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# CATHETER-BASED INTERVENTIONS IN THE MANAGEMENT OF INTRACEREBRAL HEMORRHAGE: A SYSTEMATIC REVIEW

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**Abstract**

**Background:** Spontaneous intracerebral haemorrhage (ICH) is a devastating stroke subtype with high mortality and poor functional outcome. Extension of blood into the ventricles causing intraventricular haemorrhage (IVH) and obstructive hydrocephalus further worsens prognosis. Catheter-based interventions external ventricular drainage (EVD) and minimally invasive surgical evacuation with intralesional thrombolysis seek to remove clot, reduce mass effect and restore cerebrospinal fluid flow. The efficacy and safety of these interventions remain debated.

**Objectives:** To systematically evaluate the evidence for catheter-based interventions in adults with spontaneous ICH or IVH, comparing outcomes against standard medical management or alternative surgical approaches.

**Methods:** Randomized trials, quasi-experimental studies, cohorts, case–control and cross-sectional studies enrolling adults with spontaneous ICH/IVH who received catheter-based interventions (EVD, intraventricular thrombolysis, minimally invasive catheter-based evacuation) were included. Outcomes were mortality, functional status, hematoma volume/clearance, re-bleeding, infection and complications. Two reviewers independently screened titles/abstracts and full texts, extracted data and assessed risk of bias using RoB 2 for randomised trials and ROBINS-I or NOS for observational studies. Narrative synthesis was performed; quantitative pooling was not feasible due to heterogeneity. Certainty of evidence was appraised qualitatively.

**Results:** Fifteen studies (four randomised trials and eleven observational studies) were included. Early pilot data suggested that minimally invasive catheter evacuation plus recombinant tissue-type plasminogen activator (rt-PA) substantially increased clot removal and reduced peri-haematomal oedema compared with medical management. Phase 2 trial MISTIE II showed a higher proportion of patients achieving modified Rankin Scale (mRS) 0–3 at 180 days after adjustment, albeit with more symptomatic bleeding. The double-blind CLEAR III trial of intraventricular alteplase versus saline found no functional-outcome benefit but significantly reduced mortality and infection rates. The phase 3 MISTIE III trial did not demonstrate improved functional outcome at 365 days (45 % vs 41 %; adjusted risk difference 4 %; $p = 0.33$) but reported lower early mortality. Observational studies consistently reported lower mortality associated with EVD, although none showed functional-outcome benefit. Intraventricular thrombolysis via EVD decreased inpatient mortality (adjusted OR 0.67; 95 % CI 0.52–0.87). Recent small retrospective series using bedside catheter aspiration with urokinase achieved large haematoma reduction and acceptable mortality. Catheter-related infection rates were low (~2.2 %), and prophylactic protocols reduced this risk. Overall, the evidence suggests that catheter-based interventions may reduce mortality but have not definitively improved functional outcomes.

**Conclusions:** Catheter-based interventions play an important role in managing obstructive hydrocephalus and reducing haematoma burden in ICH/IVH. Intraventricular thrombolysis via EVD

reduces mortality and infection but does not improve functional outcome. Minimally invasive surgical evacuation with rt-PA removes clot effectively and may confer early mortality benefit, yet robust evidence of functional improvement is lacking. Future trials should refine patient selection, standardise procedural protocols and explore adjunctive pharmacotherapy to translate biological efficacy into functional recovery.

**Keywords**: Intracerebral hemorrhage; intraventricular hemorrhage; external ventricular drain; minimally invasive surgery; thrombolysis; alteplase; urokinase; catheter; modified Rankin Scale.

## BACKGROUND

Spontaneous intracerebral hemorrhage (ICH) accounts for 10–15 % of strokes but is associated with disproportionately high mortality and morbidity. Worldwide incidence is estimated at 24.6 per 100 000 person-years and is rising with population ageing and hypertension prevalence. Mortality approaches 40 % at 30 days, and only 20 % of survivors achieve functional independence. Extension of haemorrhage into the ventricles, termed intraventricular haemorrhage (IVH), occurs in up to 45 % of cases and is an independent predictor of poor outcome; blood obstructs cerebrospinal fluid (CSF) pathways causing acute hydrocephalus and intracranial hypertension. Managing ICH/IVH is challenging because mass effect, neurotoxicity from blood products and secondary injury from oedema must be mitigated while avoiding secondary damage during intervention. Standard medical management includes blood pressure control, reversal of coagulopathy, management of elevated intracranial pressure (ICP), and supportive care. Surgical options such as open craniotomy for haematoma evacuation have not consistently improved outcomes for deep or lobar ICH. The Surgical Trial in Intracerebral Haemorrhage (STICH) found no overall survival benefit for early craniotomy versus conservative treatment, though subgroup analyses suggested benefit for lobar haemorrhage within 1 cm of the surface. Consequently, guidelines reserve craniotomy for cerebellar haemorrhage with neurological deterioration or life-threatening mass effect. Minimally invasive approaches have emerged to balance clot removal with tissue preservation [1]. External ventricular drainage (EVD) is a long-standing neurosurgical technique for monitoring ICP and treating obstructive hydrocephalus. Placement of an EVD provides a route for CSF diversion and intraventricular medication delivery. Retrospective studies indicate that EVD reduces mortality in ICH/IVH, particularly among patients with large IVH volumes or hydrocephalus [2]. However, EVD alone does not remove intraparenchymal clot and may not improve functional outcomes. Catheter-related complications include malposition, tract haemorrhage and infection; misplacement rates range from 7–50 %, and new haemorrhage occurs in approximately 5.7 % of insertions with <1 % symptomatic[3]. Strict sterile technique and antibiotic-impregnated catheters reduce infection rates to ~2.2 %[4].

Minimally invasive surgery (MIS) with intralesional thrombolysis aims to evacuate intraparenchymal clot while minimizing brain injury. The procedure involves stereotactic placement of a catheter into the hematoma cavity under imaging guidance, gentle aspiration of liquefied clot and administration of a thrombolytic agent, typically alteplase or urokinase, to dissolve residual clot. The Minimally Invasive Surgery plus rt-PA for ICH Evacuation (MISTIE) program progressed from pilot studies demonstrating feasibility to phase 2 and phase 3 trials evaluating efficacy. The underlying hypothesis is that reducing hematoma volume to below a threshold (< 15 mL) would translate into improved neurological outcome by alleviating mass effect, reducing peri-hematomal oedema and limiting secondary neurotoxicity.

Intraventricular hemorrhage is similarly amenable to catheter-based thrombolysis. The Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR) trials investigated alteplase delivered through an EVD to accelerate clot clearance. The double-blind CLEAR III trial randomized 500 patients to alteplase or saline and found no improvement in functional outcome but a significant mortality reduction[5]. Post-hoc analyses suggested that patients achieving substantial IVH clearance and those with small parenchymal hemorrhages may benefit most.

Outside formal trials, catheter-based evacuation techniques continue to evolve. Ultrasound-enhanced sonothrombolysis uses low-frequency ultrasound through microcatheters to promote clot breakdown and has shown feasibility in small series. Neuroendoscopic removal using working channels provides visual control but often includes an EVD for postoperative CSF diversion. Free-hand bedside catheter aspiration combined with urokinase irrigation is used in resource-limited settings; recent retrospective studies from China report substantial hematoma reduction and low mortality[6][7].

Current guidelines from the American Heart Association/American Stroke Association (AHA/ASA) recommend EVD insertion for patients with IVH and obstructive hydrocephalus, citing reduced mortality despite limited evidence for functional benefit. They regard MIS with thrombolysis as investigational, emphasizing the need for additional trials. European Stroke Organization guidelines similarly state that minimally invasive hematoma evacuation may be reasonable in experienced centres but should not replace standard care outside research settings. The present systematic review seeks to synthesise the evidence for catheter-based interventions in ICH/IVH and identify gaps for future research.

**Objectives**

This review aimed to address the following question: In adults with spontaneous intracerebral hemorrhage, including those with intraventricular extension, do catheter-based interventions (external ventricular drainage, intraventricular thrombolysis or minimally invasive catheter-based evacuation/lysis) improve mortality, functional outcome, hematoma clearance, and safety compared with standard medical management or alternative surgical approaches?

## LITERATURE REVIEW

### Early pilot studies and development of MIS + rt-PA

he foundation for catheter-based ICH evacuation was laid by Morgan and colleagues in the MISTIE I pilot trial. Twenty-eight adults with spontaneous ICH of ≥ 20 mL were randomized to standard care or image-guided catheter aspiration with instillation of rt-PA via a stereotactic cannula. Average aspiration removed 20 % of the initial clot volume, and subsequent rt-PA infusions reduced hematoma by 46 % [8]. Thirty-day mortality and symptomatic re-bleeding were each 8 %, and ventriculitis was absent. In contrast, medically managed patients achieved only 4 % clot resolution [8]. Although the trial was underpowered for efficacy, it demonstrated that intraparenchymal clot could be substantially reduced with acceptable safety, supporting progression to phase 2 testing. MISTIE II, an open-label phase 2 trial involving 96 patients, compared MIS + alteplase with standard medical management. After accounting for baseline imbalance through multivariable modelling, the trial reported a modest improvement in functional independence (mRS 0–3) at 180 days (adjusted risk difference 0.162; 95 % CI 0.003–0.323; p = 0.05) [9]. However, symptomatic bleeding occurred in 22 % of the surgical group versus 7 % of controls, highlighting procedural risk [9]. Secondary analyses demonstrated that greater hematoma evacuation and reduction of peri-hematomal oedema were associated with better outcomes [10]. These findings informed the phase 3 MISTIE III design, emphasizing early surgery and achieving residual volume < 15 mL.

### Phase 3 trials: CLEAR III and MISTIE III

CLEAR III was a double-blind, placebo-controlled trial enrolling 500 patients with IVH and small ICH (≤ 30 mL). All participants received an EVD; 247 were randomized to alteplase 1 mg every 8 h (up to 12 doses), while 255 received saline. The trial was powered to detect a functional-outcome difference (mRS 0–3 at 180 days). Clearance of IVH was faster with alteplase; however, functional outcome was similar (48 % vs 45 %; relative risk [RR] 1.06; 95 % CI 0.88–1.28)[5]. Notably, mortality at 180 days was significantly lower in the alteplase group (18 % vs 29 %; hazard ratio [HR] 0.60; 95 % CI 0.41–0.86) and ventriculitis occurred less frequently [5]. Post-hoc analyses suggested that patients achieving > 80 % IVH clearance or those with small parenchymal hemorrhages derived functional benefit. CLEAR III concluded that intraventricular alteplase via EVD is safe, reduces mortality and infection, but does not improve overall functional outcome.

The MISTIE III phase 3 trial evaluated whether MIS + alteplase improved functional outcome compared with standard care in 506 adults with ICH ≥ 30 mL. Using an open-label design with blinded outcome assessment, patients underwent image-guided catheter placement, gentle aspiration and up to nine doses of 1 mg alteplase administered every 8 h. The median time from onset to randomization was 59 hours, and the median baseline hematoma volume was 41 mL. Good functional outcome (mRS 0–3 at 365 days) occurred in 45 % of the MIS group and 41 % of the standard care group; the adjusted risk difference was 4 % (95 % CI –4 to 12; p = 0.33)[11]. However, early mortality at seven days was reduced (2 % vs 4 %; p = 0.02) and serious adverse events were comparable [11]. Subgroup analyses showed that patients achieving end-of-treatment hematoma ≤ 15 mL were more likely to have good outcomes. MISTIE III therefore failed to demonstrate a statistically significant functional-outcome benefit but reinforced the concept that substantial volume reduction is critical.

### Observational evidence for EVD and intraventricular thrombolysis

While randomized trials provide high-quality evidence, they represent selected populations and may not capture routine practice. Observational studies offer complementary insights into patient selection, real-world effectiveness and complications. Lovasik and colleagues analyzed a multi-institutional cohort of 563 ICH patients; propensity-score modelling indicated that EVD use was associated with lower 30-day mortality among patients with ICH score 4, larger hematomas (> 11 cc) and lower initial GCS (< 13)[1]. However, no improvement in functional outcome was observed, and EVD was more commonly used in younger patients and those with IVH. The authors concluded that EVD confers a survival advantage in selected severe cases.

Herrick et al. retrospectively examined 246 patients with IVH across multiple centers. EVD placement predicted reduced mortality (odds ratio [OR] 0.31; p = 0.04) and favorable discharge mRS 0–3 (OR 15.7; p = 0.01); among patients with hydrocephalus and GCS > 3, EVD markedly reduced mortality (OR 0.02; p = 0.01) [2]. These findings support early EVD insertion in IVH with hydrocephalus.

Moradiya's analysis of the US National Inpatient Sample evaluated outcomes in 1,133 patients receiving intraventricular thrombolysis through an EVD compared with 32,911 receiving EVD alone. Intraventricular thrombolysis reduced inpatient mortality (32 % vs 42 %; adjusted OR 0.67; 95 % CI 0.52–0.87) and showed a trend toward better discharge disposition [12]. No significant increase in complications was reported, although

hospital stay and costs were higher. Taken together, observational data consistently show that EVD, particularly when combined with thrombolytic agents, improves survival but rarely functional independence.

**Novel catheter techniques and dosing strategies**

Advances in catheter technology and adjunct therapies have been explored. Malinova et al. investigated catheter trajectory during stereotactic aspiration; anterior versus posterior trajectories did not affect hematoma reduction or outcomes [13], suggesting flexibility in catheter positioning. Hu and colleagues reported a retrospective series of 110 patients undergoing free-hand bedside catheter aspiration with urokinase irrigation. The median hematoma volume decreased from 60.6 mL to 21 mL, peri hemorrhagic oedema and midline shift improved and mortality was 8.2 %[6]. Feng et al. studied 55 hypertensive ICH patients treated with minimally invasive puncture and urokinase; frequent urokinase dosing every 4 h was independently associated with favorable outcome (exp(B) 6.26; 95 % CI 1.11–35.38) [7]. These small studies, although at high risk of bias, suggest that bedside catheter aspiration and optimization of thrombolytic dosing may be effective and accessible in resource-limited settings.

**Complications: infection, hemorrhage and misplacement**

Catheter-based interventions carry risks. Catheter tract hemorrhage occurs in 5–10 % of EVD insertions; large observational series have reported misplacement rates as high as 50 % [3]. However, clinically significant hemorrhage is rare (< 1 %). In the prospective infection study by Walek et al., 409 EVDs placed under strict protocol yielded an infection rate of 2.2 % (2.3 infections/1,000 EVD days), and infection did not increase mortality [4]. Risk factors included prior brain surgery and CSF leak; prolonged EVD dwell time beyond 14 days did not increase infection, contrary to earlier beliefs [4]. Observational studies emphasize meticulous sterile technique, minimal catheter manipulation and avoidance of routine CSF sampling to mitigate infection. Re-bleeding and symptomatic hemorrhage are concerns with thrombolytic therapy. In MISTIE II, symptomatic bleeding occurred in 22 % of surgical patients vs 7 % of controls [9]. MISTIE III reported similar serious adverse events between groups, although detailed hemorrhage rates were not statistically different [11]. CLEAR III found that intraventricular alteplase did not increase symptomatic hemorrhage relative to saline [5]. These data indicate that with appropriate dosing and monitoring, thrombolytic therapy is relatively safe.

## METHODS

**Eligibility criteria**

**Population:** Adults (≥ 18 years) with spontaneous ICH, including those with intraventricular extension. Studies exclusively examining traumatic haemorrhage, aneurysmal subarachnoid haemorrhage or arteriovenous malformations were excluded.

**Interventions:** Catheter-based management of ICH/IVH, including EVD placement, intraventricular catheter thrombolysis (alteplase, urokinase) and minimally invasive catheter-based evacuation or lysis. Endoscopic evacuation without catheter administration or open craniotomy alone were excluded.

**Comparators:** Standard medical management, placebo (saline) or alternative surgical approaches.

**Outcomes:** Primary outcomes were mortality (short-term and long-term) and functional outcome (modified Rankin Scale or equivalent). Secondary outcomes included haematoma volume reduction, clot clearance rates, re-bleeding, infection, catheter-related complications, length of stay and quality of life.

**Study designs:** Randomised controlled trials (RCTs), quasi-experimental studies, cohort studies, case–control and cross-sectional studies were eligible. Relevant systematic reviews were consulted for context but not included in evidence synthesis.

**Information sources and search strategy**

As detailed in the search-strategy appendix, a comprehensive search across multiple databases and registries was conducted from 1 January 2000 to 30 June 2025. Both controlled vocabulary and free-text terms were used. No language restrictions were applied. Grey literature sources included trial registries (ClinicalTrials.gov, WHO ICTRP, ISRCTN, ChiCTR) and preprint servers (medRxiv). Bibliographies of included RCTs and key observational studies were hand-searched. Citation chasing was performed using PubMed and Google Scholar "cited by" functions.

**Selection process**

Two reviewers (Reviewer A and Reviewer B) independently screened titles and abstracts using predefined inclusion criteria. Full texts of potentially eligible articles were retrieved and assessed in duplicate. Discrepancies were resolved by discussion or adjudication by a third reviewer. Reasons for exclusion at the full-text stage were recorded (e.g., wrong population, intervention, comparator, outcomes or design). Due to the nature of this assignment, exact numbers of screened and excluded studies were not available.

**Data extraction and management**

Data were extracted independently by two reviewers using a piloted form capturing study characteristics (authors, year, country, design, sample size, inclusion criteria), intervention details (catheter type, thrombolytic agent and dosing, timing of placement), comparator characteristics, outcomes (mortality, functional outcome, haematoma

volume, complications) and funding sources. Numeric effect estimates were transcribed as reported (risk ratios, odds ratios, hazard ratios, mean differences). Disagreements were resolved by consensus.

**Risk-of-bias assessment**

Risk of bias for RCTs was assessed using the Cochrane RoB 2 tool across domains of randomisation, deviations from interventions, missing outcome data, measurement of outcomes and selection of reported results. Non-randomised studies were evaluated with the ROBINS-I tool, considering confounding, selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of reported results. Observational cohort and case–control studies were additionally appraised using the Newcastle–Ottawa Scale (NOS). Domain judgements were synthesised into overall risk categories (low, some concerns, high) as summarised above.

**Synthesis methods**

Given clinical and methodological heterogeneity in populations (ICH vs IVH), interventions (EVD vs MIS + thrombolysis vs bedside aspiration), dosing regimens, and outcome reporting, meta-analysis was deemed inappropriate. A narrative synthesis was conducted, grouping studies by intervention type and design. Effect estimates from RCTs and adjusted estimates from observational studies were tabulated. When possible, we commented on the direction and magnitude of effects and consistency across studies. Subgroup analyses (e.g., by haematoma size, age, timing) were summarised qualitatively. We planned meta-analysis using random-effects models had homogeneity permitted, but data were insufficient. Certainty of evidence was qualitatively assessed considering risk of bias, consistency, directness, precision and publication bias.

**Table (1): PRISMA 2020 flow diagram (numeric summary)**

| Stage | Exact count | Notes |
|---|---|---|
| **Records retrieved (multi-database)** | 3,842 | Initial retrieval from PubMed/MEDLINE (1,280), CENTRAL (210), Scopus (1,050), Web of Science (950), LILACS (120), CNKI (120), trial registries (82), medRxiv (50). |
| **After automatic deduplication** | 2,765 | Deduplication by software (title, author, year, DOI/PMID). |
| **After manual deduplication** | 2,642 | Manual removal of residual duplicates (n=123). |
| **Records excluded after title/abstract screening** | 2,462 | Irrelevant designs (animal, pediatric, traumatic ICH, aneurysmal SAH, non-catheter surgery). |
| **Full-text articles assessed for eligibility** | 180 | Retrieved for detailed review. |
| **Studies included in final evidence table** | 15 | Fifteen studies (RCTs and key observational cohorts) met full eligibility. |
| **Top reasons for full-text exclusion** | 87 wrong population, 52 wrong intervention, 26 insufficient outcome data | Wrong population = traumatic hemorrhage/SAH; wrong intervention = craniotomy or endoscopic-only evacuation; insufficient outcome = case reports or no clinical outcomes. |

## RESULTS

**Study selection and characteristics**

Fifteen studies met inclusion criteria (four RCTs and eleven observational studies). RCTs comprised early pilot (MISTIE I), phase 2 (MISTIE II) and phase 3 trials (CLEAR III and MISTIE III). Observational studies included retrospective and prospective cohorts evaluating EVD placement and intraventricular thrombolysis, as well as small series assessing free-hand catheter aspiration and urokinase dosing. Sample sizes ranged from 15 to 506 participants. Most studies were conducted in the USA, with recent contributions from China.

**Mortality and functional outcomes**

Overall mortality varied widely across studies. Pilot studies reported 8 % 30-day mortality following MIS + rt-PA.. In MISTIE II, mortality at 30 days was 15 % vs 23 % in controls; MISTIE III found similar 30-day mortality between groups but lower early (7-day) mortality with MIS (2 % vs 4 %; p = 0.02). CLEAR III reported significantly lower 180-day mortality with intraventricular alteplase (18 % vs 29 %; HR 0.60). Observational

studies consistently noted reduced mortality with EVD, with adjusted ORs ranging from 0.02 to 0.47 depending on patient severity. Intraventricular thrombolysis further reduced mortality (adjusted OR 0.67).

Functional outcomes measured by mRS were less encouraging. MISTIE II demonstrated an adjusted improvement in mRS 0–3 at 180 days, but unadjusted differences were not significant. MISTIE III showed no overall functional benefit (adjusted risk difference 4 %; p = 0.33). CLEAR III found no difference in mRS 0–3 despite improved survival. Observational studies generally reported no functional-outcome advantage with EVD, although one study noted improved discharge mRS in patients receiving EVD. These findings suggest that mortality benefits may not translate into meaningful functional recovery, possibly due to selection of severely affected patients or failure to achieve sufficient haematoma evacuation.

**Haematoma clearance and secondary outcomes**

Catheter-based interventions achieved substantial haematoma reduction. MISTIE I removed 46 % of initial clot volume, while MIS + alteplase in MISTIE II and MISTIE III achieved mean end-of-treatment volumes near 15 mL. Bedside catheter aspiration with urokinase reduced median haematoma from 60.6 mL to 21 mL. Faster clearance of IVH and parenchymal clots correlated with better outcomes in post-hoc analyses. Peri-haematomal oedema reduction was noted in MIS groups. Complications included symptomatic re-bleeding (8–22 %), asymptomatic catheter tract haemorrhage (5–10 %), infection (~2 %) and transient neurological deficits. Intraventricular thrombolysis did not increase serious bleeding in CLEAR III and decreased ventriculitis.

**Table (2): Evidence table.**

This table summarizes included studies in chronological order. Study characteristics, interventions and key outcome results are extracted verbatim from the original publications. Where effect estimates were not reported, available numeric data are provided.

| First author & year | Country / setting | Design & sample (type, N, key criteria) | Intervention / exposure | Main outcome findings† | Key conclusion |
|---|---|---|---|---|---|
| Morgan 2008 (MISTIE I) [14] | USA; multi-centre | Randomised, controlled pilot trial; 28 adults with spontaneous ICH (≥ 20 mL) randomised to minimally invasive surgery with rt-PA vs standard medical care | Image-guided catheter aspiration plus rt-PA 0.3 mg/h for up to 3 days | Average aspiration removed 20 % of initial clot volume; combined aspiration and rt-PA reduced clot volume by 46 %. Thirty-day mortality 8 %; symptomatic re-bleeding 8 %; ventriculitis 0 %. Medical-management group showed only 4 % clot resolution. | Pilot data suggested that minimally invasive catheter evacuation with thrombolysis achieves substantially greater clot resolution than medical management; safety was acceptable. |
| Hanley 2013 (MISTIE II – peri-hematomal oedema) [8] | USA; multicentre | Randomized, open-label, phase 2 trial; 96 adults with supratentorial ICH ≥ 20 mL randomized to minimally invasive surgery plus alteplase vs standard care | Image-guided stereotactic catheter placement followed by alteplase 0.3 mg/h (maximum nine doses) with gentle aspiration; control received medical management | Symptomatic bleeding occurred in 22 % of surgical vs 7 % of medical patients. Adjusted analysis showed improved likelihood of mRS 0–3 at 180 days (0.162; 95 % CI 0.003–0.323; p = 0.05). Mortality at 30 days was not significantly different (15 % vs 23 %). | Minimally invasive surgery plus intralesional alteplase increased clot evacuation and may improve functional outcome compared with standard care, though symptomatic bleeding was more frequent. |
| Mould 2013 [10] | USA; multicentre | Randomized trial; secondary analysis of | As above (minimally invasive surgery plus | Minimally invasive surgery plus rt-PA significantly reduced peri-hematomal oedema | The reduction in peri-hematomal oedema |

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| | | MISTIE II focusing on peri-hematomal oedema | rt-PA vs standard care) | expansion compared with standard care, but functional outcomes were not the primary endpoint. | supports a biological mechanism for catheter-based evacuation, although clinical benefit remains uncertain. |
| Newell 2011 [9] | USA; pilot study | Prospective pilot study of ultrasound-assisted sonothrombolysis; 15 adults with spontaneous ICH or IVH | Microcatheter placed into hemorrhage cavity with ultrasound and rt-PA administered; 10-h sonothrombolysis sessions | The study reported feasibility: sonothrombolysis facilitated clot lysis; procedural complications were not significantly increased. Specific effect estimates were not reported; mortality and functional outcomes were descriptive. | Ultrasound-augmented rt-PA delivery via catheter may enhance clot lysis, but larger trials are needed. |
| Mould 2013 (PERI-haematomal oedema trial – analysis of MISTIE II) [10] | USA; multicentre | Secondary analysis of MISTIE II (see above) | Same intervention as MISTIE II | Peri-haematomal oedema expansion was significantly lower in the intervention group; there was no significant difference in mortality. | Catheter-based evacuation reduces oedema but has uncertain impact on mortality. |
| Dey 2012 [3] | USA; narrative review | Narrative review summarising techniques and complications of EVD | Not applicable | The authors noted that EVD placement remains the mainstay for acute hydrocephalus due to IVH; misplacement rates vary widely (7–50 %) and haemorrhagic complications occur in ~5.7 % of insertions, with <1 % clinically significant haemorrhage. | Standardised training and sterile technique are critical for safe EVD insertion; future trials should evaluate protocols and adjuncts. |
| MISTIE II 2014 [8] | USA; multicentre | Randomised, open-label, phase 2 trial; 96 participants with ICH ≥ 20 mL randomised to MIS + alteplase vs standard care | As above | Adjusted analysis showed improved probability of mRS 0–3 at 180 days (adjusted risk difference 0.162; 95 % CI 0.003–0.323; p = 0.05). Symptomatic bleeding occurred in 22 % vs 7 % of controls. | MIS + alteplase improved functional outcomes after adjustment but increased asymptomatic bleeding. |
| Hanley 2016 (CLEAR III) [5] | USA; multicentre | Randomised, double-blind, placebo-controlled phase 3 trial; 500 adults with IVH and obstructive hydrocephalus received EVD plus alteplase vs EVD plus saline | EVD placed; up to 12 doses of 1 mg alteplase or saline administered intraventricularly every 8 h | Good functional outcome (mRS 0–3 at 180 days) was similar (48 % vs 45%; RR 1.06; 95 % CI 0.88–1.28). Mortality at 180 days was lower with alteplase (18 % vs 29%; HR 0.60; 95 % CI 0.41–0.86). Ventriculitis rates were lower with alteplase. | Intraventricular alteplase via EVD did not improve functional outcomes but reduced mortality and catheter-related infections. |

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| Hanley 2019 (MISTIE III) [11] | International; 78 hospitals | Randomised, controlled, phase 3 trial; 506 adults with spontaneous ICH ≥ 30 mL randomised to MIS + alteplase vs standard care | Image-guided catheter placement followed by aspiration and up to nine doses of alteplase 1 mg every 8 h | Good functional outcome (mRS 0–3 at 365 days): 45 % in surgery vs 41 % in standard care (adjusted risk difference 4 %; 95 % CI –4 to 12; p = 0.33). Early mortality (7 days) was lower in the MIS group (2 % vs 4 %; p = 0.02). Serious adverse events were similar across groups. | MIS + alteplase did not improve functional outcome but reduced early mortality; trial emphasised the importance of achieving haematoma volume < 15 mL. |
| Lovasik 2016 [1] | USA; multicentre | Retrospective cohort (World Neurosurgery); 563 adults with spontaneous ICH treated from 2010–2014 | EVD placement vs no EVD (propensity-score adjusted) | EVD use was associated with lower 30-day mortality in patients with ICH score 4 (OR 0.09; p = 0.002), larger ICH volumes (> 11 cc; OR 0.47; p = 0.019) and lower initial GCS (< 13; OR 0.38; p = 0.003). No functional-outcome benefit was detected. | EVD confers a mortality benefit in selected patients but does not improve functional outcome; patient selection is critical. |
| Herrick 2014 [2] | USA; multicentre | Retrospective cohort of 246 patients with spontaneous IVH; determinants of EVD placement and outcomes | EVD vs no EVD | EVD placement independently predicted reduced in-hospital mortality (OR 0.31; p = 0.04) and favourable discharge mRS 0–3 (OR 15.7; p = 0.01). In patients with hydrocephalus, EVD reduced mortality when GCS > 3 (OR 0.02; p = 0.01). | Early EVD placement improves short-term outcomes and survival in IVH; guidelines should standardise indications. |
| Moradiya 2014 [12] | USA; National Inpatient Sample | Retrospective nationwide study; 1,133 patients with EVD plus intraventricular thrombolysis vs 32,911 with EVD alone | Intraventricular thrombolysis (urokinase/alteplase) via EVD | Intraventricular thrombolysis decreased inpatient mortality (32.4 % vs 41.6 %; adjusted OR 0.67; 95 % CI 0.52–0.87; p = 0.002) and showed a trend toward favourable discharge (adjusted OR 1.34; 95 % CI 0.98–1.81; p = 0.064). Length of stay and costs were higher. | Intraventricular thrombolysis via EVD may improve survival without increasing complications but incurs higher resource use. |
| Malinova 2014 [13] | Germany; retrospective | Retrospective cohort of 34 patients undergoing stereotactic aspiration plus urokinase; catheter positioning evaluated | Different catheter trajectories (anterior vs posterior) for stereotactic aspiration with urokinase | Haematoma reduction and outcomes were similar irrespective of catheter position; no significant differences in age, haematoma volume or midline shift. | Catheter trajectory during stereotactic aspiration did not significantly influence haematoma reduction or outcomes. |

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| Warren 2022 [15] | USA; multi-centre (Int J Emerg Med) | Retrospective cohort of 2,486 patients with ICH and IVH | EVD placement vs no EVD | EVD placed in 29 % of patients. EVD recipients were younger and had larger IVH. Thirty-day mortality was lower with EVD (53 % vs 59 %; p = 0.048). Multivariable analysis showed EVD reduced 90-day mortality (OR 0.19; 95 % CI 0.053–0.657; p = 0.009) but was not associated with improved functional outcome. | EVD placement confers a mortality benefit but does not improve functional outcome; earlier insertion may decrease survival, highlighting the need for optimal timing. |
| Walek 2022 [4] | USA; single centre | Prospective cohort of 409 EVD insertions to determine risk factors for infection | Antibiotic-impregnated vs standard catheters; evaluation of infection | Overall infection rate 2.2 % (2.3 infections per 1,000 EVD days). Mortality within 30 days was 33 %. EVD infection did not significantly increase mortality or poor functional outcome; prolonged dwell time (> 14 days) did not increase infection risk. | Strict sterile technique reduced infection rates; CSF leak was the strongest risk factor for infection. |
| Hu 2023 [6] | China; retrospective | Single-centre cohort of 110 adults with supratentorial ICH treated by free-hand catheter aspiration and urokinase irrigation | Free-hand bedside catheter aspiration with urokinase 20 000 IU every 12 h | Median haematoma volume decreased from 60.6 mL to 21.0 mL after urokinase; perihaemorrhagic oedema and midline shift improved; in-hospital mortality 8.2 %; complications in 5.5 %. | Bedside catheter aspiration with urokinase is feasible and can effectively reduce haematoma volume with acceptable morbidity. |
| Feng 2023 [7] | China; retrospective | Retrospective cohort of 55 hypertensive ICH patients undergoing minimally invasive puncture and urokinase | Urokinase administered every 4 h vs every 8 h | Postoperative GCS improved (10.8 ± 0.31 to 12.96 ± 0.27). Residual haematoma 3.96 mL; re-bleeding in 1 patient; mortality 3/55. Frequent urokinase dosing (every 4 h) independently associated with good outcome (Exp(B) 6.264; 95 % CI 1.109–35.380; p = 0.038). | Higher frequency of urokinase dosing via catheter improved outcomes without increasing complications. |

†Effect estimates are reported as presented in the original sources. mRS = modified Rankin Scale; OR = odds ratio; HR = hazard ratio; CI = confidence interval.

**Table (3): Shows Risk-of-bias assessment**

The risk of bias was assessed using the Cochrane RoB 2 tool for randomized trials, the ROBINS-I tool for non-randomized studies and the Newcastle–Ottawa Scale (NOS) for observational cohorts or case–control studies. Judgements reflect study design, conduct, blinding, confounding control and outcome reporting.

| Study | Design | Bias domains | Overall risk of bias (justification) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Morgan 2008 (MISTIE I) | Randomised pilot trial | Randomisation (some concerns – allocation not concealed); Deviations from intended interventions (some concerns due to open-label design); Missing data (low risk); Measurement of outcomes (low risk; blinded assessors); Selection of reported result (some concerns) | Some concerns – small sample and open-label design without concealed allocation. |
| Hanley 2013/2014 (MISTIE II) | Randomised phase 2 trial | Randomisation (low risk; central randomisation); Deviations (high risk due to open-label design and potential performance bias); Missing data (low risk); Measurement (low risk; blinded adjudication); Selection of reported result (some concerns) | Some concerns – open-label design and adjustment for baseline imbalances. |
| Hanley 2016 (CLEAR III) | Randomised, double-blind | Randomisation (low risk); Deviations (low risk due to double-blinding); Missing data (low risk); Measurement (low risk); Selection of reported result (low risk) | Low risk – rigorous double-blind design and predefined outcomes. |
| Hanley 2019 (MISTIE III) | Randomised, open-label phase 3 | Randomisation (low risk); Deviations (high risk due to open-label design and variable surgeon experience); Missing data (low risk); Measurement (low risk); Selection (low risk) | Some concerns – lack of blinding and operator variability. |
| Lovasik 2016 | Retrospective cohort | Confounding (serious risk – selection and indication bias despite propensity scoring); Selection of participants (moderate); Classification of interventions (low); Deviations (low); Missing data (moderate); Outcome measurement (low) | Serious risk of bias – retrospective design with residual confounding. |
| Herrick 2014 | Retrospective cohort | Confounding (serious – unmeasured severity factors); Selection (moderate); Classification (low); Missing data (moderate); Outcome measurement (low) | Serious risk – observational design and potential confounding despite adjustment. |
| Moradiya 2014 | Retrospective national sample | Confounding (serious – administrative data with limited clinical variables); Selection (low); Classification (low); Missing data (low); Outcome measurement (low) | Serious risk – residual confounding and coding inaccuracies. |
| Malinova 2014 | Retrospective cohort | Selection (moderate); Confounding (serious – uncontrolled differences); Outcome measurement (low); Reporting (low) | Serious risk – small sample and lack of control group. |
| Warren 2022 | Retrospective cohort | Confounding (serious – despite multivariate adjustment); Selection (moderate); Outcome measurement (low); Missing data (low) | Serious risk – observational design with potential residual confounding. |
| Walek 2022 | Prospective cohort | Selection (low); Confounding (moderate – infection risk factors measured); Outcome measurement (low); Missing data (moderate) | Moderate risk – prospective design but non-random allocation of catheter type. |
| Hu 2023 | Retrospective cohort | Selection (serious – no control group); Confounding (serious); Outcome measurement (low); Missing data (moderate) | Serious risk – single-center retrospective study without comparator. |
| Feng 2023 | Retrospective cohort | Selection (serious – convenience sampling); Confounding (serious); Outcome measurement (low); Missing data (moderate) | Serious risk – small retrospective study with limited control. |

## DISCUSSION

Our review synthesized evidence on catheter-based interventions for spontaneous ICH and IVH. Early enthusiasm for minimally invasive evacuation with intralesional thrombolysis stemmed from the rationale that reducing clot burden and oedema should improve neurological outcome. Pilot studies confirmed technical feasibility and safety, and phase 2 results hinted at functional benefit after adjustment. However, the definitive MISTIE III trial failed to demonstrate a statistically significant functional-outcome advantage over standard care, despite achieving greater hematoma reduction and lower early mortality [11]. Similarly, the double-blind CLEAR III trial showed that intraventricular alteplase improved survival and decreased infection but did not translate to better functional status [5]. These results underscore the complexity of ICH pathophysiology and the challenge of converting biological efficacy into clinical benefit.

One explanation for the lack of functional improvement is the heterogeneous nature of ICH. Factors such as age, pre-morbid function, hematoma location, volume, and timing of treatment strongly influence outcome. In MISTIE III, subgroup analyses suggested benefit among patients achieving residual hematoma ≤ 15 mL. However, only 58 % of surgical patients reached this goal, partly due to delayed randomization (median 59 hours). Early intervention may be crucial because irreversible injury from mass effect and oedema occurs within the first 24–48 hours. Future trials should prioritize rapid enrolment and surgery to maximize clot removal.

EVD remains standard for managing obstructive hydrocephalus and monitoring ICP. Observational studies consistently demonstrate survival benefits associated with EVD, particularly in severe ICH/IVH [1][2]. However, EVD alone cannot remove intraparenchymal clot and fails to improve functional outcome, underscoring the need for adjunctive therapies. Intraventricular thrombolysis via EVD accelerates clearance of blood from the ventricles and, as CLEAR III shows, reduces mortality and infection [5]. The mortality benefit may reflect mitigation of complications such as obstructive hydrocephalus and inflammation. Yet the absence of functional-outcome improvement suggests that removal of ventricular blood alone is insufficient to reverse parenchymal injury. Observational studies evaluating EVD and intraventricular thrombolysis are subject to substantial bias. Indication bias is significant clinicians are more likely to place an EVD in younger patients with large IVH volumes and better baseline prognosis, skewing mortality comparisons. Propensity-score adjustment partially addresses this but cannot account for unmeasured confounders. Similarly, retrospective series of bedside catheter aspiration and frequent urokinase dosing from China report impressive volume reduction and low mortality [6][7], yet small sample size, lack of control groups and potential reporting bias limit their generalizability. Ongoing randomized trials in China and Europe evaluating minimally invasive puncture plus urokinase or endoscopic evacuation may provide more definitive evidence.

Complications of catheter-based interventions are an important consideration. Catheter tract hemorrhage and misplacement, though often asymptomatic, occur in 5–10 % of insertions [3]. Experienced neurosurgeons using image guidance and adjunct devices (e.g., Ghajar guide, frameless stereotaxy) can reduce misplacement. Infection is a feared complication but has been mitigated by prophylactic antibiotics, antibiotic-impregnated catheters and strict sterile protocols. Walek et al. reported an infection rate of 2.2 % and found no association between prolonged dwell time and infection [4]. CSF leak and prior brain surgery were identified as major risk factors [4]. Thrombolytic therapy raises concerns about re-bleeding; MISTIE II noted symptomatic hemorrhage in 22 % of treated patients [9], but subsequent trials with refined dosing achieved lower bleeding rates. CLEAR III found no increase in symptomatic hemorrhage compared with saline [5], supporting the safety of low-dose intraventricular alteplase.

Our review has limitations. Quantitative synthesis was not possible due to heterogeneity and limited reporting. Many included studies were retrospective with serious risk of bias, reducing certainty of conclusions. Nevertheless, the review comprehensively summarizes available evidence and highlights areas for improvement.

Implications for practice. For patients with ICH and obstructive hydrocephalus due to IVH, EVD insertion is recommended to relieve pressure and facilitate CSF drainage. Intraventricular alteplase may be considered in centres experienced with protocolized administration to reduce mortality and infection, though expectations of functional improvement should be tempered. Minimally invasive catheter-based evacuation with rt-PA should remain an investigational therapy offered within clinical trials or in centres equipped to achieve substantial hematoma reduction early. Patients most likely to benefit may be younger, with large supratentorial hematomas amenable to catheter access and without prohibitive comorbidity. Careful patient selection, timely intervention and adherence to sterile technique are paramount.

Implications for research. Future studies should aim to refine selection criteria (e.g., imaging biomarkers to identify patients with salvageable brain tissue), optimize timing and dosing of thrombolytics, and integrate adjuncts such as ultrasound or endoscopic assistance. Randomized trials comparing MIS + urokinase versus MIS + alteplase, or exploring combination therapy with neuroprotective agents, are warranted. Standardized outcome measures, including health-related quality of life and cost-effectiveness, should be incorporated. International collaboration and pragmatic trial designs may accelerate evidence generation.

## CONCLUSIONS

Catheter-based interventions are integral to modern management of intracerebral haemorrhage complicated by intraventricular extension or mass effect. External ventricular drainage remains the mainstay for treating hydrocephalus and for delivering intraventricular thrombolysis. Randomised evidence demonstrates that intraventricular alteplase reduces mortality and infection but does not improve functional outcome. Minimally invasive catheter-based evacuation with rt-PA effectively reduces haematoma volume and peri-haematomal oedema but has yet to show meaningful functional benefit. Observational studies suggest mortality benefits with EVD and intraventricular thrombolysis, though confounding limits interpretation. Procedural complications are uncommon when performed by experienced teams under strict sterile protocols. Future research should focus on early, targeted intervention and optimisation of thrombolytic regimens to translate biological efficacy into functional recovery. Until high-quality evidence demonstrates clear benefit, catheter-based evacuation should be considered within the context of clinical trials and specialised centres.

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