibody was applied overnight (Dako, dilution 1:400). Secondary biotinylated goat anti-rabbit antibody (1:300) was applied for 1 hour, followed by streptavidin HRP and DAB. Areas with labeled astrocytes were compared between ipsilateral and contralateral side in the cortex and internal capsule and assigned a grade of 0 if the same, 1 if slightly greater, as 2 if much greater on the side of the hematoma. Reactive gliosis extension beside the residual cavity was measured with a calibrated ocular graticule.

Water Content
Fourteen rats were used for this experiment. Six rats had collagenase-induced hemorrhage, and 8 had collagenase-induced hemorrhage followed by aspiration as described above. Twenty-four hours after ICH, the motor-behavior tests were done, then each rat was killed by pentobarbital overdose. The brain was quickly removed and placed on a cooled surface, and the cerebellum and brain stem were removed. The cerebrum was divided into hemispheres, and each hemisphere was coronally cut into 3 parts; the first cut was through the needle entry site and the second through the midpoint of the posterior remnant. Each section was weighed, wrapped in preweighed aluminum foil, dried for 3 days in an oven at 110°C, and weighed again. Water content was calculated as the percentage change between wet weight and dry weight.

Data Analysis
All data are presented as mean±SEM. Data were analyzed using StatView version 4.1 (Abacus Concepts, Inc). Z-score histograms

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Results

Six rats were excluded before surgery because they refused to eat in the staircase apparatus during the pretraining period. No rats died immediately after surgery. Two rats were euthanized 4 to 5 weeks after ICH because of unexpected weight loss. Histological analysis showed large abscesses in the cortex and striatal region of each rat. One rat was excluded after histological analysis because the bacterial collagenase had been injected into the septal region. For final analysis, there were 18 control rats with naturally evolving hematomas and 17 treated rats with aspirated hematomas. The volume of aspirated blood ranged 20 to 100 μL. Streptokinase injection into the striatum of rats without ICH was associated with no inflammation, no neuronal changes, and minimal hemorrhage 1 to 11 days later. The changes were similar to those seen on the contralateral side that received injection of saline alone.

Motor deficit scores in the first 4 weeks after ICH are shown in the Figure. The scores were significantly better in the treated group on days 1, 2, and 28 ($P<0.03$; 1-tailed Student’s $t$ test).

were used to determine whether the data were distributed normally. For the skilled forelimb test, the mean posthematoma value was calculated for each week (5 trials) for each side separately. The means before and after hematoma were compared. Normally distributed data (behavior, areas of residual cavity, ventricle, striatum, cortical damage, neuronal count, and water content) were analyzed by Student’s $t$ test to compare the hematoma and aspiration groups. Correlation coefficient or regression analysis was used to assess the relationship between morphologic features and behavioral outcomes. The Kruskal-Wallis test was used to assess relationship between hematoma location or extension into internal capsule and the functional deficit.

Results

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Motor deficit scores in the first 4 weeks after ICH are shown in the Figure. The scores were significantly better in the treated group on days 1, 2, and 28 ($P<0.03$; 1-tailed Student’s $t$ test). Results of the skilled forelimb testing are shown in Table 1. The number of food pellets eaten reached a plateau in 5 trials during post-ICH testing. There were no differences in performance between the groups before ICH. The limb ipsilateral to the hematoma exhibited no loss in performance after ICH. There was a significant decline in function of the forelimb contralateral to the hematoma, but there was no difference between the treated and untreated rats.

In the treated rats, functional performance on day 1 was not dependent on the location of the hematoma within the striatum, hematoma extension into the thalamus, hematoma extension into the internal capsule (see below), or the volume of blood aspirated. However, the final skilled forelimb performance was dependent to some extent on the hematoma location within the striatum and extension of injury into the thalamus. Rats with medially placed hematomas had the least deficit (Table 2). By regression analysis, in the treated rats there were no significant relationships between the final skilled forelimb performance and the area of cortical damage, the size of the residual striatal cavity, or the volume of blood aspirated.

Localization of the hematomas and anatomical structures damaged by ICH is shown in Table 2. The anterior limb of the
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Table 3: Relative Size of Brain Structures and Damaged Areas

<table>
<thead>
<tr>
<th>Site</th>
<th>Untreated Controls</th>
<th>Treated Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma cavity</td>
<td>1.8±0.3</td>
<td>1.7±0.3</td>
</tr>
<tr>
<td>Cortical damage</td>
<td>0.9±0.1</td>
<td>1.5±0.2†</td>
</tr>
<tr>
<td>Striatum, ipsilateral</td>
<td>4.4±0.5</td>
<td>4.0±0.5</td>
</tr>
<tr>
<td>Ventricle, ipsilateral</td>
<td>4.6±0.6</td>
<td>3.1±0.4†</td>
</tr>
<tr>
<td>Striatum, contralateral</td>
<td>9.7±0.7</td>
<td>9.8±0.5</td>
</tr>
<tr>
<td>Ventricle, contralateral</td>
<td>1.9±0.2</td>
<td>1.3±0.2</td>
</tr>
</tbody>
</table>

* All sizes are reported in mm² (mean±SEM), as measured by planimetry on a single coronal histological section at the level of maximal hematoma diameter.
† P<0.05 vs untreated group (2-tailed t test).

Discussion

There is considerable controversy regarding the value of surgical therapy over conservative therapy for spontaneous intracerebral hemorrhage. Although many studies have been reported, most are considered inadequate to quantify reliably the risk and benefit of surgical treatment. Two recent independent reviews of the literature with meta-analysis assessment determined that there are only 4 randomized trials of surgical treatment worth considering. Both groups of authors concluded that there was insufficient information on the safety and efficacy of surgery and that more information was needed from a multicenter randomized trial to determine whether some patients with ICH would benefit from surgery.

Pilot experiments using magnetic resonance imaging before and after hematoma aspiration showed that the central contiguous portion of the hematoma could be removed (M.R. Del Bigio, unpublished data, 1997). Pilot experiments with 10 rats subjected to intrastriatal autologous blood injection of 40 to 100 μL showed that the resulting hematoma was very irregular, with extension along the white tracts; the histological changes adjacent to the hematoma, however, were almost identical to those seen in the collagenase model (H.J. Yan and M.R. Del Bigio, unpublished data, 1997). Because we believed that hematoma removal could be accomplished only in contiguous regions, we chose the collagenase model for this study. We wished to determine whether surgical aspiration of collagenase-induced hematoma could improve the final outcome in rats.

Intracerebral hemorrhage causes brain damage by multiple mechanisms. Direct tissue destruction by the hemorrhagic event and dissection of blood along tissue planes occurs immediately. Damaged cells and axons in the path are unlikely to be saved by any intervention. The space-occupying effect of the hematoma compromises local blood flow in the surrounding tissue. This has been shown by a variety of experimental methods after inflation of balloons or injection of autologous blood in the brain and in a small number of ICH patients by CT scanning combined with xenon inhalation. Our preliminary experiments in this model using magnetic resonance perfusion imaging also indicate that blood flow is reduced in an area much larger than the hematoma itself (J. Peeling and M.R. Del Bigio, unpublished data, 1997). These data suggest that ICH has a penumbral region similar to that adjacent to ischemic brain damage in which blood flow is reduced and neuronal function and survival are compromised. Important to note is the observation that deflation of a 50-μL balloon implanted into rat caudate nucleus was associated with recovery of cerebral blood flow. This may explain why we observed improved neuronal survival and reduced reactive gliosis in the striatum adjacent to hematomas that had been treated by aspiration.

In this experiment, we observed a significant treatment-related improvement in motor behavior during the first 2 days after ICH. Experiments with temporary space-occupying lesion created by balloon inflation in the caudate nucleus of rats indicate that there is a significant increase in intracerebral pressure. Intracerebral pressure in pigs with ICH is reduced after lysis of the clot using tissue plasminogen activator and aspiration. Thus, the improvement we wit-
nessed probably was related to relief of the space-occupying effect of hematoma, decreased intracranial pressure, and possibly increased local blood flow. Another postulated effect of ICH is the release of toxic agents, particularly thrombin, from the clotting blood.35,36 Aspiration of blood presumably would reduce the quantity of these agents in the brain. However, we know from our short-term experiments and the observation of residual hemosiderin that not all of the blood can be removed. Without precise information concerning the dose-response curve of these agents, it is impossible to know whether partial removal of the blood reduces their effect. A third consideration is a beneficial effect of the additional 1-hour period of anesthesia. For example, deep anesthesia induced by 5-hour thiopental infusion is associated with reduced acute infarct volume after transient middle cerebral artery occlusion in rats.37 However, this seems unlikely in the present experiment, because in our previous study rats that were anesthetized repeatedly with pentobarbital for the purposes of early sequential MR imaging showed no benefit.20

The acute motor improvement in this experiment did not appear to be due to reduction of brain edema, which develops in the first few hours and peaks at 24 to 48 hours.20 In contrast, Wagner and coworkers33 documented reduced peri-hematoma edema in the pig ICH model after tissue plasminogen activator—assisted evacuation. The edema associated with autologous blood injection into the brains of rats and pigs has a similar time course.29,33 Rosenberg and coworkers38–41 have successfully reduced brain water in rats with collagenase-induced hematomas using a variety of drugs, but outcomes were measured at 24 hours and behavior was not assessed in detail. Despite our documentation of acute motor improvements, reduced neuronal death in the striatum, and reduced striatal atrophy, surgically treated rats did not exhibit any late benefit with regard to skilled forelimb performance. This is likely a function of the brain structures that were acutely damaged by the hematoma. Most of the hematomas extended into the thalamus and internal capsule. These provide assessment of goal-directed movement abilities. For successful reaching and grasping in the staircase test, the corticospinal tract, the basal ganglia, and the ascending sensory pathway should be intact.19,42–44 Axonal damage in the internal capsule and thalamic injury would be expected to affect the outcome of this test, and it is very unlikely that axonal damage would be amenable to aspiration of blood from the striatum. We must consider the possibility that the cortical damage caused by repeated needle insertions was detrimental. It is also worth noting that hematomas involving either the lateral or entire striatum were associated with greater disability than those associated with only medial damage. This has been shown directly in other experiments in which lesions of the lateral striatum produced severe and chronic impairments of movement initiation, forelimb-reaching amplitude, and postural synergism but damage to the medial striatum produced mild or no impairment of forelimb reaching.45

We conclude that partial surgical aspiration of collagenase-induced intracerebral hematomas from rat brains improves the acute functional deficit slightly, probably through reduction of the space-occupying effect of the hematoma and consequent reduction of intracranial pressure. Acutely damaged axons do not benefit by surgical treatment. Late neuronal survival in the striatum surrounding the hematoma was also improved, possibly as a result of improved local cerebral blood flow or removal of potentially toxic blood breakdown products. It appears that intracerebral hematomas are associated with a penumbra similar to that surrounding ischemic brain tissue, in which selective neuronal loss can occur. Further investigations into the value of drug therapy to treat cerebral edema and neuronal ischemia combined with surgical treatment are warranted.

Acknowledgments

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References

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Editorial Comment

In the article published above, Altmubabic and colleagues induced deep intracerebral hemorrhage in rats by injection of bacterial collagenase. Every second rat was reanesthetized 4 hours later, streptokinase was injected, and the hematoma was aspirated. The groups were compared on “behavioral function,” histopathology, and brain edema. Hematoma aspiration resulted in a small improvement in “motor deficit score.” 1, 2, and 28 days after hemorrhage, which was determined by assessing a combination of 4 specific tests. On another test of skilled forelimb function, no differences could be detected between groups. Hematoma aspiration reduced neuronal loss and reactive gliosis but not edema. The authors argue that the additional anesthesia time in the clot removal group did not favorably affect outcome, but this remains a possible explanation for the improvements observed, particularly in the absence of measurements of vital signs, including brain temperature.

The experiment was done to address the clinical question of whether early hematoma evacuation improves functional outcome. The model used, however, does not produce clinical differences of the magnitude observed in humans. None of the rats died from the effects of intracerebral hemorrhage, unlike the clinical situation, in which up to 50% of patients with deep intracerebral hemorrhage die. A 10% to 15% improvement in motor deficit score was observed and was associated with a much more marked 70% reduction in neuronal loss. This highlights the difficulty of using tests of function in rats. Investigators have relied almost exclusively on histopathological endpoints in the study of experimental cerebral ischemia. A 70% reduction in infarct size, if approximately equal to the 70% increase in neuronal survival noted in approximately equal to the 70% increase in neuronal survival noted in humans, would be a marked effect.

The pathogenesis of neurological deficit and death is certainly multifactorial and includes direct effects of the hematoma causing direct destruction of brain tissue, destruction by mass effect and brain shift, ischemia, toxic effects of substances released from the blood clot, and secondary induction of edema, brain swelling, increased local pressure, and diffuse intracranial pressure. Broderick et al1 reported
that continued bleeding or rebleeding also may be a common cause of deterioration and morbidity and mortality. The rat model reproduces some of these features. It stands to reason that removing the clot early would prevent or decrease damage due to some of these mechanisms and therefore have the potential to improve outcome. The conclusions that are usually drawn from the prior clinical trials and other pertinent literature are as follows.2–6 Cerebellar and cerebral lobar hemorrhages should be removed surgically unless the patient is too well to need surgery or does not need surgery to make a diagnosis or remove the lesion that caused the hemorrhage, or if the chances of functional outcome are nonexistent. The following applies to hemorrhage in the pons, thalamus, and putamen, which are the most common sites for hypertensive hemorrhage and in general to patients with Glasgow Coma Scale scores between 7 and 12 or so who are not either very well or very ill. For patients such as this, with pontine and thalamic hemorrhage, surgery performed with some delay of hours after the ictus may increase the survival rate, but those who do survive are usually severely disabled. The questions to be answered, which apply more to thalamic than pontine hemorrhage, are whether removing the hematoma with less disruption of the brain, such as by a stereotactic method, or doing so sooner after the hemorrhage, will improve outcome. For putaminal hemorrhage, surgery decreases mortality but most of the survivors are disabled. There is more enthusiasm for studying whether earlier or less “invasive” hematoma evacuation will improve outcome.

Animal models are important for investigating the pathogenesis of intracerebral hematoma and the effect of neuroprotective strategies, but the call for a clinical trial has been made so many times that the decision does not rest on results of more experimental data. Experimental studies are unlikely to be able to answer the question of effect on functional outcome. Answers to clinical questions such as this one, in which randomization is difficult, have been sought by prospectively collecting large numbers of patients.

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