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Research Article

Platform for preclinical screening of neuroprotective strategies: a clinically relevant ICH model and standardized functional test battery

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Abstract

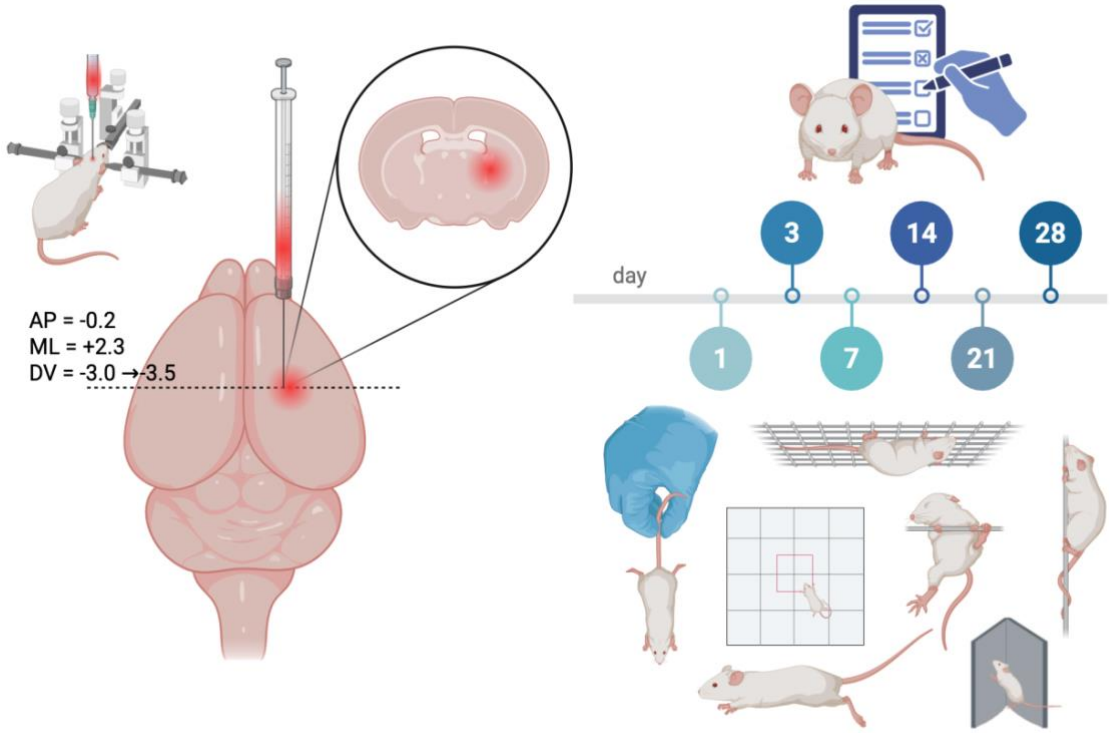
Introduction: Intracerebral hemorrhage (ICH) is among the most severe forms of stroke. Whereas traditional hemorrhagic stroke models reproduce hemorrhage within the striatum (specifically the putamen), localization of the hematoma with involvement of the internal capsule and globus pallidus may better recapitulate clinically relevant sensorimotor deficits due to more extensive basal ganglia involvement and damage to dense clusters of white matter tracts.

Materials and Methods: Male CD1 mice (3–4 months, 30–35 g) were assigned to intact control (n=15) or ICH (n=15) groups. ICH was induced by stereotaxic injection of 30 μL autologous blood into the right cerebral hemisphere (2.3 mm lateral, 0.2 mm caudal to bregma, depths 3.0 and 3.5 mm). Neurological status was assessed using the modified Garcia scale, limb placement tests, horizontal and vertical pole tests, inverted grid test, corner test, and open field test at baseline and on days 1, 3, 7, 14, 21, and 28.

Results and Discussion: The model showed high reproducibility with 33–40% acute mortality. All ICH mice developed contralateral sensorimotor-pyramidal deficits with predominant forelimb involvement. Garcia scores declined from 21 to 14.83±1.72 on day 1 with gradual but incomplete recovery by day 28 (18 [18;18.5]). Forelimb placement showed >50% acute deficit with a nonlinear recovery pattern, whereas hindlimb deficits appeared later (days 3–7) and persisted to day 21. The modified Garcia scale, forelimb placement, modified horizontal bar, and open field tests were most sensitive to functional impairment and recovery.

Conclusion: Stereotaxic autologous blood injection into the basal ganglia (putamen and globus pallidus) with involvement of the internal capsule in mice reproduces clinically relevant, reproducible sensorimotor deficits with persistent functional impairment, making this model suitable for preclinical testing of neuroprotective strategies.

Graphical Abstract



Keywords

hemorrhagic stroke, internal capsule, ICH model, mice, Garcia scale, behavioral assessment, sensorimotor deficit

Introduction

Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes, but is associated with higher mortality and disability rates when compared to other cerebrovascular diseases (Nesterova et al. 2019). Despite advances in understanding the pathophysiology of ICH, to date, none of the proposed neuroprotective treatment strategies have proven effective in clinical practice, highlighting the critical need for improved preclinical research models (Matsushita et al. 2013).

Current experimental models of ICH predominantly reproduce striatal hemorrhage (specifically the putamen) either by autologous blood injection or collagenase administration (Krafft et al. 2012). Although these models demonstrate reproducible hematoma formation and acute neurological deficits, they do not fully reflect the clinical presentation of striatocapsular hemorrhage (with involvement of the internal capsule and globus pallidus), which is quite common in humans (Chung et al. 2000). The internal capsule, particularly its posterior limb, contains dense accumulations of corticospinal and thalamocortical white matter tracts that play a critical role in integrating cortical sensory and voluntary movement centers with subcortical structures (thalamus, cranial nerve nuclei, and spinal cord). Hemorrhage involving this area causes characteristic contralateral hemiparesis and sensory impairment (Gupta et al. 2024).

Unfortunately, only a few studies have focused on damage to axonal tracts such as the internal capsule, likely because the rodent brain contains substantially less white matter than the human brain. Nevertheless, several independent studies support the rationale for targeting the internal capsule as a site for experimental ICH modeling. Clinical studies demonstrate that internal capsule involvement correlates with worse functional outcomes and higher mortality in basal ganglia hemorrhages (Gupta et al. 2024). Experimental data confirm that hemorrhage extending into the internal capsule in mice leads to high mortality and poor sensorimotor outcomes compared to purely striatal lesions (Matsushita et al. 2013). Moreover, internal capsule lesions

cause long-term axonal damage and persistent functional deficits, whereas striatal hemorrhage demonstrates more rapid spontaneous recovery (Liu et al. 2018).

The selection of adequate behavioral assessment methods is equally critical for model validation. The modified Garcia scale has been widely validated for rodent stroke models, demonstrating sensitivity to sensorimotor deficits and recovery dynamics (Bachour et al. 2016, Matsumura et al. 2019). Additional tests evaluating specific functional domains – including limb placement (sensorimotor integration), beam walking (coordination), corner test (spatial neglect), and open field (locomotor activity) – provide comprehensive characterization of post-stroke behavioral changes (Ruan and Yao 2020).

The aim of this study was to validate a relevant hemorrhagic stroke model in mice with blood injection into the striatocapsular region and to standardize a behavioral test battery for comprehensive evaluation of neurological deficit dynamics, thereby establishing a reliable platform for future preclinical evaluation of neuroprotective interventions.

Materials and Methods

Experimental animals

The study used 3-4-month-old male CD1 mice weighing 30-35 g. Animals were housed under standard conditions with a 12:12 hour light-dark cycle and free access to food and water. The study was approved by the Institutional Animal Care and Use Committee of Belgorod State National Research University (expert opinion No. 01-01i/25 dated January 9, 2025) and was conducted in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes.

Experimental groups

Animals were randomized into two groups (15 animals per group):

1. Intact control group (no surgical intervention),
2. ICH group.

ICH modeling

ICH was modeled using stereotaxic injection of autologous blood into the right cerebral hemisphere. Animals were anesthetized with Zoletil 100 (Virbac, France) 30 mg/kg + Xylazine (Biogel, Belarus) 12 mg/kg intraperitoneally. Blood (30-40 μL) was collected from the retroorbital venous plexus immediately before stereotaxic surgery.

After anesthetization, mice were fixed in a stereotaxic frame. Following a midline scalp incision and creation of a burr hole (1 mm diameter) in the right parietal bone (coordinates: 2.3 mm lateral, 0.2 mm caudal to bregma), a 30G needle was advanced stereotaxically to a depth of 3.0 mm below the dura mater. At this position, 5 μL of autologous blood was injected at a rate of 2 μL/min (Krafft et al. 2012). The needle was then advanced to a final depth of 3.5 mm, and after a 5-minute waiting period, 25 μL of blood was injected into the striatocapsular region (Paxinos and Franklin 2012). The needle was left in place for 10 minutes after injection to prevent blood reflux, then slowly withdrawn at 1 mm/min (Krafft et al. 2012). The burr hole was sealed with bone wax; the wound was sutured, and animals recovered on a heated pad (40°C) until fully conscious.

Functional tests

All animals underwent comprehensive neurological function testing at baseline (pre-surgery) and on days 1, 3, 7, 14, 21, and 28 after ICH.

Modified Garcia scale

Neurological deficit was assessed using the modified Garcia scale for mice (Matsumura et al. 2019), including seven independent subtests: spontaneous activity (0-3 points), axial sensation (1-3 points), vibrissae proprioception (1-3 points), limb movement symmetry (0-3 points), lateral turning (0-3 points), forelimb walking (0-3 points), and climbing (1-3 points). Total score ranged from 3 (maximal deficit) to 21 (no deficit).

Forelimb placement test

Forelimb placement was assessed as follows: the animal was held by the torso parallel to the table surface and slowly moved up and down, allowing the vibrissae on the left side of the head to contact the table. The number of reflexive placements of the impaired (left) forelimb was recorded from 10 consecutive trials.

Hindlimb placement test

Mice were positioned so that hindlimbs extended beyond the table edge. The contralateral hindlimb was gently pulled downward, and the speed/ability to return the limb to the table edge was scored: 0 (immediate return), 1 (delayed return), or 2 (inability to return).

Corner test

Sensorimotor asymmetry and spatial neglect were evaluated using the corner test (Ruan and Yao 2020). Mice were placed between two cardboard plates forming a 30° angle. Upon entering the corner, vibrissae stimulation prompted the mouse to turn and exit. The turning direction (left or right) was recorded for 10 trials. The laterality index (LI) was calculated: LI = (right turns – left turns)/10.

Modified horizontal bar test

Motor coordination and lateralized deficits were assessed using the modified horizontal bar holding test. Mice were placed perpendicular to a horizontal bar (15 mm diameter, 50 cm height) for three 30-second trials. Behavior was scored: 1 point (hangs underneath, falls within 1-10 sec), 2 points (hangs 11-20 sec), 3 points (hangs 21-30 sec), 4 points (hangs 30 sec with both left limbs hanging), 5 points (hangs with one left limb hanging), 6 points (cannot sit on bar from above), 7 points (sits with both left limbs hanging), 8 points (sits with one left limb hanging or asymmetric movement), 9 points (moves freely with symmetric four-limb support). The final score for each mouse was calculated as the mean of the three trials.

Open field test

Locomotor activity and exploratory behavior were evaluated in an open field apparatus (50×50 cm, 50 cm height) for 5 minutes (Ruan and Yao 2020). Software automatically determined: total distance traveled (cm), average speed (cm/s), number of center entries, time in central zone (sec), and activity percentage.

Inverted grid test

Muscle strength and coordination were assessed using the inverted grid test (Balkaya et al. 2013). Mice were placed on a metal grid (50×50 cm, mesh size 1 cm^2), which was then inverted 180° at 50 cm height above soft bedding. Fall latency was recorded (maximum 60 seconds) in three consecutive trials with 10-minute rest intervals. The average latency was calculated.

Vertical pole test

Fine motor coordination was assessed using a vertical pole (50 cm height, 1 cm diameter). Mice were placed head-up at the top of the pole and the ability to turn 180° and descend was evaluated. The protocol included three consecutive days: two training sessions and a test day. Three trials per animal were performed each day. On test day, two parameters were recorded and analyzed for each trial: time to initiate descent (interval from animal placement at top to head-down turn), descent time after turning, and total descent time.

Statistical analysis

Data normality was assessed using the Shapiro-Wilk test, and variance homogeneity using Levene's test. Normally distributed data are presented as mean ± SD, non-normally distributed data as median [Q1; Q3]. For intergroup comparisons, Student's t-test or Mann-Whitney U-test were used as appropriate. For intragroup comparisons at different time points, paired t-test or Wilcoxon signed-rank test were applied. Statistical significance was set at $p<0.05$. All analyses were performed using IBM SPSS Statistics 26.

Results

Mortality and model reproducibility

The employed experimental ICH model induced severe acute injury with early mortality of 33.3% (5/15 animals) within 24 hours after hemorrhage, reaching 40% (6/15) by day 1. Kaplan-Meier survival analysis demonstrated stable survival from day 1 to day 28 without additional deaths during the observation period (Fig. 1). No mortality occurred in the intact control group.

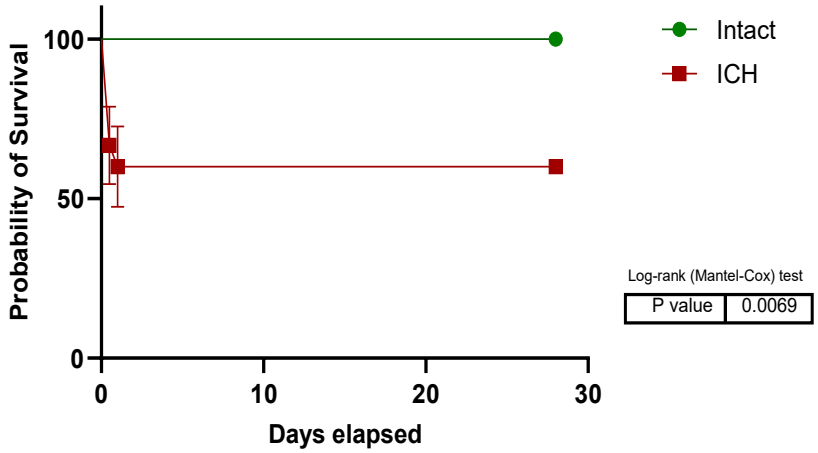


Figure 1. Kaplan–Meier survival curves illustrating early mortality and long-term survival in mice with internal capsule intracerebral hemorrhage compared with intact controls (0–28 days post-hemorrhage). ***Note:*** ICH – intracerebral hemorrhage group.

Acute neurological deficit assessment

All mice demonstrated baseline Garcia scale scores of 21 [21;21] before ICH induction, confirming normal neurological function. Striatocapsular hemorrhage caused development of pathological neurological symptoms. On day 1 after ICH, Garcia scale scores dramatically decreased to 14.83±1.72 ($p<0.001$ vs intact group). Neurological deficit was characterized by contralateral sensorimotor-pyramidal syndrome with predominant forelimb involvement. Specific impairments included: asymmetric limb movement with left-sided paresis, reduced spontaneous activity, impaired climbing ability, and decreased vibrissae sensitivity. The severity and pattern of neurological deficit were highly reproducible among animals, confirming model reliability.

Temporal dynamics of neurological recovery

Garcia scale assessment revealed a complex, nonlinear recovery pattern (Fig. 2). Initial deficit (day 1: 14.83±1.72) somewhat worsened by day 3 (13.778±0.972), which is characteristic of this pathology. Moderate recovery became evident by day 21 (16 [15;16], $p<0.001$ vs day 3 score). By day 28, significant functional recovery was observed (18 [18;18.5], $p=0.008$ vs day 1 score). However, recovery was limited, with day 28 scores not comparable to those of intact animals (21 [21;21], $p<0.001$).

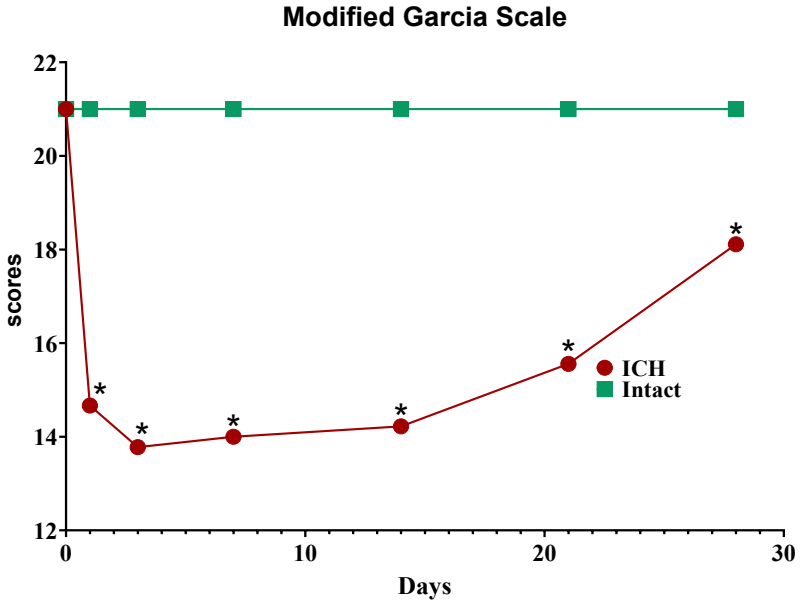


Figure 2. Dynamics of neurological deficit over 28 days after internal capsule intracerebral hemorrhage in mice, assessed by the modified Garcia scale, showing early worsening followed by partial but incomplete functional recovery compared with intact controls. ***Note:*** *$p<0.05$ vs intact group. ICH – intracerebral hemorrhage group.

Forelimb sensorimotor function

ICH modeling caused significant limb placement impairment, manifested as reduced number of successful placements of the contralateral forelimb upon vibrissae stimulation. All intact animals demonstrated 10/10 successful placements. After ICH, scores sharply declined to 4.33±2.06 on day 1 ($p<0.001$ vs intact group, representing >50% deficit). Recovery followed a nonlinear trajectory (Fig. 3) with transient improvement on day 7 (9 [5;10], $p>0.05$), subsequent deterioration on day 14 (7±2.65, $p=0.004$), and eventual normalization by day 28 (10 [9.5;10], $p>0.05$).

Hindlimb function

In contrast to immediate forelimb impairment, hindlimb deficits demonstrated delayed onset (Fig. 3). Significant hindlimb placement impairments were not detected during the first 24 hours (0 [0;0]). Significant differences between groups were observed only during the period from day 3 to day 21. Hindlimb function recovery was observed only on day 28.

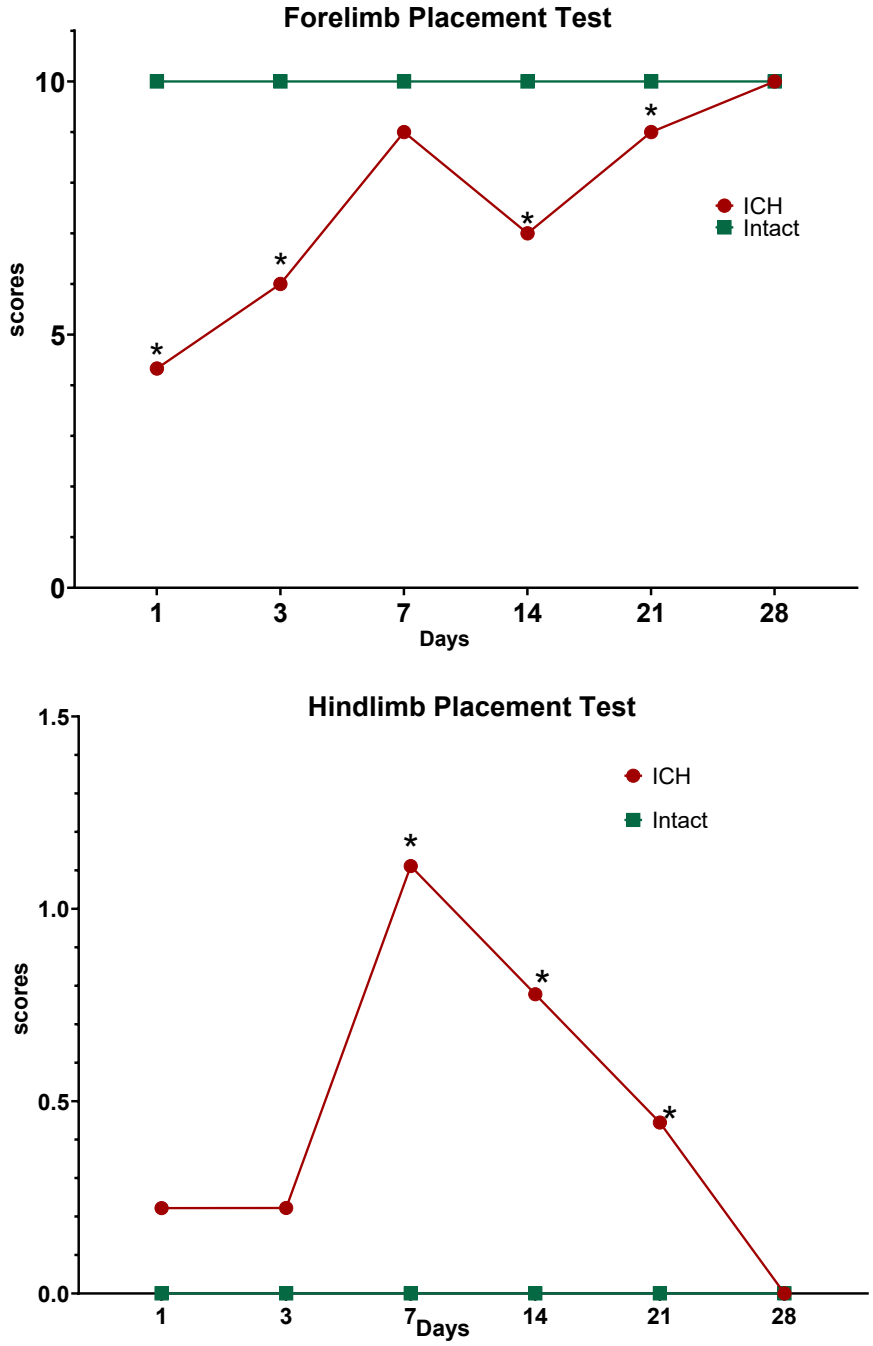


Figure 3. Temporal profile of tactile forelimb and hindlimb placement deficits in mice over 28 days after internal capsule intracerebral hemorrhage, showing an immediate, pronounced forelimb impairment and a delayed, transient hindlimb deficit relative to intact controls. ***Note*:** *$p<0.05$ vs intact group. ICH – intracerebral hemorrhage group.

Motor coordination and balance

The modified horizontal bar test revealed significant coordination impairments persisting throughout the 28-day observation period (Fig. 4). Baseline scores (9 [9;9]) decreased to 5.33 [4.17;5.67] on day 1 ($p<0.001$), indicating severe impairment of coordinated limb use and balance. Gradual recovery occurred through day 21, but deficits remained evident even on day 28 (7.67 [6.67;8.33], $p<0.001$), demonstrating incomplete recovery of fine motor coordination.

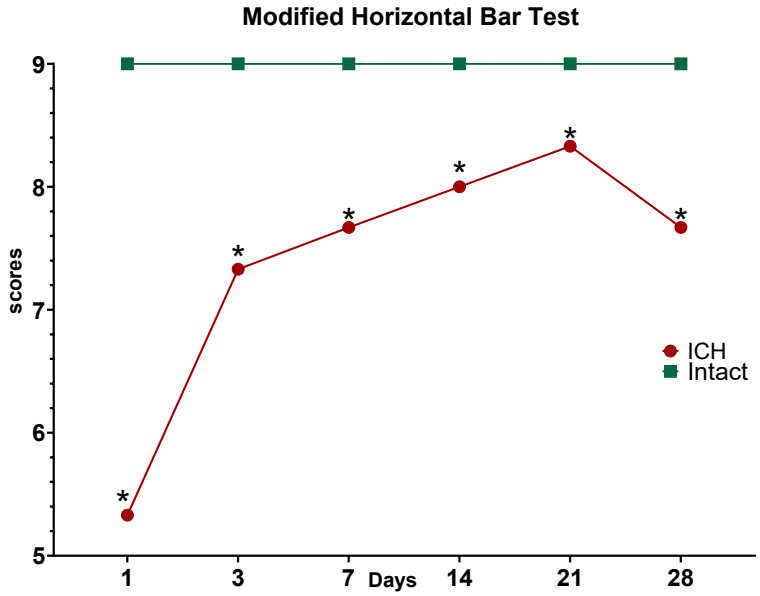


Figure 4. Time course of motor coordination and muscle strength impairments in mice over 28 days after internal capsule intracerebral hemorrhage, assessed by the modified horizontal bar test, demonstrating marked early dysfunction and incomplete late recovery compared with intact controls. ***Note:*** *p<0.05 vs intact group. ICH – intracerebral hemorrhage group.

Spatial attention and sensory neglect

Corner test analysis revealed development of contralateral spatial neglect following ICH (Fig. 5). At baseline, mice showed no turning direction preference (0 [-0.4;0.2]). After ICH, animals demonstrated significant ipsilateral turning bias on day 1 (0.6 [0;0.7], $p=0.039$), reflecting left-sided sensory neglect. However, despite the observed tendency toward right-side preference, at later observation time points the test power did not allow detection of clinically significant statistically reliable patterns.

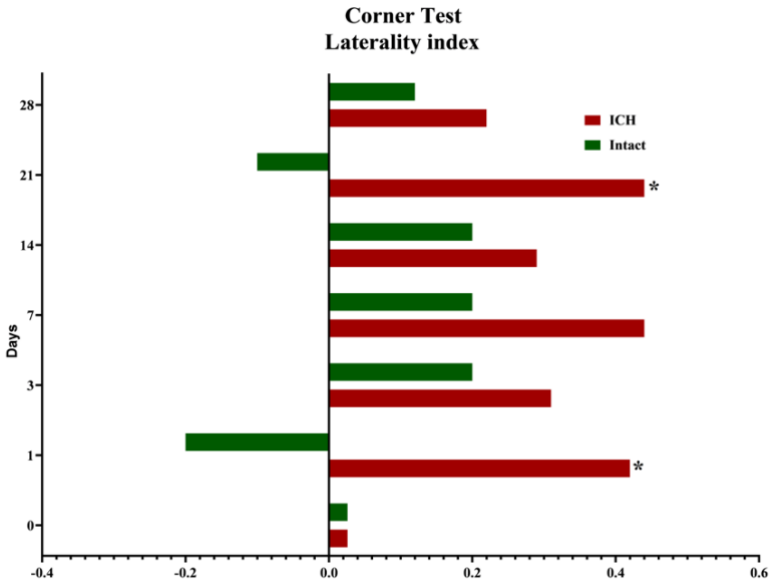


Figure 5. Time course of spatial attention impairment in mice after internal capsule intracerebral hemorrhage, assessed by the corner test, showing early development of contralateral neglect with ipsilateral turning bias and absence of robust, sustained asymmetry at later time points compared with intact controls. ***Note:*** *p<0.05 vs intact group. ICH – intracerebral hemorrhage group.

Locomotor activity and exploratory behavior

Open field test assessment demonstrated acute suppression of locomotor activity after ICH. Total distance traveled decreased from baseline 2107.26±441.66 cm to 1391.21±455.81 cm on day 1 (p=0.009) with corresponding speed reduction from 7.13±1.56 cm/s to 4.64±1.52 cm/s (p=0.009). By day 21, locomotor parameters demonstrated recovery of motor functions (1741.79±352.8 cm distance, 5.8±1.18 cm/s speed) to the level of intact animals (Fig. 6).

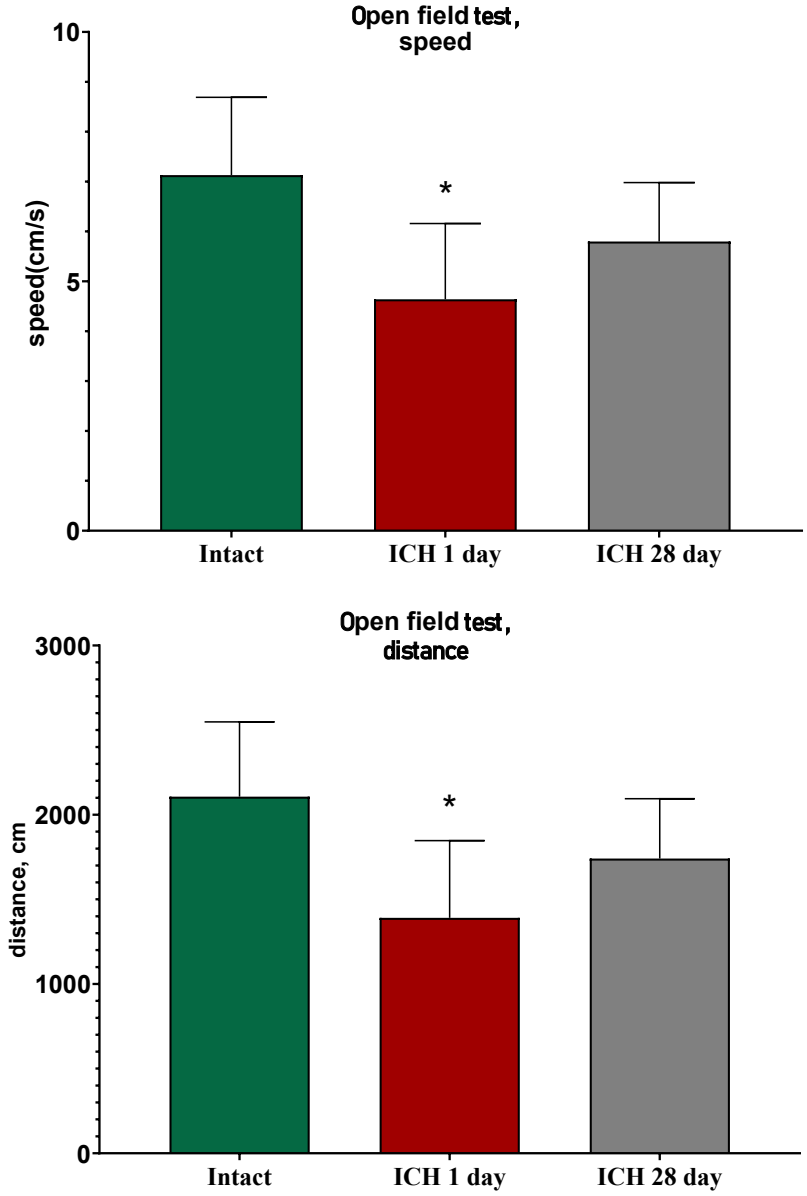


Figure 6. Time course of locomotor activity in mice after internal capsule intracerebral hemorrhage, assessed in the open field test, demonstrating acute suppression of movement with recovery of distance traveled and speed to control levels by day 28. ***Note:*** *p<0.05 vs intact group. ICH – intracerebral hemorrhage group.

Limitations of inverted grid and vertical pole tests

The inverted grid and vertical pole tests showed limited sensitivity for detecting functional impairments in this model (Table 1).

In the inverted grid test, no statistically significant differences between groups were found at control time points. This may be related to the "ceiling effect" due to the test time limit (60 seconds), as well as compensatory behavioral strategies: unlike intact animals that actively moved across the grid, mice with ICH predominantly maintained a static position, which reduced functional load and limited test sensitivity.

The vertical pole test also did not show high prognostic significance. This phenomenon may be related to a methodological error – animals with neurological deficit slid down the pole under gravity due to muscle weakness.

Table 1. Dynamics of locomotor functions in the inverted grid and vertical pole tests after ICH modeling

Test		Group			
		Intact	ICH		
			1 day	3 day	7 day
Inverted Grid		60 [27; 60]	60 [20.42; 60]	60 [39.5; 60]	60 [23.93; 60]
Vertical Pole	time to initiate descent	3.7 [2.5; 7.7]	4.92±2.27	3.76±1.33	3.25 [2.1; 4.88]
	descent time after turning	4.50 [3.9; 5.3]	3 [2.4; 4.36]*	3.46±1.35*	3.62±1.28
	total descent time	8.85 [7.15; 12.85]	8.72±3.02	7.26±2.08	7.1 [6.42; 8.3]

Note: *p<0.05 vs intact group.

Discussion

This study establishes and validates a model of hemorrhage in the basal ganglia (putamen and globus pallidus) with involvement of the internal capsule in mice, which reproduces clinically relevant, reproducible sensorimotor deficits with persistent functional impairment. Several key findings support the utility of this model for preclinical neuroprotection research.

First, the anatomical localization of hemorrhage in the basal ganglia (putamen and globus pallidus) with involvement of the internal capsule provides clear advantages over traditional striatal models. The internal capsule contains dense clusters of white matter tracts, particularly corticospinal fibers in the posterior limb, making it a critical point for motor and sensory information transmission (Gupta et al. 2024). Clinical data demonstrate that internal capsule involvement is the primary determinant of poor prognosis in subcortical hemorrhages (Matsushita et al. 2013). Additional involvement of the globus pallidus fundamentally enhances the clinical relevance of the model, as this structure plays a key role in the regulatory influence of the basal ganglia on motor cortex excitation (control of thalamocortical projections) and in the modulation of corticospinal output (Young et al. 2025). Its involvement is typical of the "middle" subtype of striatocapsular hemorrhage, in which the hematoma extends into the medial putamen, globus pallidus and, frequently, the internal capsule. Such combined damage is associated not only with contralateral hemiparesis and sensory deficits, but also with more pronounced and persistent disturbances of postural control and movement regulation than in isolated putaminal hemorrhage. For preclinical testing of neuroprotective agents intended for patients with severe subcortical strokes, modeling putaminal injury together with concomitant involvement of the globus pallidus and internal capsule better reproduces the typical human striatocapsular syndrome and the range of persistent sensorimotor deficits that therapeutic interventions aim to target (Chung et al. 2000).

Second, the model demonstrates high reproducibility and clinically relevant severity. The acute mortality rate of 33-40% is comparable to human ICH mortality and reflects the devastating impact of striatocapsular hemorrhage. All surviving animals developed measurable neurological deficits with comparable phenotype (sensorimotor-pyramidal deficit with forelimb emphasis), which is critical for ensuring statistical power in therapeutic studies. Comparison with putamen hemorrhage models reveals important differences: striatal lesions often show rapid spontaneous recovery within 1-2 months (Liu et al. 2018), whereas our hemorrhage model with internal capsule reproduces detectable neurological deficits for 28 days, providing an extended therapeutic window for intervention testing.

Third, the standardized functional assessment battery effectively captures the multidimensional nature of post-stroke neurological deficit. The modified Garcia scale proved most sensitive for quantifying global neurological deficit, consistent with previous studies in stroke models (Bachour et al. 2016; Matsumura et al. 2019). Importantly, we observed temporal dissociation between forelimb dysfunction (immediate deficit) and hindlimb dysfunction (delayed onset), likely reflecting primary hemorrhagic damage to anterior capsular regions with secondary injury to posterior regions through inflammation, edema, and hemotoxicity. This observation has methodological implications: single time-point assessment may miss important deficit components, requiring longitudinal evaluation.

The nonlinear recovery pattern observed in several tests warrants discussion. Transient improvement on day 7 followed by deterioration corresponds to known ICH pathophysiology: initial behavioral compensation may mask true deficit severity, while secondary injury mechanisms (neuroinflammation peaking on days 3-7, hemosiderin-mediated oxidative stress, perihematomal ischemia) cause functional deterioration in the subacute phase (Shcheblykina et

al. 2022). Final improvement by day 28 likely represents endogenous neuroplastic reorganization. This pattern argues against using early time points (≤7 days) as sole efficacy endpoints, as apparent early benefits may not persist.

Our findings regarding test sensitivity merit emphasis. The modified Garcia scale, forelimb placement test, and horizontal bar test demonstrated reliable deficit detection and clear separation from intact controls at multiple time points. In contrast, inverted grid and vertical pole tests showed limited sensitivity due to ceiling effects, high behavioral variability, and compensatory strategies. Specifically, the inverted grid test allows animals to use all four limbs with preferential loading on the unaffected side, masking unilateral deficits (Balkaya et al. 2013; Niewiadomski et al. 2016). The vertical pole requires coordinated hindlimb and tail work, whereas our model causes more pronounced forelimb impairment, reducing test relevance (Bouet et al. 2009; Niewiadomski et al. 2016). These results align with recent comparative studies of behavioral assessments in stroke (Bouet et al. 2009; Ruan and Yao 2020) and underscore the importance of test battery validation for specific anatomical lesion localization.

Several limitations warrant consideration. First, we used only male mice of one age range; sex and age likely modulate ICH pathophysiology and recovery (Krafft et al. 2012). Second, our 28-day observation may not capture chronic recovery processes extending beyond 1 month. Third, histopathological characterization of lesion size and white matter damage was not performed in the current study, but represents an important future direction for correlating behavioral deficits with specific anatomical injury. Fourth, while we included a broad range of behavioral tests, some (inverted grid, vertical pole) proved insufficiently sensitive for this model, highlighting the need for careful assessment method selection depending on lesion localization and character (Balkaya et al. 2013; Bouet et al. 2009; Niewiadomski et al. 2016; Ruan and Yao 2020).

The practical implications for preclinical drug development are significant. This model provides: (1) a clinically relevant deficit pattern corresponding to capsular hemorrhage in humans, (2) persistent functional impairment allowing testing of chronic therapeutic interventions, (3) standardized, validated outcome measures with established effect sizes for power calculations, and (4) sufficient deficit severity without excessive mortality. The recommended core battery – Garcia scale, forelimb placement, horizontal bar, and open field – balances comprehensive phenotyping with practical feasibility.

Conclusion

Hemorrhage in the basal ganglia (putamen and globus pallidus) with involvement of the internal capsule in mice reproduces a clinically relevant striatocapsular stroke model characterized by reproducible contralateral sensorimotor-pyramidal deficits, persistent functional impairment, and limited spontaneous recovery. This model closes a critical gap in ICH research by targeting white matter-rich structures that better reproduce human disease compared to traditional putamen hemorrhage. The validated behavioral assessment battery – based on the modified Garcia scale, forelimb placement test, and motor coordination tests – provides comprehensive, sensitive quantification of acute injury severity and recovery dynamics. Together, this experimental platform establishes a robust foundation for preclinical evaluation of neuroprotective interventions, potentially accelerating translation of effective treatments for this devastating disease.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

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Ethics statement

The study was approved by the Institutional Animal Care and Use Committee of Belgorod State National Research University (expert opinion No. 01-01i/25 dated January 9, 2025).

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The authors have no support to report.

Data availability

All of the data that support the findings of this study are available in the main text.

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