

Comparison of Different Preclinical Models of Intracerebral Hemorrhage

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Abstract Intracerebral hemorrhage (ICH) is the most devastating type of stroke. It is characterized by spontaneous bleeding in brain parenchyma and is associated with a high rate of morbidity and mortality. Presently, there is neither an effective therapy to increase survival after intracerebral hemorrhage nor a treatment to improve the quality of life for survivors. A reproducible animal model of spontaneous ICH mimicking the development of acute and delayed brain injury after ICH is an invaluable tool for improving our understanding of the underlying mechanisms of ICH-induced brain injury and evaluating potential therapeutic interventions. A number of models have been developed. While different species have been studied, rodents have become the most popular and widely utilized animals used in ICH research. The most often used methods for experimental induction of ICH are injection of bacterial collagenase and direct injection of blood into the brain parenchyma. The “balloon” method has also been used to mimic ICH for study. In this summary, we intend to provide a comparative overview of the technical methods, aspects, and pathologic findings of these types of ICH models. We will also focus on the similarities and differences among these rodent models, achievements in technical aspects of the ICH model, and discuss important aspects in selecting relevant models for study.

Keywords Animal model · ICH · Intracerebral hemorrhage · Stroke · Rat · Mouse · Rodent

Introduction

Intracerebral hemorrhage (ICH) is a devastating disease accounting for approximately 5–15% of all types of stroke. In the United States, as many as 50,000 individuals are affected annually with a large number of those individuals facing chronic morbidities and early mortalities. ICH is more than twice as common as subarachnoid hemorrhage (SAH); it results in more disability and death than SAH or ischemic stroke [1]. Currently, there is neither an effective therapy to increase survival after intracerebral hemorrhage nor a treatment to improve the quality of life for survivors [2]. For improvement of existing therapies and development of new ones, an animal model that mimics the clinical situation and effects of intracerebral hemorrhage as closely as possible is absolutely essential.

The effects of intracerebral hemorrhage upon brain tissue are biphasic. Initial injury occurs in response to the expanding hematoma imposing shear force and mass effect upon the cerebral tissues [3]. Intracerebral bleeding leads to increased intracranial pressure, which could lead to transtentorial herniation secondary to the resulting mass effect [4]. A later phase involves multiple “toxic” factors present in activated blood components [5], infiltration of the brain by systemic immunocells [6], activation of microglia [7], and hematoma-induced apoptotic death of neuronal and glial cells in the surrounding parenchymal rim [8] followed by progressive rupture of the blood-brain barrier and rising brain edema [9].

In creating a model, it should be kept in mind that although in most patients’ bleeding stops soon after ictus, secondary bleeding is often observed. Fuji et al. reported that hematoma extension happens in 14% of patients in the first 24 h after ICH [10]. Similarly, Kazui et al. observed hematoma enlargement in 17% of patients during the first 6 h and in 22% of patients during first 24 h after ICH onset [11]. In this review, we will describe the most common models of ICH. Because rodents are the most used experimental animals in ICH models, we will concentrate on technique details of ICH induction in those species and compare the technical and pathological advantages and short-term outcomes of the existing models.

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Single Blood Injection

The most straightforward method for the introduction of blood and hematoma formation in the brain is singular injection. In rodents, blood injection was first used by Ropper et al. in 1982 [12]. The authors used Sprague-Dawley rats as experimental subjects. They permanently implanted a 27-gauge needle in the right basal ganglia, allowed the animals to awake, and infused 0.24–0.28 ml of whole or centrifuged blood from another rat, without anesthesia, over 1 s. In the control animals, they inserted plastic polymer. Two out of their eight subjects died. The authors reported early and delayed hyperperfusion of one or both cortical regions of brain. Comparison between ICH and control animals demonstrated that the subsequent effects were caused by blood and not by mass effect. One clear advantage of this model is that it does not require use of anesthetized animals. There are several shortcomings in this model. By using donor blood, there is always a risk of inflammatory reaction not typically seen in the clinical setting. Also, blood infusion was done not under arterial blood pressure. It does not mimic the clinical situation seen in humans.

To overcome this disadvantage, Bullock et al. presented another model of ICH 2 years later. They stereotactically inserted a needle filled with non-heparinized blood and connected it via a catheter to the femoral artery. As soon as the needle was inserted, the catheter was opened, and blood flowed until arrested spontaneously. A disadvantage of this model is that it is not well reproducible. Blood pressure variations from animal to animal were considered to have resulted in the observed variation in injury volumes. The authors reported a variation in hemorrhage sizes ranging between 6% and 43%.

Nath and coauthors tried to improve the model to make it more reproducible by producing hemorrhage via the pumping of a predetermined amount of whole blood [13]. They withdrew arterial blood and placed this blood into a 25- μ L tube, which they connected to a no. 25 needle. The infusion system was filled prior to needle placement. They used a constant pressure reservoir set to 100 mmHg. Blood was injected over approximately 10 s. To avoid blood clotting, the injection was performed within 2.5 min after withdrawal. The authors injected 25, 50, or 100 μ L of blood, and did not observe any relationship between the volume of hemorrhage and the degree of resultant hematoma.

A similar technique was presented by Yang et al. in 1994 [14]. However, this group instead used a constant pressure reservoir and micropump. They withdrew autologous blood from the femoral artery into a syringe of 1 mL, mounted it immediately to an infusion pump, and then infused 100 μ L of blood. They then placed the glue around the hole and quickly removed the needle. The needle was introduced vertically. (One modification of this technique is the introduction of the

needle at an angle of 20° to help avoid disruption of blood in the vertical space [15]). Although Yang and coauthors injected a predetermined amount of blood, this model failed to reproduce the dynamic interplay between systemic arterial pressure and brain tissue resistance [14].

In general, all models produced one solid hematoma noted to occur in up to 50% of patients in a clinical setting, as well as mimic the mass effect of a hematoma and reproduce the toxic effects of blood elements, but these characteristics are not well reproducible. The success rate in lesion production is low, and ruptures in the ventricular and subdural spaces have been noted. Bullock discussed 70.8% success after they operated on 24 animals and observed rupture into the ventricular space in 4 and into the subdural space in 3 [16]. Nath et al. indicated that the hematomas produced varied in size and shape, and often in addition to the intracerebral clot there was some surface collection [13]. Yang did not mention success rates in his publication [14]. Masuda failed to produce hematomas in 7% and mentioned that in most cases some extension into the ventricular system was observed [17].

To overcome these disadvantages, two other models were developed: the microballoon and multiple blood injection models. To improve upon the blood injection model, Deinsberger presented the double injection model in 1996 [18]. They figured out that the most adequate total hematoma volume is 50 μ L and separated the blood into two parts. First they injected 15 μ L of blood and waited 7 min for the building of the blood clot along the needle. Then they injected the major volume of blood: 35 μ L. The model was successful. This technique led to hematomas consisting of a clot in the caudate nucleus linked to a thin elongated clot in the white matter by a small clot along the needle track. Only one animal out of 13 had an extension of hematoma into the subdural space.

This technique is widely used and was adapted to mice, too. Belayev et al. in 2003 used mice, which is more challenging because of the smaller sizes [3]. The authors used a 30-gauge stainless steel cannula. Each mouse received a 5- μ L injection of either whole blood or CSF over 3 min, followed 7 min later by 10 μ L injected over 5 min with a micro-infusion pump. Sham animals received just needle trauma. Blood was taken from the heart of a donor mouse, which was flushed with heparin before blood withdrawal. The injection cannula was slowly withdrawn 10 min after the second injection, and the wound was sutured. The authors evaluated the neurological deficit 60 min after blood injection and determined that the animals after blood, but not after CSF and only needle trauma developed significant neurological deficits. Histological examination of the brain after 48-h survival revealed the presence of a localized hematoma in all animals with blood infusion. The measured hematoma volume in the blood injection group was highly reproducible. In contrast, the CSF and cannula groups showed only a small

non-hemorrhagic lesion. Residual swelling of the ipsilateral hemisphere at 48 h was 5.7% in hematoma mice and 1.5% in the CSF group.

Further improvement of the model was done by Ma et al. in 2006 [20]. They developed a triple injection model. The blood was rapidly taken from the orbital veins (not from the heart as Belayev did [19]) of a donor mouse using a glass capillary. During the ICH process, the injection was paused for 7 min after the first 5 μ l (to generate a clotting along the needle track), then paused for 1 min after the second 5 μ l (important to reinforce the clotting), and the remaining 20 μ l was injected in the following 4 min. Sham animals were subjected to the same manipulations as the ICH mice, but no blood was injected.

Microballoon-Induced Formation of ICH

Microballoon insertion was developed by Sinar and coauthors in 1987 as a way to study the mass effects of ICH [21]. A microballoon was mounted on a no. 25 blunted needle and inserted stereotactically into the right caudate nucleus. The burr hole was then sealed with dental cement. After a 30-min stabilization period, the balloon was inflated to 50 μ l over a period of 20 s with radiopaque contrast medium. In the sham-treated control group, the balloon was inserted but not inflated. Brain edema formation was successfully produced, much as occurs in the presence of any intracerebral mass, but the potentially significant effects of the presence of blood and clot in ICH cannot be addressed by this method.

Microballoon insertion alone can only demonstrate the mass effects of an introduced volume. This model does not reproduce such factors as the toxicity of blood elements and blood brain barrier disruption. While one can use this model for evaluation of the potential benefits of surgical hematoma evacuation, even in this kind of experiment there is a limitation. This model does not mimic the surgical brain injury caused by hematoma evacuation.

Collagenase Injection

Hematoma expansion and vasogenic edema following ICH has been considered to result from elevated local concentrations of collagenase released from injured cells [1] following tissue injury [10, 11]. From this concept, models for study of spontaneous ICH were developed using collagenase. Rosenberg et al. used microinfusion pumps to deliver 2- μ l volumes of 0.01–0.1 units of bacterial collagenase into the left caudate nucleus over a 9-min period [22]. Initial bleeding could be seen as early as 10 min after collagenase injection.

Different authors observed the expansion of hematoma at 1 and 4 h [22, 23]. However, in 1995 Brown et al. noted the presence of fresh blood much later as well [24].

Choudri performed collagenase injection in mice via 4-min infusion of bacterial collagenase into the right basal ganglia [25]. Clark performed a 2-min, 0.5- μ l injection into the right caudate and globus pallidus of mouse subjects, with a 3-min pause after the injection to minimize pathway reflux [26]. Later studies have shown similar adjustments in injection parameters [7], often raising the needle-withdrawal delay and the infusion course. Such adjustments to procedural parameters may improve the accuracy and precision of this model. In addition to the achievement of greater injury from the generation of a spontaneous ICH in this model, a key point is that the histological changes observed in the brain after collagenase injection have been consistent with the changes noted in human brain tissue after ICH [27]. The model does not involve the handling of blood products and the associated technical complications. This model allowed for successful evaluation of intracerebral hemorrhage, edema formation, and histological changes resulting from the spontaneous hemorrhages that followed infusion [22]. This model mimics spontaneous ICH.

However, studies have used collagenase levels significantly greater than the levels of endogenous collagenase in clinical ICH, which may not allow this model to faithfully emulate the pathologic alterations involved in ICH in the clinical setting. The disadvantages of this model are related to bacterial collagenase's ability to introduce a significant inflammatory reaction. Moreover, in opposition to the ICH in patients where the solid hematoma is a result of bleeding from the arterial source in brain tissue, bleeding in the collagenase model is diffuse and results from rupture of small blood vessels around the site of collagenase injection.

Comparison of the Collagenase and Blood Models

Hematoma Size

Direct comparison of the collagenase and blood injection models was performed by MacLellan and coauthors [23]. The authors used the previously described model of blood injection used in rats [16]. They took 100 μ l of blood from the tail (it was not clearly established whether the blood was venous or arterial). They then injected the withdrawn blood over 10 min into the striatum through a small burr hole made 3.5 mm to the right of and at the anteroposterior level of the bregma to a depth of 6.0 mm. The authors then used the same coordinates to administer an injection of 0.2 U of

bacterial collagenase in 1.0 μl sterile saline (as described [28]). They performed a hemoglobin assay to compare the hematomas produced by injection of collagenase with that produced following direct injection of 100 μl of blood directly into the striatum. One hour after the operation, the hematomas of both models were comparable (approximately 65 μl in the blood infusion model versus 50 μl in the collagenase model). The hematoma in the blood injection model remained stable during the first 4 h. Well in agreement with a previous publication [24], MacLellan observed a significant increase in hematoma size within this time period in the collagenase model.

Hematoma size and lesion volume were evaluated at later time points using magnetic resonance imaging (MRI). From the imaging the authors [23] concluded that, despite similar initial hematoma volumes measured by using hemoglobin assay at 4 h, the injury observed between 4 and 6 weeks was greater in the collagenase model. The authors explained that as opposed to the blood model (in which the blood remains pooled), blood in the collagenase model diffuses from the hemorrhage site into the parenchyma. They also conclude that the hematoma observed in the blood model resolved more quickly in comparison with that seen in the collagenase model.

Functional Outcome

Functional outcomes were evaluated using a neurological deficit scale as described previously [29]. They established a baseline by testing the animals prior to ICH and continued evaluation through 28 days after induction of ICH. While on day 1 the hematoma volumes in both models were comparable, neurological evaluation revealed significant aggravation of the neurological deficits in the collagenase versus blood injection subjects. Complete recovery was observed in the blood infusion model at day 21. From this time point onward, no recovery was noted to occur in the collagenase model.

Takamatsu et al. noted the lack of spontaneous recovery in the collagenase model of ICH [30]. Takamatsu evaluated neurological motor deficits using four tests from days 1 after ICH induction. In contrast to MacLellan's group who tested for 28 days, Takamatsu performed neurological testing up to a maximum of 15 days, and did not observe improvement of neurological deficits between days 10 and 15, which leads to the conclusion that there is no spontaneous recovery in that model [30]. Kim et al. performed testing for 35 days after collagenase injection and reported about the lack of spontaneous recovery even up to day 35 [31]. Beray-Berthet et al. extended the time of observation after collagenase-induced ICH up to 56 days. They used five different neurological

tests and reported that they revealed long-term deficits at up to 2 months following ICH [32].

In contrast, Karki et al. induced ICH by infusion of 100 μl of nonheparinized autologous whole blood into the right striatum adjacent to the SVZ (exact coordinates undisclosed). Karki assessed the functional outcome using the neurological severity score between day 1 and day 28, and found partial recovery [33]. Similar results were observed using the "corner test" (common for evaluation of neurological deficits, by measuring the number of times an animal turns to the right or left after placement in a corner). Grasso et al. injected 100 μl of autologous whole blood under stereotactic guidance into the right basal ganglia, and evaluated for neurological deficits using a neurologic symptom score and the "corner test" at days 1, 7 and 14. The authors did not observe spontaneous recovery in neurological scoring and noted only slight recovery in the corner test [34]. Yang et al. injected 100 μl of nonheparinized autologous blood stereotactically and evaluated for neurological deficits at days 1, 4, 7, and 14 using the neurological severity score and corner test. They demonstrated a time-dependent resolution of the neurological deficit. Even if on the last day of observation deficits were still present, this time-dependent resolution suggests that complete spontaneous recovery is possible [14]. Similar results were presented by Seyfried et al., who injected 100 μl of blood stereotactically and evaluated for neurological deficits through severity scoring and corner test at days 1, 7, and 14. The authors observed a clear time-dependent resolution of neurological deficits in both tests [35].

It appears that the injection of collagenase causes severe injury with persistent neurological deficits without spontaneous recovery, similar to that observed in the clinical setting. Because spontaneous recovery in this model is possible, the value of the blood injection model for long-term study may be limited. MacLellan et al. [20] pointed out that because of the described differences between the models, it is valuable to utilize both models in testing for the potential beneficial effects of therapeutics.

Blood-Brain Barrier

MacLellan et al. also evaluated time-dependent development of blood-brain-barrier disruption by using MRI in both induction models. They reported that at all tested time points (12 h, 2 and 4 days), disruption of the blood-brain barrier caused by collagenase injection was significantly higher in comparison with the blood model. The authors observed a time-dependent increase in blood-brain barrier permeability in the collagenase model, but not in the blood model of induction [23].

Knight et al. observed only small increases in blood-brain barrier permeability in the surrounding rim of the hematoma 1 day after injection of 100 μ l autologous blood. This parameter remained slightly elevated through day 14, where the authors observed decreases in permeability at the rim area [36]. In the collagenase model, Rosenberg et al. investigated the blood-brain barrier disruption via another method, measurement of [14C]-sucrose uptake in the brain from the blood. The blood-brain barrier in the collagenase model was noted to be open 30 min after ICH induction. [14C]-Sucrose uptake in the brain tissue was noted to stay significantly elevated for 7 days [37]. Taken together, it seems that the damage caused by ICH induction via blood injection is moderate when compared with the outcomes from collagenase injection.

Cell Death

Because infiltration of brain parenchyma with immunologic cells such as neutrophils is considered to be a significant mechanism leading to cell death [7], there was a study directly comparing brain injury in the collagenase and blood models of ICH [38]. The authors compared the inflammatory reactions and cell death following collagenase versus blood injection in the brains of rats. The authors first collected mixed (arterial and venous) blood by cutting the tip of the tail, then injected that blood or 0.4 U of collagenase following coordinates similar to those used by MacLellan [33] (3 mm lateral to the midline, 0.02 mm anterior to the coronal suture, 5.5 mm below the surface of the skull). The authors reported that neutrophil infiltration of the striatal or cortical tissue around the hematoma was observed at 1 day in both models. However, only in the collagenase model was there a significant difference at this time point compared with the other observed time point. The neutrophils were almost completely diminished in number at day 3 in the blood model and still present in the collagenase model.

Similar temporal patterns of neutrophil infiltration have been observed by other authors. Pelling et al. observed significant neutrophil infiltration at day 2 after collagenase-induced ICH [9]. Wang observed neutrophil infiltration at day 1 and 3 in the same model [39]. MacLellan et al. reported significant neutrophil infiltration at day 4 after collagenase injection [40]. In the blood model Gong et al. also observed peak neutrophil infiltration on day 1. While neutrophils were still present at day 3, at later time points (at day 7 and 10), the authors observed a marked decrease in the number of neutrophils present [41].

Xue et al. [38]. investigated the number of dying neurons (identified by cytoplasmic pyknosis or eosinophilia) in both models. They reported that the number of dying neurons in

the penumbra peaked at day 2 in both models. But the measured differences between day 2 and the other evaluated time points (1 and 4 h; 1, 2, 3, 7, and 21 days) were significant only in the collagenase model. Dying neurons were observed through day 7 in the blood model and through day 21 in the collagenase model.

Conclusion

In conclusion we can say that the blood injection and collagenase models are technically similar. They are easy to perform and are reproducible; the size of hematoma in these two models is well controllable. The location of hematoma formation is easier to control in the collagenase model. Since in the blood model the amount of liquid injected into the brain is significantly higher, there is always a risk of blood disruption in the subarachnoid and ventricular spaces. The collagenase model mimics the time-dependent extension of the hematoma, which has been observed in a relatively small portion of patients. Damage caused by comparable initial hematoma was significantly higher in the collagenase model subjects. Damage resulted in extension of the hematoma over time, with greater tissue and neuron loss, greater BBB disruption, and lack of spontaneous neurological recovery in animals after collagenase compared to blood injection.

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Conflict of interest statement We declare that we have no conflict of interest.

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