



# Optimizing The Timing of Stereotactic Minimally Invasive Drainage for Hypertensive Intracerebral Hemorrhage

Jingchen Li · Zhiyong Li · Lin Zhao · Yuanyu Wang · Jiankai Yang ·  
Yan Feng · Xiaowei Zhang · Xiuwen Wu

Received: November 30, 2022 / Accepted: March 13, 2023 / Published online: April 18, 2023  
© The Author(s) 2023

## ABSTRACT

**Introduction:** Intracerebral hemorrhage is a high-risk pathological event that is associated with formidable mortality rates. Here, our objective was to perform a retrospective study to determine the best timing for drainage using physiological data on patients who received drainage at different timings.

**Methods:** In this retrospective study, we reviewed 198 patients with hypertensive cerebral hemorrhage who underwent stereotactic drainage at the conventional timing (surgery within 12 h of admission; control group) and 216 patients who underwent stereotactic drainage at a customized surgical timing (elective group). Follow-ups were performed at 3 and 6 months after surgery.

**Results:** The clinical indicators, including prognosis, hematoma clearance, recurrent hemorrhage, intracerebral infection, pulmonary infection, deep venous thrombosis, gastrointestinal hemorrhage, National Institutes of Health Stroke Scale scores, and matrix metalloproteinase 2 and 9 levels, were compared between the control and elective groups. Our data indicated that the elective group had significantly better prognosis compared to the control group ( $p = 0.021$ ), with a higher rate of hematoma clearance ( $p = 0.004$ ) and a lower rate of recurrent hemorrhage ( $p = 0.018$ ). The total occurrence rate of post-surgery complications was also lower for the elective group ( $p = 0.026$ ). NIHSS scores and serum MMP2/9 levels of the elective group were lower than those of the control group.

**Conclusions:** Customized timing of stereotactic drainage may be superior to conventional fixed timing (within 12 h post-hemorrhage) in reducing post-surgery complications and promoting recovery, which supports the potential use of customized timing of stereotactic minimally invasive drainage as a new convention in clinics.

**Keywords:** Stereotactic minimally invasive drainage; Hypertensive intracerebral hemorrhage; Surgery timing

---

J. Li · L. Zhao · Y. Wang · J. Yang · Y. Feng ·  
X. Zhang

Department of Neurosurgery, The Second Hospital  
of Hebei Medical University, No. 215 Heping West  
Road, Shijiazhuang 050000, Hebei, China

Z. Li

Department of Neurosurgery, Northern War Zone  
General Hospital, Chinese People's Liberation Army,  
Shenhe District, No.83 Culture Road, Shenyang  
110000, Liaoning, China

X. Wu (✉)

School of Pharmaceutical Sciences, Hebei Medical  
University, Shijiazhuang 050000, Hebei, China  
e-mail: wuxiuwen@hebm.u.edu.cn

### Key Summary Points

Intracerebral hemorrhage is a pathological event in the middle-aged and elderly population that is associated with high morbidity and mortality rates

This retrospective study determined the best timing for drainage using physiological data from patients who received drainage at different timings

Customized timing of stereotactic drainage may be superior to conventional fixed timing (within 12 h post-hemorrhage), as it improved the prognosis, reduced post-surgery complications, and promoted recovery

Our findings support the potential use of customized timing of stereotactic minimally invasive drainage as a new convention in clinics

## INTRODUCTION

Intracerebral hemorrhage (ICH) is a pathological event in the middle-aged and elderly population that is associated with high morbidity and mortality rates. Hypertensive atherosclerosis is one of the main causes of ICH [1]. Changes in people's dietary structure, hyperlipidemia, diabetes, and obesity are important risk factors for cerebrovascular diseases caused by ICH. However, ICH cannot be overlooked in the younger population because of the possibility of Moyamoya disease, cerebrovascular malformations, hemangiomas, etc. [2]. Regardless of the age of onset and etiology, ICH is linked to severe neurological deficits, i.e., small amounts of bleeding at critical sites and large amounts of bleeding at relatively general sites, both of which are associated with death in most patients, and survivors are often left with varying degrees of physical disability and impaired higher neurological functions such as

compromised speech and mental functionalities [3]. Hence, ICH severely affects patients' quality of life and places a tremendous burden on their families and society. Unfortunately, there is a lack of effective treatment and standardized treatment principles for ICH in clinical practice.

Conservative medical treatment is mainly aimed at reducing brain edema caused by ICH, repairing the damaged tissues around the hemorrhage, and promoting neurological recovery. However, thus far, surgical hematoma removal has only been shown to be valuable for saving patients' lives [4]. Stereotactic minimally invasive drainage, a technique that has emerged over the past 20 years, has to some extent compensated for the deficiencies of the previous surgical treatment of ICH, such as its high damage and high cost, making it a highly promising treatment method that can be widely applied [5].

Previous studies have shown that early hematoma clearance for cerebral hemorrhage, i.e., at 3–6 h after onset, is beneficial, as mechanical damage and secondary damage caused to brain tissue by the hematoma is modest at that stage [6, 7]. However, in clinical practice, only very few patients can be operated on at 3–6 h after onset due to the delays caused by admission, examination, and diagnosis confirmation. In addition, premature removal of the hematoma may lead to a compensatory response from the coagulation system, increasing rebleeding [5]. Therefore, the long-term prognosis of patients with ICH remains poor. A previous study suggested that minimally invasive removal of the intracranial hematoma at 8–24 h after a cerebral hemorrhage can achieve more satisfactory results in terms of the complete clearance rate and neurological recovery [8]. However, it has also been shown that surgery should be avoided at an ultra-early stage because of the risk of hematoma enlargement, making the patient prone to postoperative rebleeding and thus making late surgery safer [9].

Given that the optimal timing of hematoma removal for cerebral hemorrhage remains to be determined, in this study, we aimed to perform a comparative study of conventional timing

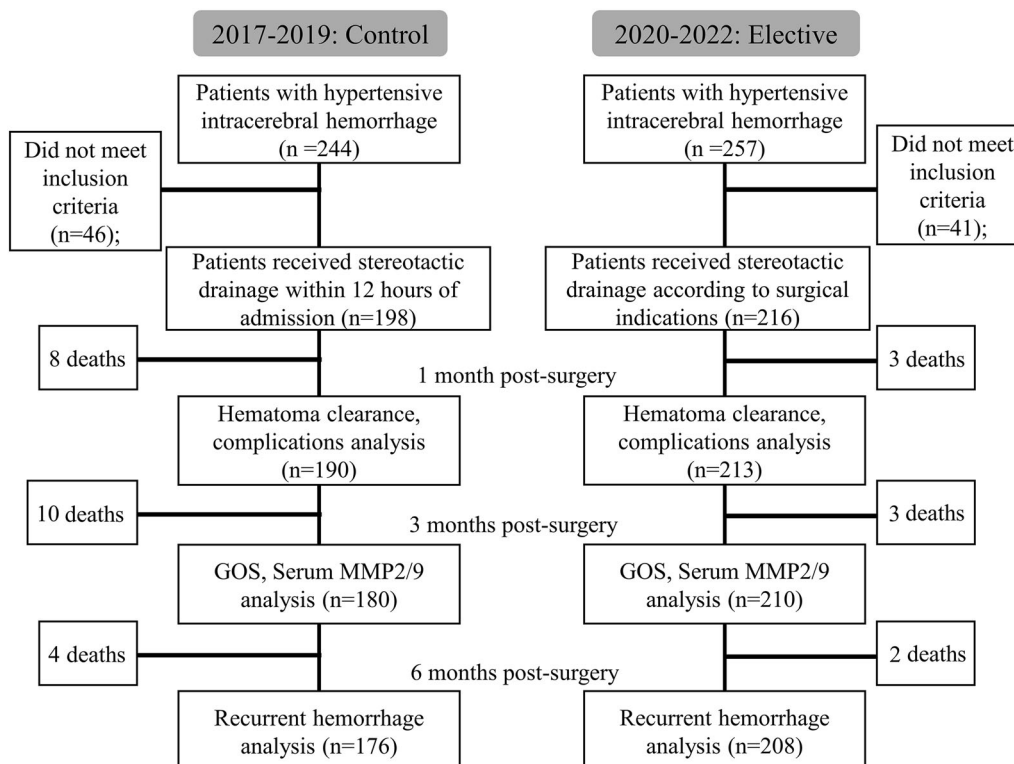
(within 12 h after onset) vs. customized timing by referencing a set of clinical indicators of patients and a set of heuristic rules based on our clinical experience to test the hypothesis that customized surgery timing can reduce post-surgery complications and promote recovery.

## METHODS

### Patients and Study Design

Our retrospective study was conducted by the Department of Neurosurgery of the Second Hospital of Hebei Medical University and Neurosurgery Centers of the General Hospital of the Northern Theater of the Chinese People’s Liberation Army. Cases admitted during 2017–2022 were reviewed. To validate our summarized surgical indications for hemorrhage, we reviewed 198 patients with hypertensive cerebral hemorrhage who underwent stereotactic hematoma aspiration and drainage

with conventional surgical indications (surgery within 12 h of admission)—the control group, and 216 patients who underwent stereotactic hematoma aspiration and drainage with the surgical timing determined by the grading system for surgical indications for hemorrhage—the elective group (see Fig. 1). Among the patients in the elective group, 112 patients received surgery within 12 h of admission, and 104 patients underwent elective surgery. The grading system was not applied to the control group. We started to use elective (customized) surgical timing in 2017; patients with elective surgical timing were then compared to patients with traditional surgical timing. The outcomes of patients for whom the selected surgical indications for hemorrhage was adopted were compared for two time periods with the outcomes of those for whom the bleeding surgical indication was not adopted. The scientific validity of our summarized indications for hemorrhage surgery was determined by reviewing baseline clinical data at admission



**Fig. 1** Study flow of this trial

and comparing the short-term prognosis, associated complications, neurological deficit scores, and serum matrix metalloproteinase 2 and 9 (MMP2/9) concentrations between the two groups. The study was approved by the ethics committee of Hebei Medical University (2022-AE165). Informed written consent was obtained from the participants. The study was performed in strict accordance with the ethical principles for medical research involving human subjects in the Declaration of Helsinki.

### Inclusion Criteria

We included patients that met the diagnostic criteria established by the Fourth National Cerebrovascular Conference: (1) patients should have a clear history of hypertension and symptoms of an acute intracranial pressure increase; (2) age  $\geq$  18 years; (3) first presentation; (4) the site and amount of bleeding were confirmed by computed tomography (CT), computed tomography angiography (CTA), magnetic resonance imaging (MRI), etc. after admission; (5) clinical symptoms included varying degrees of hemiparesis, impaired consciousness, language impairment, etc., and some patients had headache, nausea, and vomiting; (6) the patient and/or family members gave their informed consent; (7) the patients were admitted within 24 h from symptom onset.

### Exclusion Criteria

We excluded (1) patients with a traumatic brain injury, intracranial vascular malformation, cerebral amyloidosis, intracranial tumors, neurological and psychiatric diseases, cognitive dysfunction, coagulation abnormalities, intracranial infections, or combined systemic infectious diseases, (2) patients with obvious intracranial compression symptoms and those who had undergone brain herniation, and (3) patients who intended to withdraw life-sustaining therapies early or who had DNR orders. After admission, the patient was examined using CT, CTA, and MRI to exclude amyloidosis, intracranial vascular malformation, and intracranial compression symptoms.

**Table 1** Grading system for elective timing of stereotactic minimally invasive drainage

Cerebral hemispherical hemorrhage		Cerebellar hemispherical hemorrhage	
Characteristic	Score	Characteristic	Score
Consciousness		Consciousness	
Sober	1	Sober	1
Hazy	2	Hazy	2
Coma	3	Coma	3
Ambient cistern		Ambient cistern	
Exists	1	Exists	1
Disappeared	2	Disappeared	2
Brain stem compression	3	Brain stem compression	3
Hematoma volume (mL)		Hematoma volume (mL)	
< 30	1	< 10	1
30–40	2	10–20	2
> 40	3	> 20	3
Encephalatrophy		Cerebral edema	
Mixed or white matter type	1	< The hematoma volume	1
Cortex type	2	= The hematoma volume	2
No	3	> The hematoma volume	3
< 6: elective surgery; 7–9: hospitalization for observation; 10–12: immediate surgery		< 6: elective surgery; 7–9: external ventricular drainage; 10–12: immediate surgery	

### Grading System for Selecting the Timing of Stereotactic Minimally Invasive Drainage

Table 1 shows the grading system for elective timing for stereotactic minimally invasive drainage, as developed in our department based on many years of clinical surgery. Different scoring

systems were used for two different sites of hemorrhage, i.e., cerebral hemisphere hemorrhage and cerebellar hemisphere hemorrhage. The scoring system also took into account indicators including consciousness, ambient cistern, brain stem compression, hematoma volume, and encephalatrophy. Encephalatrophy is mainly divided into white matter brain atrophy, cortical brain atrophy, and mixed brain atrophy (white matter and cortex); an increase in intracranial pressure occurs after a brain hemorrhage because the space in the skull is relatively fixed and the hematoma has to occupy the skull space. The intracranial pressure and space is mainly regulated through the cerebrospinal fluid. The degree of brain atrophy gradually increases with increasing age, clinically it is observed that the symptoms suffered by many patients with severe brain atrophy and a large brain hemorrhage are not particularly serious because brain atrophy creates extra intracranial space to the hematoma. For cerebral hemispherical hemorrhage, elective surgery was performed on those with scores < 6, hospitalization for observation was recommended for those with scores of 7–9, and immediate surgery was performed for those with scores of 10–12. For those with cerebellar hemispherical hemorrhage, similar criteria were used except that those with scores of 7–9 received external ventricular drainage.

## Treatments

Based on a CT examination and the calculation of Tian's formula, craniotomy was performed on those with a bleeding volume of > 50 ml, a Glasgow Coma Scale (GCS) score of  $\leq 8$  points, a midline structure deviation of > 1 cm, and bleeding within 12 h. Stereotactic surgery was performed on the rest.

During stereotactic surgery, the patient's head was mounted in a stereotactic head frame to perform a cranial CT scan with a layer thickness of 5 mm and an interval of 0 mm in order to observe the location and morphology of the hemorrhage. The data were transferred to Leksell SurgiPlan 10.1 software to design the

surgical position and surgical path that avoided important cortical functional areas.

After precisely calculating the target point, a 3-cm incision was made, after which the scalp and subcutaneous tissues were cut. Then one hole was drilled, the dura was cut, and the target point was reached (avoiding the venous sinus) via a penetrating needle of the stereotactic instrument to aspirate the hematoma. Cranial CT images were acquired 2 h after surgery, and the residual hematoma was dissolved, if necessary, by injecting urokinase through the drainage tube; the hematoma cavity drainage tube was removed 2–5 d after surgery [8]. Urokinase was injected slowly into the hematoma cavity by incorporating 20,000 units into 5 ml of saline. After stereotactic surgery, the end of the retained drainage tube remained in the hematoma cavity and the outside end had a three-way valve. The injection of urokinase required closed-tube observation for 2 h, and it was necessary to frequently review the head CT.

All patients were followed for up to 6 months. A prognostic assessment was performed at 3 months postoperatively with the Glasgow Outcome Scale (GOS) score [10]. No impact on daily life, mild symptoms and signs, and an ability to socialize, live, and work normally were considered to correspond to a good recovery; a partial loss of ability to live and work but an ability of the patient to move on their own with disabilities such as neural palsy and ataxia were considered to correspond to moderate disability; some consciousness but no ability of the patient to live on their own and the presence of speech and sensory impairment were considered to indicate severe disability; no consciousness and only partial movements such as blinking and breathing were considered to correspond to vegetative survival.

Hematoma volume was determined using the Coniglobus formula: hematoma size =  $1/2 \times$  the longest diameter of the hematoma layer with the largest area on axial cuts (cm)  $\times$  the diameter perpendicular to the longest diameter mentioned (cm)  $\times$  the thickness of the hematoma (cm).

Follow-up CT exams were performed at 6 months after surgery. Patients were diagnosed with a recurrent hemorrhage if they were seen

again within 6 months because of symptoms or if a recurrent hemorrhage was found after a CT review performed 6 months after surgery without obvious symptoms.

### Neurological Deficit Evaluation

Neurological deficit evaluation was performed preoperatively and at 3 months after surgery using the National Institutes of Health Stroke Scale (NIHSS) [11]. NIHSS scores range from 0 to 42, with scores of 0–1 for a normal status, 2–4 for mild neurologic impairment, 5–15 for moderate neurologic impairment, 16–20 for severe neurologic impairment, and 21–42 for extremely severe neurologic impairment. Patients were followed up for 1 month postoperatively to check for complications and were recorded.

### Measurement of MMP2/9 Levels

MMP2/9 concentrations in patients' sera were measured preoperatively and at 3 months post-surgery using ELISA kits from Abcam. Briefly, 4 mL of fasting venous blood were collected and processed by centrifugation at 2500 r/min for 15 min. The supernatant was taken and stored in a constant-temperature refrigerator at  $-80\text{ }^{\circ}\text{C}$ .

### Statistical Analysis

Values were expressed as  $n$  (percentage, %) or as scatter points in figure plots.  $p$  values were derived from the chi-square test, Fisher's exact test, or two-way ANOVA followed by Tukey's multiple comparisons tests.  $p < 0.05$  was considered statistically significant.

## RESULTS

### Study Design and Patient Characteristics

The grading system was used to evaluate 198 patients with hypertensive cerebral hemorrhage in 2020 who underwent drainage with conventional timing (i.e., the surgery occurs within

12 h of admission to the hospital for diagnosis; control group) and 216 patients who underwent stereotactic drainage in 2021 with the surgical timing determined by the grading system (elective group). Comparison of the baseline data between the two groups revealed no significant differences in age, sex, time from symptom onset to admission, site of bleeding, or Glasgow Coma Scale (GCS) score at the time of admission (Table 2). Briefly, both groups of patients had a mean age of 48–49 years, and the proportions of males in the two groups were slightly higher than the proportions of females. Time from onset to admission was  $5.62 \pm 1.72$  for the control group and  $4.99 \pm 1.83$  for the elective group ( $p = 0.168$ ). The most common hemorrhage location in both groups was the basal ganglia region (77.% of the control group and 69.9% of the elective group). The two groups did not significantly differ in terms of GCS score, hematoma volume, or consciousness.

### Prognosis Evaluation for Patients with ICH Who Underwent Stereotactic Minimally Invasive Draining at Customized or Conventional Timing

We further conducted prognostic analysis at 3 months during the follow-up. Patients for whom daily life was not affected and who showed mild symptoms and signs and were able to socialize, live, and work normally were considered to have a good prognosis (see Table 3). Those with a partial loss of living and working abilities and who presented disabilities such as neural palsy and ataxia but were able to move on their own were considered to have moderate disability. Those with some consciousness but who were unable to live on their own and showed speech and sensory impairment were considered to have severe disability. Those with no consciousness and only partial movements such as blinking and breathing were considered to be in a vegetative state. Our data revealed that in both groups, the largest fraction of the patients (about half) had a good prognosis, followed by those with moderate disability. Overall, the elective group had significantly higher

**Table 2** Demographic and clinical characteristics of the hypertensive intracerebral hemorrhage patients who received stereotactic minimally invasive drainage at the conventional timing or at an elective timing

Characteristics	Study group		<i>p</i> value
	Control ( <i>n</i> = 198)	Elective ( <i>n</i> = 216)	
Age (years)	48.32 ± 11.36	49.41 ± 13.29	0.328
Gender			
Male	106 (53.5%)	109 (50.5%)	0.556
Female	92 (46.5%)	107 (49.5%)	
Time from onset to admission (h)	5.62 ± 1.72	4.99 ± 1.83	0.291
Hemorrhage location			
Temporal lobe	12 (6.0%)	24 (11.1%)	0.198
Parietal lobe	19 (9.6%)	20 (9.3%)	
Basal ganglia region	153 (77.3%)	151 (69.9%)	
Cerebellum	14 (7.1%)	21 (9.7%)	
GCS			
13–15	75 (37.9%)	73 (33.8%)	0.682
9–12	106 (53.5%)	124 (57.4%)	
≤ 8	17 (8.6%)	19 (8.8%)	
Hematoma volume (mL)			
< 30	96 (48.5%)	103 (47.7%)	0.822
30–40	69 (34.8%)	72 (33.3%)	
> 40	33 (16.7%)	41 (19.0%)	
Consciousness			
Sober	86 (43.4%)	79 (36.6%)	0.348
Hazy	95 (48.0%)	118 (54.6%)	
Coma	17 (8.6%)	19 (8.8%)	
Encephalatrophy			
Mixed or white matter type	67 (33.8%)	82 (38.0%)	0.552
Cortex type	84 (42.4%)	91 (42.1%)	
No	47 (23.8%)	43 (19.9%)	
Ambient cistern			
Exists	91 (46.0%)	103 (47.7%)	0.859
Disappeared	84 (42.4%)	86 (39.8%)	
Brain stem compression	23 (11.6%)	27 (12.5%)	
Diabetes history			

**Table 2** continued

Characteristics	Study group		<i>p</i> value
	Control ( <i>n</i> = 198)	Elective ( <i>n</i> = 216)	
Yes	102 (51.5%)	122 (56.5%)	0.325
No	96 (48.5%)	94 (43.5%)	

Values are expressed as *n* (percentage, %) or mean  $\pm$  SD. *p* values for the groups were derived from the Mann–Whitney test. The chi-square test or Fisher's exact test was used for assessing the distribution of observations or phenomena between different groups

GCS Glasgow Coma Scale

proportions of patients with a good prognosis and moderate disability and lower proportions of patients with severe disability, patients in a vegetative state, and patients who died ( $p = 0.021$ , Table 3), suggesting the benefit of customized drainage timing for the prognosis.

#### Evaluation of the Incidence of Recurrent Hemorrhage

The clinical outcomes were further evaluated based on hematoma clearance assessed at 1 month and the occurrence of rebleeding during the 6-month postoperative follow-up. The rate of hematoma clearance was significantly higher in the elective group than in the control group at 1 month after surgery ( $p = 0.004$ ), and the incidence of rebleeding was significantly lower in the elective group than in the control group at 6 months after surgery ( $p = 0.018$ , Table 4).

#### Evaluation of Complications Associated with Surgery and ICH

Table 5 shows a comparison of the complications in the control and elective groups at 1 month after surgery. While there were no significant differences between the two groups in the individual comparisons of the incidence rates of intracranial infection, pulmonary infection, deep venous thrombosis, and gastrointestinal hemorrhage, the overall rate of complications (which took into consideration all of the above complications) differed significantly between the two groups ( $p = 0.026$ ).

#### Comparisons of Serum Concentrations of MMP2 and MMP9 Before and 3 Months After the Operation

MMP2/9 are associated with oxidative stress and injury in the brain, so we also evaluated the MMP2/9 levels as another metric for clinical outcome assessment. As shown in Fig. 2, serum MMP2 (Fig. 2A; pre-operation: control  $467.67 \pm 176.71$  ng/mL vs. elective  $474.69 \pm 176.59$  ng/mL,  $p = 0.976$ , post follow-up: control  $390.64 \pm 169.73$  ng/mL vs. elective  $334.64 \pm 167.46$  ng/mL,  $p = 0.008$ ) and MMP9 (Fig. 2B; pre-operation: control  $688.31 \pm 213.24$  ng/mL vs. elective  $653.08 \pm 217.11$  ng/mL,  $p = 0.333$ , post follow-up: control  $465.59 \pm 212.42$  ng/mL vs. elective  $391.14 \pm 208.35$  ng/mL,  $p = 0.003$ ) concentrations had decreased significantly in both groups at 3 months after surgical treatment, suggesting recovery, but the elective group had even lower MMP2/9 levels than the control group.

## DISCUSSION

Previously, surgical therapies for ICH have shown mixed results, as exemplified by the fact that the rigorous randomized clinical trials STICH (Surgical Treatment for ICH) I and II failed to replicate the successes of previous studies [12]. While factors that affect the success of drainage surgeries, including the interpretation of imaging features and surgical techniques [13, 14], have been extensively studied recently, questions also remain regarding the timing of



**Table 3** Comparison of the prognoses made using the GOS between the two groups 3 months after treatment

Characteristics	Study group		<i>p</i>
	Control ( <i>n</i> = 198)	Elective ( <i>n</i> = 216)	
Good prognosis	90 (45.4%)	106 (49.1%)	0.021
Moderate disability	55 (27.8%)	77 (35.6%)	
Severe disability	21 (10.6%)	18 (8.3%)	
Vegetative state	14 (7.1%)	9 (4.2%)	
Death	18 (9.1%)	6 (2.8%)	

Values are expressed as *n* (percentage, %). The *p* value was derived from the chi-square test  
GOS Glasgow Outcome Scale

surgery. This study focused on comparing conventional and customized timing of stereotactic minimally invasive surgery in terms of clinical outcome. Indeed, the critical role of surgery timing has been underscored by multiple studies. For example, early drainage performed with the aim of mitigating secondary injury and improving the neurological outcome has been

**Table 4** Comparison of hematoma clearance between the two groups 1 month after stereotactic minimally invasive drainage, and comparison of recurrent hemorrhage between the two groups 6 months after stereotactic minimally invasive drainage

Characteristics	Study group		<i>p</i>
	Control ( <i>n</i> = 198)	Elective ( <i>n</i> = 216)	
Hematoma clearance	139 (70.2%)	178 (82.4%)	0.004
Recurrent hemorrhage	26 (13.1%)	13 (6.1%)	0.018

Values are expressed as *n* (percentage, %). *p* values were derived from Fisher’s exact test

demonstrated to be beneficial preclinically [15], but some clinical studies have suggested advantages of early drainage [16], while others have shown no benefit or even harm, raising concern about the risks of early evacuation, such as collateral damage to normal brain structures, intraoperative bleeding, and post-operative rebleeding [9].

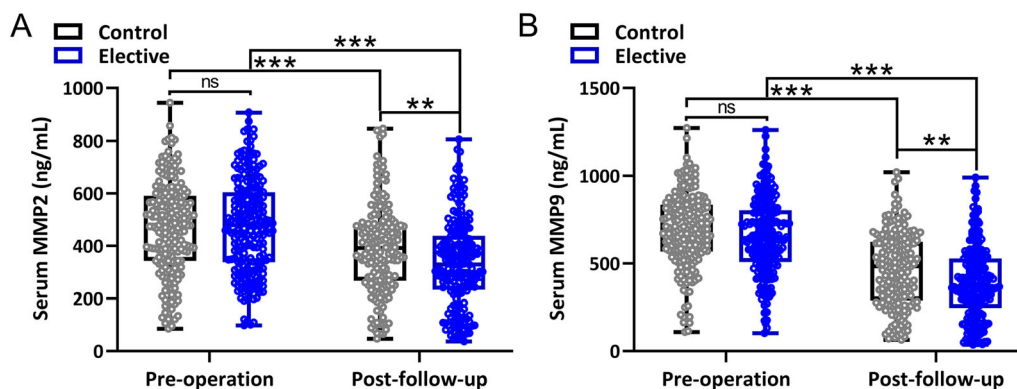
Based on our experiences in the clinic, for the elective group, the hematoma turned into blood, so it was easier to suck out and remove. For the control group, the blood encountered in emergency surgery was like jelly, so it was not easy to suck out and remove. That should explain the higher rate of hematoma clearance in the elective group. The recurrence rate was lower in this group, mainly due to the relatively stable and thorough removal of the hematoma and the good control of blood pressure during and after the operation.

Our results indicate that the optimal timing of hematoma removal for cerebral hemorrhage cannot be simply defined as early or late; it should be customized based on the physiological indicators of the patient, which allow a comprehensive judgment. The surgical

**Table 5** Comparisons of the complications in the two groups during 1 month of follow-up after stereotactic minimally invasive drainage

Characteristics	Study group		<i>p</i>
	Control ( <i>n</i> = 198)	Elective ( <i>n</i> = 216)	
Intracerebral infection	5 (2.5%)	3 (1.4%)	0.488
Pulmonary infection	7 (3.5%)	5 (2.3%)	0.563
Deep venous thrombosis	8 (4.1%)	3 (1.4%)	0.127
Gastrointestinal hemorrhage	5 (2.5%)	2 (0.9%)	0.267
Total occurrence	25 (12.6%)	13 (6.0%)	0.026

Values are expressed as *n* (percentage, %). *p* values were derived from Fisher’s exact test



**Fig. 2** Comparisons of serum concentrations of MMP2 (A) and MMP9 (B) before and 3 months after the operation. The box plots show all the data.  $**p < 0.01$ ,

$***p < 0.001$ , *ns* no significance. P values were derived using two-way ANOVA followed by Tukey's multiple comparisons tests

indications for cerebral hemorrhage that we have summarized here are suggested to have value for determining the timing of stereotactic hematoma drainage. Contrary to the notion that early drainage is beneficial for preventing hematoma expansion, which is a well-documented disease progression associated with worse mortality and morbidity [17], our study demonstrated that customized timing was in fact superior at enhancing hematoma reduction. This pronounced improvement in hematoma reduction translated into a significantly improved prognosis and markedly mitigated postoperative complications in the patients in our study. This finding is consistent with our hypothesis that a customized timing that allows complete stabilization and avoids compensatory responses will lead to a better prognosis. Our results are also echoed by earlier studies which showed that early drainage surgeries are associated with a high risk of rebleeding. Another factor that contributes to the benefit of customized timing is that radiological features can be better established with a stabilized pathology [4]. The lower MMP2/9 levels are also in line with the conclusion that customized timing allows reductions in oxidative stress and injury at operating sites, promoting speedy recovery [18]. It is worth noting that our study is limited by its retrospective nature, and the conclusions need to be validated in future larger prospective trials.

## CONCLUSIONS

By comparing the clinical outcomes of patients who received stereotactic drainage at a customized timing with the clinical outcomes of those who received stereotactic drainage at a conventional fixed timing (within 12 h post-hemorrhage), it was demonstrated that customized timing improves the prognosis, reduces post-surgery complications, and promotes recovery, which supports the potential use of customized timing of stereotactic minimally invasive drainage as a new convention in clinics.

## ACKNOWLEDGEMENTS

We thank the participants of the study.

**Funding.** This study was supported by the Natural Science Foundation of Hebei Province (H2022206456). The authors funded the journal fee.

**Author Contributions.** Jingchen Li, Zhiyong Li, Lin Zhao, Yuanyu Wang, Jiankai Yang, Yan Feng, Xiaowei Zhang, and Xiuwen Wu conducted the experiments, analyzed the data, and wrote the manuscript. Xiuwen Wu conceived this study.

**Disclosures.** Jingchen Li, Zhiyong Li, Lin Zhao, Yuanyu Wang, Jiankai Yang, Yan Feng, Xiaowei Zhang, and Xiuwen Wu declare that they have no competing interests.

**Compliance with Ethics Guidelines.** The study was approved by the ethics committee of Hebei Medical University (2022-AE165). Informed written consent was obtained from the participants. The study was performed in strict accordance with the ethical principles for medical research involving human subjects in the Declaration of Helsinki.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Open Access.** This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

## REFERENCES

- Boulouis G, Charidimou A, Auriel E, et al. Intracranial atherosclerosis and cerebral small vessel disease in intracerebral hemorrhage patients. *J Neurol Sci.* 2016;369:324–9.
- Ruiz-Sandoval JL, Cantu C, Barinagarrementeria F. Intracerebral hemorrhage in young people: analysis of risk factors, location, causes, and prognosis. *Stroke.* 1999;30:537–41.
- Garton ALA, Gupta VP, Sudesh S, Zhou H, Christophe BR, Connolly ES Jr. The intracerebral hemorrhage score: changing perspectives on mortality and disability. *World Neurosurg.* 2020;135:e573–9.
- Huang X, Jiang L, Chen S, et al. Comparison of the curative effect and prognosis of stereotactic drainage and conservative treatment for moderate and small basal ganglia haemorrhage. *BMC Neurol.* 2021;21:1–8.
- Zhou H, Zhang Y, Liu L, et al. Minimally invasive stereotactic puncture and thrombolysis therapy improves long-term outcome after acute intracerebral hemorrhage. *J Neurol.* 2011;258:661–9.
- Vespa P, McArthur D, Miller C, et al. Frameless stereotactic aspiration and thrombolysis of deep intracerebral hemorrhage is associated with reduction of hemorrhage volume and neurological improvement. *Neurocrit Care.* 2005;2:274–81.
- Wu G, Wang L, Wang F, Feng A, Sheng F. Minimally invasive procedures for intracerebral hematoma evacuation in early stages decrease perihematomal glutamate level and improve neurological function in a rabbit model of ICH. *Brain Res.* 2013;1492:140–7.
- Zhu H, Wang Z, Shi W. Keyhole endoscopic hematoma evacuation in patients. *Turk Neurosurg.* 2012;22:294–9.
- Kellner CP, Chartrain AG, Nistal DA, et al. The Stereotactic Intracerebral Hemorrhage Underwater Blood Aspiration (SCUBA) technique for minimally invasive endoscopic intracerebral hemorrhage evacuation. *J Neurointerv Surg.* 2018;10:771–6.
- Tang Y, Yin F, Fu D, Gao X, Lv Z, Li X. Efficacy and safety of minimal invasive surgery treatment in hypertensive intracerebral hemorrhage: a systematic review and meta-analysis. *BMC Neurol.* 2018;18:1–11.
- Mahdy ME, Ghonimi NA, Elserafy TS, Mahmoud W. The NIHSS score can predict the outcome of patients with primary intracerebral hemorrhage. *Egypt J Neurol Psychiatry Neurosurg.* 2019;55:1–5.
- Broderick JP. The STICH trial: what does it tell us and where do we go from here? *Stroke.* 2005;36:1619–20.
- Nishihara T, Morita A, Teraoka A, Kirino T. Endoscopy-guided removal of spontaneous intracerebral hemorrhage: comparison with computer tomography-guided stereotactic evacuation. *Childs Nerv Syst.* 2007;23:677–83.

- 
14. Chartrain AG, Kellner CP, Fargen KM, et al. A review and comparison of three neuronavigation systems for minimally invasive intracerebral hemorrhage evacuation. *J Neurointerv Surg*. 2018;10:66–74.
  15. James ML, Warner DS, Laskowitz DT. Preclinical models of intracerebral hemorrhage: a translational perspective. *Neurocrit Care*. 2008;9:139–52.
  16. Li Y, Wang J, Li Z, et al. Computed tomography angiography spot sign as an indicator for ultra-early stereotactic aspiration of intracerebral hemorrhage. *World Neurosurg*. 2018;109:e136–43.
  17. Bakar B, Akkaya S, Say B, et al. In spontaneous intracerebral hematoma patients, prediction of the hematoma expansion risk and mortality risk using radiological and clinical markers and a newly developed scale. *Neurol Res*. 2021;43:482–95.
  18. Hernandez-Guillamon M, Martinez-Saez E, Delgado P, et al. MMP-2/MMP-9 plasma level and brain expression in cerebral amyloid angiopathy-associated hemorrhagic stroke. *Brain Pathol*. 2012;22:133–41.