Minimally Invasive Surgery for Intracerebral and Intraventricular Hemorrhage

Rationale, Review of Existing Data and Emerging Technologies

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Spontaneous intracerebral hemorrhage (ICH) is the most common type of hemorrhagic stroke, ≈4 times more common than subarachnoid hemorrhage and accounting for 15% of all strokes.1 ICH is associated with higher rates of morbidity and mortality than all stroke subtypes. Overall, mortality rates for ICH are estimated to be as high as 40% to 50%, with the vast majority of survivors disabled at 6 months. When ICH is associated with intraventricular hemorrhage (IVH), outcomes are even worse, with estimated rates of mortality between 50% and 80%.1

Current standards recommend that patients with cerebellar hemorrhages measuring >3 cm with associated neurologic deterioration or significant mass effect be managed with emergency surgical decompression. Similarly, patients with supratentorial hemorrhage and impending herniation are frequently taken for surgical decompression with or without hematoma evacuation. ICH patients who do not fall into either of these 2 categories are, in the vast majority of cases, managed medically.2

With the exception of aggressive blood pressure normalization, no medical therapy has been shown to improve outcomes or reduce mortality in patients with ICH.2 In the absence of clinical evidence to guide therapy, many aspects of medical management are based on local practice patterns with significant variations between institutions.

Mechanisms of Injury in ICH

Spontaneous supratentorial ICH may be divided into 2 general categories based on anatomic location—deep (involving the deep gray matter nuclei) or lobar. Deep hematomas are generally caused by hypertension, whereas lobar hematomas are most often caused by either hypertension or amyloid angiopathy.3 Either type of hemorrhage may be caused or exacerbated by an inherent or pharmacologically induced coagulopathy.1

Brain injury caused by spontaneous ICH is believed to be a biphasic process. The initial hemorrhage dissect through the brain parenchyma, creating a direct traumatic injury to the regional neurons. Although some neurons are irreversibly injured by this process, others in the region are likely compressed, displaced, and only transiently dysfunctional. In the hours after hemorrhage, if the bleeding stops, this regional compression may dissipate and varying degrees of early clinical improvement may be observed.1 Early clinical deterioration is typically related to an extension of the original hemorrhage.1 This early expansion occurs in one quarter to one third of patients.5,6

A second phase of injury manifests as perihematomal edema (both vasogenic and cytotoxic) and occurs in the days following the initial hemorrhage. This perihematomal edema is typically attributed to 2 phenomena. First, it is hypothesized that pressure on the brain adjacent to the hemorrhage limits regional perfusion, causing ischemic injury. Evidence to support this mechanism is somewhat limited. On the contrary, existing positron emission tomographic data suggest that the level of perfusion impairment in the perihematomal region may not be severe enough to generate an infarction.7 Second, preclinical data have indicated that blood degradation products are directly toxic to the brain—that is, the hemotoxicity concept. This hemotoxicity induces edema within the brain adjacent to the hematoma and may result in delayed clinical deterioration with progression of mass effect days after the original hemorrhage.8 This process has been observed as late as 3 weeks after the original hemorrhage.4 Moreover, the edema resulting from ICH has been described to persist for much longer than that associated with acute ischemic stroke, reaching maximum severity between 10 and 20 days.9,10 Thus, these 2 physiological mechanisms of secondary injury may extend the initial mechanical injury, sometimes leading to delayed clinical deterioration. This prolongs recovery and potentially reduces the capacity of the patient to achieve a functional outcome.

Conventional Surgical Evacuation of ICH

The putative benefit of surgery for these patients is based on avoiding or mitigating the secondary wave of injury after ICH. Two large surgical trials have investigated this strategy. The Surgical Trial in Intracerebral Hemorrhage (STICH I) was a multicenter, randomized, controlled trial of 1033 patients with...
MIS Evacuation of ICH

As opposed to open surgical evacuation, no definitive trials evaluating minimally invasive approaches to ICH evacuation have been completed. However, several smaller trials have generated encouraging data. In addition, new technologies are being developed to facilitate the minimally invasive evacuation of intracranial hemorrhage.

Methods of ICH Evacuation

There are two general approaches to MIS ICH evacuation—primarily pharmacological catheter–based and primarily mechanical. The first typically involves the placement of a drainage catheter under image guidance, followed by the irrigation of the catheter with a lytic solution to prevent clogging and facilitate passive drainage of the hematoma. This requires the maintenance of an in situ catheter for several days with intermittent imaging to verify a stable catheter position and to monitor the progress of the drainage. Secondarily, mechanical methods for hemorrhage evacuation involve the removal of the hematoma in a single procedure. The evacuation of the hematoma is performed with either an endoscope or exoscope. In some cases, a drainage catheter is left in place after the procedure.

Data Supporting MIS for ICH

Mechanical MIS for ICH

Auer et al reported the results of an early pilot trial of 100 patients randomized between mechanical endoscopic evacuation of ICH and medical management. The surgical goal of this study was to achieve partial evacuation, with most patients achieving 50% to 70% reduction of hematoma volume after the procedure. The study demonstrated the feasibility and general safety of this approach. Lower mortality rates at 6 months were observed in the MIS group (30% with MIS versus 70% with medical management). Although better functional outcomes were not observed throughout the entire cohort, in patients with smaller hemorrhages (<50 cm³), functional outcomes were improved after MIS. In addition, no analyzable subgroup in the study performed better with medical management than MIS.

A larger study evaluating a second, primarily mechanical, evacuation method of MIS for ICH was reported by Kim et al. In this trial, 387 patients with small (<30 cm³) basal ganglia or thalamic hematomas were randomized to either MIS using an Archimedes aspirator or to medical management. If a residual hemorrhage of >10 cm³ was observed after the evacuation, the operator could elect to place a drain and irrigate it with a lytic solution. Patients treated with MIS demonstrated better functional outcomes with lower average modified Rankin scale (mRS) scores at 180 days (1.2 after MIS versus 3.0 after medical management) and higher average Barthel scores (90.9 versus 62.4) at 180 days.

Pharmacologically Based MIS for ICH

Wang et al conducted a randomized, controlled MIS trial in 377 patients with relatively small (25–40 cm³) basal ganglia hemorrhages. Patients were allocated to undergo either computed tomography (CT)-guided craniopuncture with aspiration followed by 3 to 5 days of lytic infusion or medical management. The MIS resulted in a substantial reduction in dependence at 90 days, which was observed in 40.9% of patients versus 64% of those undergoing medical management (P<0.01). The procedure had no effect on mortality.

The Minimally Invasive Surgery Plus Tissue-Type Plasminogen Activator for ICH Evacuation (MISTIE II) trial was a phase II, randomized, controlled trial which included 123 patients randomized (2:1) between pharmacologically based MIS and medical management. In patients randomized to MIS, catheter irrigation with tissue-type plasminogen activator (tPA) was allowed for ≤4 days. MIS led to a significant reduction in peri-hematoma edema volume at the end of treatment. Moreover, a 14% absolute reduction in the percentage of patients with mRS score >3 was reported for those with 1-year follow-up. Patients undergoing MIS also demonstrated greater gains in mobility and activities of daily living scores on the Stroke Impact Scale, with the majority of improvement seen between 180 and 365 days. Patients undergoing MIS also had a shorter overall length of stay and reduced hospital costs. End of treatment hemorrhage volumes were shown to correlate closely with the clinical status at 180 days.

Meta-Analyses of MIS Trials

Gregson et al presented a meta-analysis of 14 ICH surgical trials including 2186 patients. This analysis included both conventional surgical trials and MIS trials. The authors concluded that there was evidence of benefit for surgery in patients randomized within 8 hours of ictus with hemorrhage volumes between 20 and 50 cm³ and in patients between 50 and 69 years of age. Interestingly, the aggregate data in each of the cohorts demonstrating benefit were heavily influenced by the aforementioned Wang et al data set, which ultimately drove the overall signal. So although most of the open surgical trials did not show a definitive benefit for intervention, the Wang...
et al MIS data set was sufficiently positive to influence the overall conclusion.

Zhou et al compiled a meta-analysis of 12 high-quality trials of MIS for ICH which enrolled 1855 patients collectively. These authors reported a highly significant reduction in the end points of both death and dependence and death alone at the end of study follow-up. They determined that ICH patients with smaller hemorrhages (25–40 cm³) and good presenting clinical status (Glasgow Coma Scale ≥9) were the most likely to benefit from MIS.

Thus, several small to moderate-sized trials of MIS have yielded encouraging results, particularly in patients with smaller hemorrhage volumes involving the basal ganglia and also those with better presenting clinical status. The influence of these data on clinical practice varies worldwide. Although MIS for ICH is a routine clinical procedure in the Far East, with over 150,000 cases being performed per year, it is much less common in North America and Europe. The current American Heart Association guidelines provide a Class IIb, Level of evidence B recommendation for the minimally invasive surgical treatment of ICH.

New MIS Technologies for ICH Evacuation

Several new minimally invasive technologies are being developed specifically for the evacuation of ICH. These technologies are designed to maximize the efficiency of hemorrhage removal through the lowest profile system possible, thus minimizing any injury to adjacent tissue. The 2 most frequently applied technologies are the NICO devices (Indianapolis, IN) and the Apollo System (Penumbra Inc, Alameda, CA).

NICO manufactures 2 devices used for ICH removal (Figure 1)—the Myriad Handpiece and the BrainPath sheath. The NICO Myriad handpiece (NICO Corporation, Indianapolis, IN) is cleared by the United States Food and Drug Administration for the morcellation and removal of tissue during pelviscopic, laparoscopic, percutaneous, and open surgical procedures whenever access to the surgical site is limited. The NICO BrainPath (NICO Corporation, Indianapolis, IN) is cleared by the United States Food and Drug Administration to provide access to and allow for visualization of the surgical field during brain and spinal surgery. It consists of a 13.5 mm access sheath, an internal obturator designed to minimize damage to the underlying white matter tracts during placement. The BrainPath is placed through a small (≈20 mm) craniotomy with the NICO BrainPath endoport. They reported an average reduction in hemorrhage volume of 87%. Three patients

The sheath is stereotactically placed into the distal aspect of the clot, typically along the longest axis of the hematoma. Once the sheath is in place, the obturator is removed, and the hemorrhage can be resected either with traditional surgical tools (including standard suction catheters) or with the Myriad handpiece. The Myriad handpiece has an aspiration mechanism that pulls tissue into a small side aperture where it is then morsealized by a reciprocating cutting blade. The surgeon can control the aspiration level and activate the cutter using a foot pedal. Visualization is achieved through an exoscope that is placed over the sheath in a coaxial fashion. After the procedure, a post-op CT study is done to confirm adequate evacuation of the hematoma (Figure 2).

The Apollo System (Figure 3) received Food and Drug Administration clearance for the evacuation of tissue and fluid from the ventricular system in 2014. Since approval, the system has been used clinically for the evacuation of both ventricular and cerebral hemorrhages (off-label). In March of 2016, the clearance for the Apollo System was expanded with the current labeling: device is a nonclogging aspiration–irrigation system which allows the removal of hemorrhagic products through a low-profile (2.1 or 2.6 mm diameter) wand for the controlled aspiration of soft tissue and fluid during surgery of the ventricular system or cerebrum. A vibrational element housed within the wand vibrates at high frequency to break down the hemorrhagic products inside of the wand and prevent clogging. No energy is transferred to the tissue outside of the device. The 2 wand sizes fit through the working channels of commercially available endoscopes, and the hemorrhage evacuation is performed under continuous endoscopic visualization. The entire procedure may be performed through a standard endoscopic sheath (19–20 French) that is positioned in the distal third of the hemorrhage, along its long axis, under stereotactic guidance (Figure 4). The cranial access for the case is typically a burr hole; however, a mini craniotomy can also be performed. The dural incision need only be large enough to accommodate the sheath diameter (≈7 mm). Intraoperative cross-sectional CT imaging (cone-beam CT or portable conventional CT) immediately after the evacuation is advantageous for the active monitoring of the status of the hemorrhage evacuation. Alternatively, burr hole ultrasound may be used.

Existing Data on New Technologies

No published randomized controlled trial (RCT) data are available for either of these technologies.

Przybylowski et al presented a series of 11 patients treated with the NICO BrainPath endoport. They reported an average reduction in hemorrhage volume of 87%. Three patients

Figure 1. A. NICO BrainPath System consists of a 13.5 sheath with an internal dilator. The dilator–sheath systems are available in 75, 60, and 50 mm lengths (with both standard [blue] and short-tipped [gold] dilators available in the 50 mm length). B. NICO myriad handpiece is designed for use through the BrainPath sheath. The device is a low-profile, side-port cutter with aspiration. Material is aspirated into the side port and then sheared by a reciprocating blade mechanism. The morsealized material is then aspirated through the device tubing and into a peripheral collecting chamber.
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(27%) in this series experienced postoperative complications, including one fatal rehemorrhage.21 Labib et al presented a retrospective series of 35 ICH patients treated with the BrainPath system from 10 centers. In 3 quarters of the patients treated, the authors reported achieving ≥90% hemorrhage evacuation by volume. Thus, both of the existing case series have shown the feasibility of the system in achieving a substantial evacuation of hemorrhagic products.23

The feasibility of the Apollo System for the removal of ICH has similarly been demonstrated in initial case reports.22,24 Spiotta et al reported a retrospective analysis of 29 patients with ICH treated with the Apollo system at 4 centers. The authors reported a mean reduction in hemorrhage volume of 54%, with 2 procedural complications.23

Although direct comparisons between the 2 techniques are not possible at this point, the BrainPath system in general seems to facilitate a more complete and aggressive removal of blood products and tissue, albeit through a considerably larger access port (13.5 mm versus 6.3 mm). More clinical data will be required to determine what extent of hematoma removal is required to effect a clinical improvement and whether the drawbacks of larger access are offset by the ability to achieve a more complete evacuation of blood products.

Future Directions

Although existing data have been encouraging, a more definitive evaluation of the existing MIS techniques is required within the context of RCTs. MISTIE III is a 500-patient, phase III RCT comparing MIS plus tPA with medical management. The primary efficacy end point is an improvement in clinical outcome (mRS score ≤3) at 180 days. The study was initiated in December 2013 and is expected to be complete by September 2018.

The Minimally Invasive Endoscopic Surgical Treatment With Apollo Versus Medical Management for Supratentorial ICH (INVEST) trial is a phase II trial which will compare MIS with the Apollo system and medical management in 222 patients with moderate to large (30–80 cm³) spontaneous supratentorial hemorrhages. The study will initiate enrollment early in 2016. The NICO BrainPath System will also be studied in a prospective trial, which is scheduled to begin enrollment in 2016. Details of the trial design have not yet been publically disclosed.

Data from these trials will considerably advance our understanding of the role of MIS for the management of ICH in the coming years.

Intraventricular Hemorrhage

IVH is most frequently related to trauma or the rupture of an underlying vascular lesion (eg, an aneurysm or arteriovenous malformation). Spontaneous IVH usually results from extension of deep parenchymal, typically hypertensive, hemorrhage into the ventricular system, but sometimes may be seen as an isolated occurrence either without an identifiable cause (ie, idiopathic) or in the setting of an inherent or drug-induced coagulopathy.26

As discussed earlier, when observed within the setting of a spontaneous ICH, the finding of an associated IVH substantially worsens the prognosis.26–28 The volume of IVH has been independently correlated with clinical outcome after ICH.27,29

Mechanisms of Injury in IVH

The initial injury caused by IVH is caused by acute obstructive hydrocephalus, an abrupt elevation in intracranial pressure and reduced global cerebral perfusion. These issues may be addressed initially with the placement of an external ventricular drain (EVD).30,31 However, there are several mechanisms of secondary injury by which IVH may exacerbate the acute injury associated with the hemorrhage and reduce the odds of achieving a good functional outcome. First, as with ICH, massive IVH has the capacity to induce local mass effect and potentially reduce regional perfusion, creating dysfunction and ultimately ischemic injury to the brain adjacent to the ventricular system.32,33 Second, as with ICH, the hemotoxicity associated with the blood breakdown products may induce secondary brain injury in the days and weeks after IVH.34–37 Third, blood products within the ventricular system have the capacity to induce long-term impairment in the function of normal cerebrospinal fluid absorption mechanisms, resulting in chronic hydrocephalus, requiring treatment with an indwelling permanent shunt.38,39

Minimally Invasive Surgical Evacuation of IVH

The application of MIS for IVH is based on the hypothesis that a reduction in the overall IVH volume and the restoration of normal physiological CSF drainage pathways will mitigate these secondary mechanisms of injury. As with ICH, there are 2 general approaches to IVH, one being primarily or exclusively pharmacological catheter–based and the others being mechanically based. The pharmacologically based mechanisms involve the administration of lytic medications (urokinase or tPA) through conventional indwelling EVDs which have been placed for the management of the initial hemorrhage.40 The mechanically based mechanisms involve the direct evacuation of IVH under endoscopic visualization, either using the endoscope itself or an adjunctive device.26 In most IVH patients, the placement of an EVD represents standard treatment, for this reason, the administration of a lytic agent through an in situ catheter represents a minimal extension of the standard
care already being delivered. However, the disadvantages of this method include the potential for lytic-induced expansion of the original hemorrhage, infection from repeated access of the EVD catheter, the prolonged period of time (typically 2–4 days) required for adequate clearance of blood products, and potentially the failure of the technique to achieve a substantial reduction in IVH volume in some patients.41 The mechanically based methods have the disadvantage of being more invasive and requiring a larger profile access than a standard EVD. Also, MIS constitutes a second surgical procedure (beyond the initial EVD placement), which would not be required for a pharmacologically based approach. On the contrary, MIS offers the potential for an immediate and substantial reduction in IVH without the requirement for lytic medications.

Data Supporting MIS for IVH

Until the recent presentation of the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III) trial results, no large randomized, controlled trial data were available for either pharmacologically based or mechanically based treatments for IVH.42 Encouraging data from several smaller studies had supported some clinical application of these technologies to remove IVH and formed a foundation for the subsequent pivotal CLEAR III trial.

Pharmacologically Based IVH Treatment

Recently, the initial data regarding the safety and efficacy of intra-thecal tPA in the setting of IVH became available for the CLEAR III trial.42 In this pivotal trial, patients with small or no ICH (≤30 cm³) with associated IVH requiring an EVD were randomized to either placebo (normal saline) or t-PA (1.0 mg) q8 hours (for ≤12 doses) infused through the EVD. The primary outcome measure was mRS at 180 days. The trial demonstrated that although intraventricular-tPA had no effect on clinical outcomes in the entire cohort, there was a significant (10%) reduction in mortality at 180 days. In the subset of patients with IVH volumes >20 cm³,
intraventricular-tPA significantly improved rates of good functional outcome (mRS score 0–3). More efficient and more complete (>80%) removal of IVH were directly correlated with patient outcomes. However, most patients (>70%) did not achieve a substantial (>80%) reduction in IVH with the CLEAR III tPA infusion technique.

This pivotal trial was predicated on encouraging results from a phase II trial which enrolled 48 IVH patients who were similarly randomized to receive either intraventricular-tPA or placebo through indwelling EVDs. In this phase II trial, tPA administration significantly increased the rate of clearance of IVH. In CLEAR IVH, the authors also reported a signal toward improved clinical outcomes at 30 days, as well as a close correlation between the rate of IVH resolution and early clinical improvement. Of note, these signals toward clinical improvement with tPA administration were observed despite a 23% rate of symptomatic bleeding events in the tPA group (versus only 5% in the control arm).40

Several smaller randomized and observational studies of transcatheter-based lytic studies in IVH were evaluated in a meta-analysis performed by Gaberel et al41 of 316 IVH patients from 12 high-quality studies. These authors reported substantial benefit for lytics on both mortality (47.6% in the EVD-only cohort versus 22.7% with lytic therapy; odds ratio 0.32, confidence interval 0.19–0.52) and good functional outcome at ≥3 months (54% in lytic group versus 34% in the EVD-only cohort) without an associated increase in either bleeding complications or ventricular infections. An absolute reduction in the incidence of shunt-dependent hydrocephalus was observed with lytic therapy (13% versus 18.2%); however, this observation failed to meet significance.

Mechanically Based MIS for IVH
Several small case series and individual case reports have demonstrated the feasibility of endoscopic MIS for the treatment of IVH using both rigid and flexible endoscopy systems. However, only 2 small, prospective, RCTs evaluating endoscopic MIS are available to date.42,43

Chen et al reported results on a population of 48 patients with thalamic hemorrhage and IVH, who were randomized 1:1 between either endoscopic-guided suction evacuation of IVH followed by EVD placement or EVD placement alone. In the endoscopic procedure, a standard suction tube was placed side-by-side with an endoscope through a rigid sheath to achieve evacuation of blood products from the ventricular system ipsilateral to the thalamic hemorrhage. These investigators reported a significant reduction in the mean length of intensive care unit stay in the MIS group (11 days versus 18 days; P=0.04) and a marked reduction in the rates of shunt-dependent hydrocephalus in the MIS group (48% after MIS versus 98% in the EVD alone group; P=0.002). However, mortality rates and Glasgow Outcome Scores were similar in both the cohorts.43

Zhang et al randomized 44 patients (1:1) to either endoscopic IVH evacuation or EVD alone. In the endoscopic group, EVDs were placed after the procedure, and if IVH volumes remained ≥10 cm³, a urokinase solution was infused through the ventricular drain. In patients allocated to receive an EVD alone, a lytic solution was also administered through the drain. These authors observed that more patients in the neuroendoscopy group had higher rates of favorable Glasgow Outcome Scores at 2 months (P<0.05), but they failed to observe any improvement in the overall mortality rate.

In summary, the available data supports the feasibility of mechanically based techniques to effectively remove IVH. Although they suggest the potential for improved neurological outcome in some patients, additional data are needed.

New Technologies for IVH Evacuation
The Apollo System, in 2014, was cleared by the US Food and Drug Administration for the controlled aspiration of soft tissue and fluid during endoscopically guided neurosurgery of the ventricular system. Its use for the treatment of IVH represents an on-label application, and it has been implemented for this purpose commercially in the United States for just over 1 year. Currently, there are no available clinical studies describing either the safety or efficacy of the system in the setting of IVH. However, conceptually, the Apollo system may provide a significant advantage over existing simple suction catheters, which are prone to clogging with tenacious blood products during these procedures. A retrospective multicenter case series describing the technical feasibility and providing a preliminary safety assessment of the Apollo System for the evacuation of IVH is anticipated.

Future Directions
The current American Heart Association guidelines report a Class IIb, Level of evidence B categorization for interventional approaches to IVH treatment; however, this may be revised after the publication of the CLEAR III data.2 The CLEAR III data demonstrate great promise for techniques which are able to achieve a reliable, safe, efficient, and substantial reduction of IVH volume to improve functional outcomes in IVH patients. The CLEAR III investigators have proposed a CLEAR IV trial, which will look at a more refined technique for intraventricular-tPA administration. The role for mechanical devices in the minimally invasive evacuation of IVH remains to be defined. Given that the CLEAR III technique was successful in removing >80% of IVH volume in only a minority of patients over 4 days of treatment, such alternate approaches certainly merit consideration. Although the potential of mechanical devices, like Apollo, to reproducibly and quickly evacuate large volume IVHs is intriguing, RCTs will be important to define their effectiveness in improving outcomes in IVH patients.

Summary
ICH, particularly when associated with IVH, remains a common and devastating disease, resulting in either death or permanent disability in most patients affected. To date, no neurosurgical interventions have been definitively shown to improve outcomes for ICH patients. However, encouraging data are emerging to indicate that MIS may reduce the secondary injury after both ICH and IVH and, thereby, potentially reduce both mortality and dependence. Currently, trials are underway evaluating several new minimally invasive approaches for ICH and IVH evacuation, and much more definitive evidence is expected in the near future.
Disclosures
Dr Fiorella receives research funding from Microvention, Sequent Medical, and Penumbra, serves as a consultant for Microvention, Medtronic, Sequent, Codman Neurovascular, and Penumbra; Dr Arthur serves as a consultant for Penumbra and Stryker; Dr Bain is a consultant for NICO; Dr Mocco has ownership interest in Blockade Medical and Lazarus Effect and serves as a consultant to Lazarus Effect, Reverse Medical, Pulsar, Edge Therapeutics, and Medina.

References


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In the article by Fiorella et al (Fiorella D, Arthur A, Bain M, Mocco J. Minimally invasive surgery for intracerebral and intraventricular hemorrhage: rationale, review of existing data and emerging technologies. Stroke. 2016;47:1399–1406. DOI: 10.1161/STROKEAHA.115.011415.), which published online on April 5, 2016, and appeared in the May 2016 issue of the journal, a correction was needed.

On page 1399, in the title, “Minimally invasive surgery for intracerebral hemorrhage: rationale, review of existing data and emerging technologies,” has been changed to read “Minimally invasive surgery for intracerebral and intraventricular hemorrhage: rationale, review of existing data and emerging technologies.”

This correction has been made to the online and print version of the article, which is available at http://stroke.ahajournals.org/content/47/5/1399.
微创手术治疗脑出血和脑室内出血
合理性、目前治疗综述和新技术

Minimally Invasive Surgery for Intracerebral and Intraventricular Hemorrhage
Rationale, Review of Existing Data and Emerging Technologies

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自发性脑出血（spontaneous intracerebral hemorrhage, ICH）是最常见的出血性卒中，发病率大约是蛛网膜下腔出血的四倍，约占所有卒中发病率的 15%。ICH 的发病率和死亡率都超过所有其他类型的卒中亚型。总计，ICH 的死亡率估计高达 40% ~ 50%，并且大多数存活者在半年内仍然瘫痪。当 ICH 与脑室内出血（intraventricular hemorrhage, IVH）相加统计时，结果更加严重，估计死亡率将达到 50% ~ 80%。

目前的标准建议小脑出血（直径）> 3 cm 伴随相关神经功能缺损或者明显占位效应的需要紧急手术减压。与之类似，幕上出血以及伴有脑疝征象时则需要经常采取手术减压，可予血肿评估或者不予评估。不属于上述 2 种情况下的 ICH 患者，绝大多数情况下仅需要药物治疗。

ICH 传统外科手术评价
ICH 患者外科手术获益是基于假定手术避免或者减轻了 ICH 后第二波损伤。2 个大型外科临床试验探究了这一治疗策略。ICH 外科治疗试验（Surgical Trial in Intracerebral Hemorrhage, STICH）I 是一个多中心、随机、对照试验，包含了 1033 个中等量幕上 ICH（平均 40 cm³）患者，采用早期外科干预与内科保守治疗相对照（在 24 h 内随机化分组）。结果显示，外科治疗和内科保守治疗的结果几乎完全相同，这个乐观的结果来自 26% 的患者采取外科干预，24% 患者采取内科保守治疗。亚组分析结果提示，浅表部位的 ICH（皮层下 1 cm）可从外科治疗中潜在获益。这些数据导致了 STICH II 的研究开展，也是个多中心、随机、对照试验，包含了超过 600 例清醒的 ICH 患者，出血部位在浅表部位（皮层下 1 cm 范围内）脑叶出血不伴有相关 IVH。这个研究结果也表明，ICH 外科清理血肿手术并不优于内科保守治疗。在 2 组患者中可观察到 40% 患者治疗结果乐观。

ICH 的损伤机制
ICH 根据解剖位置不同一般分为 2 大类：深部（包括深部灰质核团）和脑叶。脑叶出血通常是由高血压导致，而脑叶出血则大多数是由高血压或者病理性淀粉样变性导致。任何一种类型的 ICH 都可能由内源性或者药物性的凝血机制障碍导致或者加重。

ICH 导致的脑损伤是一个双相过程。最初的出血断了正常的脑实质，直接对临近的神经元造成了创伤。虽然某些神经元在这个过程中发生了非可逆性损伤，但是其他的神经元可能只是受到挤压、发生了移位，或者只是短暂的功能异常，如果出血停止的话，那么在出血后的几小时内，这个局部的压迫效应可能会消散，并且可以观察到不同程度的早期临床改善。晚期的脑损伤通常与最初出血量的扩大相关。大约有 1/4 ~ 1/3 的患者会在这次早期临床症状的恶化。

第二阶段的损伤表现为血肿周围水肿（包括血管源性和细胞源性水肿），它紧随 ICH 发生。这种水肿周围水肿的出现要归因于 2 个原因。第一，它假设来自血肿区域的脑区的压力限制了局灶的灌注，造成缺血性损伤，但是支持这一机制的证据有限。另一方面，现有的正电子发射计算机断层显像 (positron emission tomography, PET) 资料提示来自血肿周围水肿区域的氧代谢减低程度并没有严重到导致硬的死的损伤。第二，临床前期数据显示 ICH 后的血肿代谢产物对大脑有直接毒性作用，即血液毒性概念。这种血液毒性可诱导血肿临近脑组织发生水肿，并且在 ICH 数天后因为血肿变化导致临床表现迟迟性恶化。这个过程可在 ICH 发病后 3 周观察到。而且，出血导致的脑水肿持续时间远远长于急性缺血性卒中引起的脑水肿，最严重的情况脑水肿可长达 10 ~ 20 d。因此，这 2 种二次损伤的生理机制可能会延长 ICH 引起的初次损伤持续时间，有时可导致复发性脑水肿恶化。这就延长了病情恢复时间，同时也潜在性降低了患者神经功能恢复的程度。

ICH 的 MIS 微创血肿清除术
ICH 的 MIS 微创血肿清除术相对于 ICH 的开颅血肿清除术，目前尚无已结束的确定的试验来评估微创手术对颅内血肿的效应。但是，几个小型实验已经得出令人振奋的证据。而且，不断出现的新技术手段也使得微创手术成为颅内血肿清除的治疗手段。
ICH 血肿清除的方法

通常 ICH 血肿清除的 MIS 有 2 种方式——一种是主要基于药物导管的，另一种是基于器械的。第一种通常包括在影像引导下放置一个引流管，之后使用一种血肿溶解药物通过导管注入，防止血液凝固，并且利于血肿的被动引流。这就需要连续几天放置原位导管，并且间歇性影像学检查以确保导管位置稳定，同时监测引流的进展情况。第二种，血肿清除术的机械方法是指一步到位的血肿移除。通常血肿清除术可使用内窥镜或者外视镜。在某些病例中，血肿清除术后需要继续放置引流管。

ICH 的 MIS 的支持数据

ICH 的 MIS 机制

Auer 等报道了一个 100 例 ICH 患者的临床早期预实验结果。该试验在 100 例患者中随机采用机械内窥镜血肿清除或者药物保守治疗方法。该试验的手术目的是为了达到部分血肿的清除，大多数患者术后血肿体积可减少 50%～70%。该研究显示了这个方法的便利性和安全性。在 MIS 组观察到了在第 6 个月时间点更低的死亡率（MIS 组是 30% vs 药物治疗组 70%）。在所有队列研究中并未观察到更好的功能改善，但是在那些血肿体积小于 50 cm³的患者中，MIS 术后的确获得了功能改善。亚组分析表明药物治疗组并不优于 MIS 治疗组。

Kim 等报道了一个更大规模的研究，评价第二种机械方法的 MIS 对 ICH 的效果。该试验纳入 387 例基底节或者丘脑出血（血肿体积小于 50 cm³）患者，随机分配到使用 Archimedes 吸引器治疗组或者药物治疗组。如果清除术后残余血肿大于 10 cm³，手术者可在颅内放置引流管并且注射裂解酶。接受 MIS 治疗的 ICH 患者可获得更好的功能改善，在术后 180 d 更低的改良 Rankin 量表（modified Rankin Scale, mRS）评分（MIS 组 1.2 分 vs 药物治疗组 3.0 分）以及更高的 Barthel 评分（MIS 组 90.9 分 vs 药物治疗组 62.4 分）。

ICH 的基于药物的 MIS 治疗

Wang 等进行了一项随机对照试验，纳入 377 例基底节出血量小于 25~40 cm³的患者。患者被随机分配到 MIS 组，进行计算机断层扫描（computed tomography, CT）引导下锥颅穿刺抽吸并在之后 3~5 d 注射裂解酶组或者药物治疗组。结果显示，MIS 组在术后第 90 天显示患者（生活）依赖性大幅降低，MIS 组 40.9% 的患者 vs 药物治疗组 64% 的患者，与药物治疗组相比差异有显著性（P<0.01）。微创手术加组织型纤溶酶原激活物对于 ICH 血肿清除的研究（Minimally Invasive Surgery Plus Tissue-Type Plasminogen Activator for ICH Evacuation, MISTIE II）是一项 II 期、随机对照试验，纳入 123 例患者随机（2:1）分配到药物治疗组和药物治疗组。MIS 组予导管置入并且注射重组型组织型纤溶酶原激活剂（tissue-type plasminogen Activator, tPA），时间不超过 4 d。结果提示，在治疗结束时 MIS 治疗可明显减少血肿周围水肿体积。而且随访 1 年后结果提示，MIS 治疗可使 mRS 评分 >3 的患者比例下降 14%。经过 MIS 治疗的患者在卒中影响量表（Stroke Impact Scale, SIS）中的活动能力和日常活动评分更高，这种改善在 180~365 d 之间最明显。同时接受 MIS 治疗的患者住院花费更少，住院时间也更短。

MIS 试验的 Meta 分析

Gregson 等报道了一项共纳入 2386 例患者的 14 个 ICH 外科治疗试验的 meta 分析。这项分析既包括传统外科试验也包括 MIS 试验。作者总结：有证据表明在 8 h 内 20~50 cm³出血量最高峰以及 50~69 岁的随机纳入的患者可受益于外科手术治疗。有趣的是，在每个队列研究的整合数据显示，患者的受益程度严重受到前述的 Wang 等人的数据包影响，而且最终影响了全部信息。因此，虽然大多数外科手术试验并未显示其对 ICH 治疗有明确的获益，但是 Wang 等人的数据包已经可以对整个结论产生足够正面的影响。

Zhou 等编译了一项包含 12 个高质量 MIS 干预 ICH 的外科试验的 meta 分析，总共纳入 1855 例患者。这些作者提到，在研究的随访终点，MIS 可以极其显著的降低患者死亡与依赖度和单纯死亡率。他们认为，那些出血量在 25~40 cm³并且临床情况表现良好 [Glasgow 昏迷量表评分 (Glasgow Coma Scale, GCS) ≥ 9] 的 ICH 患者从 MIS 治疗中获益最大。

因此，几个中小型 MIS 试验已经取得了令人振奋的结果，尤其在那些出血量较小（包括基底节区出血）以及那些临床情况较好的 ICH 患者中。这些数据对临床实践的影响随地域不同而有差异。虽然 ICH 的 MIS 治疗在远东地区是一项常规临床治疗，每年有超过 150000 例 MIS 患者，但是在北美和欧洲 MIS 并不普遍。目前的美国心脏协会（American Heart Association, AHA）指南给出了一个 IIb 的评级，建议 MIS 作为治疗 ICH 的 B 级推荐。
ICH 血肿清除的新型 MIS 技术

目前已发明了几个专门针对 ICH 血肿清除的微创新技术。这些技术的设计目的就是为了通过最低配置文件系统可能性达到最大化血肿清除的效果，同时最小化血肿周围脑组织产生的损伤。其中 2 个最经常使用的技术就是 NICO 设备（Indianapolis, IN）和阿波罗系统（Penumbra Inc, Alameda, CA）。

NICO 公司制造了 2 个设备用于 ICH 血肿清除（图 1）- Myriad 手持器和 Brainpath 套管。NICO Mariad 手持器（NICO 公司, Indianapolis, IN）是经美国食品和药品管理局（the United States Food and Drug Administration, FDA）许可的用于在腹腔镜手术，以及经腹腔、经皮和任何到达手术区域受限的开放性外科手术中分离破碎，并且移除组织的设备。NICO BrainPath（NICO Corporation, Indianapolis, IN）是经美国 FDA 许可的用于在脑和脊髓手术中提供手术接入通路并且可视化手术视野的设备。它包括一个 13.5 mm 的接入套管，一个内部穿刺头，是被设计用来在放置过程中对底盖骨质通路的损伤达到最小化。BrainPath 被放置在带有硬脑膜开孔的小的开颅手术（≈ 20 mm）中，硬脑膜的开口大小只需和设备的直径大小相配就可以了。这种开颅手术可以在磁共振成像下进行，以利于尽可能在创伤最小的情况下达到脑内穿刺。套管被立体定位放置在血凝块的远端，通常与血肿的最长轴平行。一旦套管被放置好，则穿刺头会被移除，使用标准外科手段（包括标准的抽吸导管）或使用 Myriad 手持器将血肿移除。Myriad 手持器有一种抽吸机制，可以将组织拉入一个侧孔，随后组织会被一个来回切割的刀片切割粉碎。手术者可以控制抽吸强度，通过控制脚踏板来激活切割刀片。可视化是通过放置在套管上的一个平行于套管的外视镜做到的。操作完成后，复查一个术后 CT 以确认血肿已被尽可能多的清除掉（图 2）。

2014 年美国 FDA 批准了 Apollo 系统（图 3）用于组织和脑室系统液体的清除。自从被批准后，这个系统就被用于临床脑室和脑实质血肿清除术（使用适应证范围）23,24。2016 年 3 月，Apollo 系统被许可扩展目前的适应证：该设备作为一种非堵塞抽吸 - 灌注系统，允许控制抽吸强度并且通过控制脚踏板来激活切割刀片。可视化是通过放置在套管上的一个平行于套管的外视镜做到的。操作完成，复查一个术后 CT 以确认血肿已被尽可能多的清除掉（图 2）。

目前关于新技术的数据

关于这些新技术，目前尚无公开发表的随机对照试验（randomized controlled trial, RCT）数据。

Przybylowski 等 21 报告了一系列的使用 NICO Brainpath endoport 治疗的 11 个病例。他们的试验结果显示，使用该设备可以平均减少 87% 的出血量。其中 3 例患者（27%）发生了术后并发症，包括一例致命性的再出血。Labib 等 25 报道了一项包含来自 10 个医疗中心的 36 例使用 BrainPath 系统治疗的 ICH 患者的回顾性研究。在经过治疗的 3/4 患者中，作者报告血肿清除体积超过 90%。因此，以上 2 个系列病例报道表明，这个系统在大量血肿清除手术中具有可行性。关于 Apollo 系统在血肿清除术中的可行性，也在最初的病例报告中有所描述。23,24 Spiotta 等 23 报道了一项包含来自 4 个医疗中心的 29 例 ICH 患者使用 Apollo 系统的回顾分析。作者报道，该系统平均可以减少 54% 的血肿体积，出现 2 例手术并发症。

虽然目前不可能对这两种技术优劣直接对比，但是 BrainPath 系统总体上似乎更胜一筹，它可以更完全有力的清除血肿和相关组织，虽然手术创口稍微比另一个系统大了一些（13.5 mm vs 6.3 mm）。血肿清除到什么程度可以达到改善临床症状的目的，较大创口的缺点能否抵消其更完全彻底清除血肿的优点，这些都需要更多的临床资料来证明。

未来方向

虽然目前关于 MIS 新技术的临床数据令人振奋，但仍需要更多的 RCT 试验来评价目前的 MIS 技术。

MISTIE III 是一项纳入了 500 例患者的 III 期 RCT 试验，对比 MIS 加 tPA 和药物治疗效果。主要疗效终点是在第 180 天时临床结果的改善（mRS ≤ 3）。这项研究在 2013 年 12 月启动，计划于 2018 年 9 月结束。

对于幕上 ICH 使用 Apollo 系统进行微创内镜手术治疗对比药物治疗效果的试验（The Minimally Invasive Endoscopic Surgical Treatment With Apollo Versus Medical Management for Supratentorial ICH, INVEST）是一项 II 期试验，共纳入 222 例中到大量自发性幕上 ICH 患者。该研究在 2016 年开始招募志愿者。在一项前瞻性试验中将使用 NICO BrainPath 系统进行研究，该研究计划在 2016 年启动，尚未公开发布研究设计细节。

未来几年来自这些研究的试验数据必将更新我们对 MIS 在治疗 ICH 中的地位的理解。

IVH

IVH 通常与肿瘤或者潜在的血管畸形破裂有关（比如动脉瘤或动静脉畸形）。自发性 IVH 通常是由大型的高血压病导致深部脑实质出血破入脑室系统，但有时也可独立发生，即没有明确病因（特发性），或者有低凝血药物导致的凝血障碍。26

正如之前讨论过的，当有自发性 ICH 发生时，之后或同时发生的 IVH 会严重的影响疾病的预后 26-28。IVH 的出血量并不与 ICH 后的临床症状正相关 27,28。
IVH 的损伤机制

IVH 早期损伤是因为梗阻性脑积水, 导致脑室压力突然升高和全脑灌注减少。这种情况可以用提前放置脑室外引流管 (external ventricular Drain, EVD) 的方法来处理。但是 IVH 引起的二次损伤可能会加剧出血引起的急性损伤，并且降低患者将来良好功能恢复的几率。首先, 与 ICH 一样, 大量的 IVH 可以引起局部占位效应, 严重降低局部脑区灌注量, 从而导致功能障碍, 最终引起脑室系统旁的脑区缺血性损伤。其次, 与 ICH 一样, 血肿分解时的毒性代谢产物也会在 IVH 数天和数周后引起二次损伤。第三, 脑室系统内的血肿分解产物可引起正常脑脊液吸收机制的长期受损, 导致慢性脑积水, 必须永久性留置分流治疗。

IVH 的微创外科血肿清除

IVH 的 MIS 治疗是基于下列假说, 即整体 IVH 血肿体积的减少和正常生理化脑脊液 (cerebral spinal fluid, CSF) 引流通路的恢复将会减轻二次损伤, 和 ICH 一样, 通常有 2 种 IVH 治疗方法。一种是主要或者仅以药物加微创导管治疗, 另一种是机械清除。前者包括在出血位置留置传统的 EVDs 并注入血肿裂解药物 (尿激酶或 tPA)。后者是指在可视化内镜下直接清除 IVH 血肿, 包括内窥镜本身或者辅助设备。在大部分 IVH 患者中, 放置 EVD 是一项标准治疗手段, 因此, 使用这种原位放置导管注入溶解药物的方法治疗, 只能得到标准治疗区域最低程度的扩大。同时, 这种治疗的缺点就是清解药物引起的原发血肿的扩大, 反复放置 EVD 导管引起的感染, 充分消除血肿时间的延长, 以及在某些患者中因可能操作失败引起清除 IVH 血肿体积大量减少。机械清除血肿的方法缺点是创伤更大, 和标准 EVD 相比需要更大的有创性手术通路。同时, MIS 构成了手术的第二步骤 (除了放置 EVD 之外), 它并不需要注入药物。相反, MIS 提供了一种并不需要依赖溶解药物就可以迅速有效的清除 IVH 血肿的潜在治疗方法。

支持 MIS 治疗 IVH 的数据

目前尚无大型随机、对照试验数据证明关于对 IVH 的 2 种治疗孰优孰劣, 即基于药物或者基于机械方法清除血肿, 直到最近出现的关于“血肿溶解”的报告: 对脑室内出血的加速溶解方法的第三阶段 试验 (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III, CLEAR III) 的评价得出了结果。来自几个小型研究的数据令人振奋, 研究结果支持在临床清除 IVH 血肿时应用这些新技术, 并且为随后的 CLEAR III 试验打下了基础。

基于药物清除血肿的 IVH 治疗

最近 CLEAR III 试验得出了关于套管管内注射 tPA 溶解 IVH 血肿的安全有效性的初始数据。在这个关键试验中, 研究者分别对不同量的 IVH(≤ 30 cm£¡) 患者随机分配到安慰剂组 (普通生理盐水) 或 tPA (1.0 mg) 组, 每 8 h (≤ 12 次) 通过 EVD 注射一次。主要结果衡量指标是第 180 天时点的 mRS。该试验结果表明, 虽然脑室内注射 tPA 对整个队列研究组中的临床结果没有影响, 但是第 180 天时间点的死亡率显著降低了 10%。在 IVH 出血量 >20 cm £¡的亚组患者中, 脑室内注射 tPA 显著改善功能评分结果 (mRS 评分 0 ~ 3 分)。IVH 血肿清除的有效性与常规治疗 (>80%), 直接与患者预后相关。但是大部分在 CLEAR III tPA 注射组的患者 ( ≈ 70%) 并没有得到 IVH 血肿的大量 (≥ 80%) 清除。

其实从纳入 48 例 IVH 患者并发有类似相似分组 II 期试验就已经预示到了 III 期试验的结果令人鼓舞。在 II 期试验中, tPA 治疗组显著提高了 IVH 血肿的清除率。在 CLEAR IVH 研究中, 作者也报道了在第 30 天时间点上的一个倾向改善的临床结果的信息, 以及 IVH 血肿溶解率与早期临床改善密切相关。注意, 虽然研究并得到了使用 tPA 改善临床症状的信息, 在 tPA 组仍有 23% 的症状性出血事件 ( vs 在对照组仅 5%)。Gaberel 等进行了一项 meta 分析, 包括几十例 IVH 套管管内注射溶血酶治疗的随机观察性试验, 包含 316 名来自 12 个高质量研究的 IVH 患者。这些作者报道了溶血酶治疗的重大获益, 分别在死亡率 [EVD 治疗组 47.6% vs 溶血酶治疗组 22.7%; 比值比 (odds ratio, OR) 0.32, 可信区间 0.19~0.52] 和 3 个月之后的良好功能结局 (溶血酶治疗组 54% vs EVD 治疗组 24% ) 方面, 而没有相关出血并发症或者脑室感染率的升高。溶血酶治疗组的分流依赖性脑积水的发生率发生了下降 (13% vs 18.2%); 但是这项结果差异并无显著性。
大部分患者可致死亡或者永久性瘫痪。目前为止，并没有神经外科干预手段可明确有效的改善ICH患者的临床结局。但是，令人鼓舞的是目前有数据表明，MIS可能也会减少ICH和IVH的二次损伤，进而使在性减少患者死亡率和生活依赖性。目前正在进行几项试验，评价ICH和IVH血肿清除术的几种微创治疗新方法，在不久的将来会得出更多确定性依据。

IVH血肿清除的新技术

2014年，美国FDA通过了Apollo系统的应用，在内窥镜指导下的脑室系统的神经外科手术中，有控制的抽吸软组织和液体。Apollo系统用于治疗IVH是符合器械适应证范围内的，而且在美国已经上市并临床使用了1年。目前尚无关于IVH治疗的安全有效性的临床研究数据，但是从理论上说，Apollo系统显著优于目前简单的抽吸导管器。

未来的方向

目前AHA指南报道了一个ICH介入治疗方法的IIb级，B等证据，然而，在CLEAR III研究数据发表后这个评级将被修正。CLEAR III研究数据显示这些技术将对ICH患者的血肿清除具有可靠安全有效，可成功清除>80%的IVH血肿体积，仍要考虑这种替代性的治疗方法作用仍欠明晰。即使CLEAR III技术在4d的治疗中只是在少数患者可成功清除>80%的IVH血肿体积，仍要考虑这种替代性的治疗方法的某些优点。虽然这样的机械性设备可以多次重复的快速清除IVH的大量血肿，比如Apollo系统，应用前景诱人，但是RCTs仍然是重要的方法，用以明确这些设备是否可有效改善ICH患者的结局。