Fibrinolysis for Intraventricular Hemorrhage
An Updated Meta-Analysis and Systematic Review of the Literature

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Background and Purpose— Intraventricular hemorrhage is associated with high mortality and poor functional outcome. The use of intraventricular fibrinolytic (IVF) therapy as an intervention in intraventricular hemorrhage is an evolving therapy with conflicting reports in the literature. The goal of this study is to investigate the impact of IVF on mortality, functional outcome, ventriculitis, shunt dependence, and rehemorrhage.

Methods— During March and April 2014, a systematic literature search was performed identifying 1359 articles. Of these, 24 met inclusion criteria. A random effects meta-analysis was performed using both pooled and subset analysis based on study type.

Results— Our meta-analysis demonstrated that IVF reduced mortality in intraventricular hemorrhage by nearly half (relative risk [RR], 0.55; 95% confidence interval [CI], 0.42–0.71; P=0.00001), increased the likelihood of good functional outcome by 66% (RR, 1.66; 95% CI, 1.27–2.19; P=0.0003), and also decreased the rate of shunt dependence (RR, 0.62; 95% CI, 0.42–0.93; P=0.02). IVF was not found to be associated with increased rates of ventriculitis (RR=1.46; 95% CI, 0.77–2.76; P=0.25) or rehemorrhage (RR=1.06; 95% CI, 0.66–1.70; P=0.80). We detected no evidence of publication bias.

Conclusions— Our meta-analysis showed that IVF is safe and could be an effective strategy for the treatment of intraventricular hemorrhage. It may reduce mortality, improve functional outcome, and diminish the need for permanent ventricular shunting, while not increasing the risk of ventriculitis or rehemorrhage. (Stroke. 2014;45:2662-2669.)

Key Words: fibrinolysis • meta-analysis

Intracerebral hemorrhage (ICH) accounts for 10% to 15% of all strokes representing ≤2 million cases annually worldwide.1 Intraventricular hemorrhage (IVH) complicates ≤40% of cases and increases morbidity and mortality through factors such as obstructive hydrocephalus, raised intracranial pressure, and direct contact of toxic blood products with the ependymal lining.2–4 The 30-day mortality associated with IVH ranges from 40% to 80%, and the volume of blood has been found to be an independent predictor of mortality following ICH.2,3,7,8

The most common current treatment for ICH complicated by IVH is placement of an extraventricular drain (EVD) for relief of hydrocephalus and removal of blood products. However, the EVD may become obstructed by clot requiring repeated flushing or replacement, placing the patient at risk for raised intracranial pressure secondary to hydrocephalus.9–11 The administration of intraventricular fibrinolysis (IVF) through the EVD has been studied as a possible intervention treatment for IVH and has produced mixed results. Previous analyses in patients with ICH and IVH have demonstrated potential benefit of IVF administration, but at the cost of increased complications such as rebleeding and ventriculitis.12,13 On the other hand, a recent meta-analysis that was limited to patients with aneurysmal subarachnoid hemorrhage and IVH demonstrated an improved survival rate with IVF and a complication rate no higher than an EVD alone.14 This systematic review and meta-analysis was undertaken to provide an updated, more thorough review about the use of IVF in IVH. The primary aim of our analysis was to...
determine if IVF decreases mortality following IVH at the end of study follow-up. The secondary goals were to determine if IVF improved functional outcome and influenced rates of ventriculitis, shunt dependence, and rehemorrhage.

Methods

Specific Aims, Inclusion Criteria, and Data Extraction

This study was conducted using the Assessment of Multiple Systematic Reviews15 measurement tool and Preferred Reporting Items for Systematic reviews and Meta-Analyses.16 The research question for this study was, “Does IVF decrease mortality in IVH?” Our formal review protocol is available in the online-only Data Supplement.

The following served as our inclusion criteria: (1) described a group of adult (> 18 years of age) patients who had nontraumatic IVH treated with EVD placement and IVF, (2) described a control group not treated with IVF, (3) used IVF as the main treatment difference between groups, and (4) reported the number of patients and outcomes of interest for each group. Uncontrolled studies, case reports, and pediatric reports were excluded. There were no restrictions based on dosing, fibrinolytic agent (eg, urokinase and alteplase), or frequency of drug administration. Two separate individuals (N.R.K. and S.L.L.) screened all potential articles and extracted data independently. The data extracted from each article included the following: (1) patient population, (2) number of participants per group, (3) the dose and method of application of IVF used, (4) the outcomes as defined below, (5) any complications related to the use of IVF, and (6) any potential conflict of interest as reported by the authors. All studies were classified in the following 3 categories: retrospective cohort studies, prospective cohort studies, and randomized controlled trials (RCTs). The level of evidence for each study was evaluated using the Oxford Center for Evidence-Based Medicine (OCEBM) guidelines.17 Observational studies were further graded using the Newcastle–Ottawa Quality Scale18 and RCTs were graded using the Jadad scale.19 Disagreements among any of the above data points were resolved through discussion among the authors.

Outcome Definitions

The primary outcome of this analysis was all-cause mortality at the end of study follow-up, which ranged from hospital discharge to as long as 1 year. Secondary end points included the impact of IVF administration on functional outcome and the rates of ventriculitis, rehemorrhage, and need for a cerebral spinal fluid shunt. Good functional outcome was defined as retaining functional independence in performing daily activities (most commonly using a modified Rankin score 0–3 or Glasgow Outcome Scale score of 4–5). Ventriculitis was defined as clinical signs of infection with positive cerebral spinal fluid bacteriological studies or need for antibiotic therapy. Rehemorrhage was defined as any new ICH or IVH after placement of EVD alone or EVD and IVF.

Results

Search Results and Included Articles

The initial search strategy identified 1359 articles. After excluding articles not directly related to the clinical use of IVF in IVH, a total of 528 articles remained. We eliminated 497 duplicate studies and articles not meeting inclusion criteria. Of the remaining 31 articles, 9 were excluded for the following reasons: 3 studies were excluded because they had no control group20–22 and 6 studies were excluded because there was insufficient information for analysis.23–28 One study identified through the previous meta-analysis was unpublished data and excluded from our analysis. Two additional studies were incorporated from a search of the reference lists of inclusion articles, resulting in 24 studies eligible for analysis (Figure 1).

Eight RCTs had 90 patients who received IVF for IVH compared with 81 controls. Five of the 8 had a Jadad score of >3. Of the 3 prospective cohort studies included, 140 patients were evaluated and 71 of them received IVF. Two studies reported in the previous meta-analysis as RCTs were classified as prospective cohort studies in our analysis due to inadequate randomization process.29,30 Two of these studies received 5 stars (out 9 possible) using the Newcastle–Ottawa Scale for cohort studies and one received a grading of 6 stars. Retrospective cohort studies made up the largest portion of the literature on the use of IVF in IVH, with a total of 343 patients receiving IVF. The majority of these studies (61.5%) received 5 stars on the Newcastle–Ottawa Quality Scale. A full summary of all included literature, including an assessment of study quality, is provided in Table I in the online-only Data Supplement.

Mortality

In the pooled analyses, IVF treatment revealed a decreased likelihood of mortality by nearly half (relative risk [RR]=0.55; 95% confidence interval (CI), 0.42–0.71; P<0.00001; Figure 2). IVF treatment was independently associated with reduced mortality in prospective cohort studies (RR=0.35; 95% CI, 0.17–0.71; P=0.004), retrospective cohort studies (RR=0.58; 95% CI, 0.41–0.83; P=0.003), and trended toward significance in RCTs (RR=0.60; 95% CI, 0.35–1.01; P=0.05). There was no evidence of heterogeneity, with an F statistic of 0% (P=0.94 by Cochran Q test).

Figure 1. Flow diagram of search strategy. IVF indicates intra-ventricular fibrinolysis.
Functional Outcome
IVF was associated with a higher likelihood of good functional outcome in the pooled analyses (RR, 1.66; 95% CI, 1.27–2.19; P=0.0003) of all studies and in the secondary analyses of prospective cohort studies (RR=2.05; 95% CI, 1.28–3.29; P=0.003; Figure 3). There was no evidence of heterogeneity, with an I² statistic of 0% (P=0.74 by Cochran Q test). We identified no association between IVF and good functional outcome in the subgroup analyses of retrospective cohort studies and RCTs.

Ventriculitis and Rehemorrhage
IVF was not associated with an increased likelihood of ventriculitis (Figure 4) or rehemorrhage (Figure 5) in the pooled analyses or in any of the subgroup analyses. For ventriculitis, there was evidence of substantial heterogeneity across the different trials with an I² statistic of 56% (P=0.003 by Cochran Q test). There was no evidence of heterogeneity across the different studies I² statistic of 0% (P=0.74 by Cochran Q test) regarding rehemorrhage.

Shunt Dependence
IVF was independently associated with reduced likelihood of shunt requirement by 38% (RR=0.62; 95% CI, 0.42–0.93; P=0.02) in the pooled analyses of all studies (Figure 6). No such association was detected in any of the subgroup analyses. There was no evidence of heterogeneity with an I² statistic of 11% (P=0.32 by Cochran Q test).

Publication Bias and Conflict of Interest
There was no evidence of publication bias (P=0.19223 by Egger test). The symmetrical funnel plot (Figure I in the online-only Data Supplement) of all included studies also corroborates the absence of publication bias. Only 2 studies by the same author reported any conflicts of interest related to IVF research.

Discussion
Our systematic review and meta-analysis represents the largest and most comprehensive review of IVF for IVH,
Intra ventricular Fibrinolysis in IVH

Our results suggest that IVF for IVH is a safe intervention and may be an effective strategy for reducing mortality and improving functional outcome. Additionally, our analysis is the first to demonstrate a decreased rate of shunt dependence in those treated with IVF, which is likely due to inclusion of a larger sample of patients. This observed benefit may support the theory that IVF results in faster clearance of ventricular blood, lower contact time of blood with the ependymal lining, and possibly allows a faster resumption of cerebral spinal fluid homeostasis. The treatment was not associated with an increased risk of complications such as ventriculitis or rehemorrhage.

The first meta-analysis on this topic was published in 2002 and included only anecdotal evidence from 10 uncontrolled studies. Nearly a decade later, a second analysis of 12 randomized or observational studies demonstrated that the use of IVF resulted in better functional outcomes and improved survival; however, they also found an increased incidence of rebleeding and no difference in shunting requirements. Compared with this previous analysis, we identified 14 additional studies for inclusion in our review. We excluded one study from the prior meta-analysis which was unpublished (V. Porhiel, et al, unpublished data, 2005) and another which had another significant intervention (lumbar drainage) other than IVF between treatment and control groups thus not meeting our inclusion criteria. Further, we found that 4 of the studies in their meta-analysis had incorrectly extracted data on mortality (Table I in the online-only Data Supplement). Therefore, all of the 12 studies included in the study by Gaberel et al are different than this analysis. We also reclassified 2 studies reported as RCTs in the previous analysis as prospective cohort studies as we thought their design was more consistent with this research approach and were insufficient in quality to be conceivably classified as an RCT.

Although the question of the risk of ventriculitis after IVF treatment has been raised, we found no significant association. Gaberel et al also suggested that proven neurotoxicity associated with alteplase may counterbalance any beneficial effects associated with IVF use, largely due to a small difference in outcomes seen between alteplase and urokinase in their meta-analysis. It is unclear as to why the previous analysis observed a potential decreased effect when alteplase was utilized, but may have potentially been due to publication bias and small sample size. Although we chose not to perform further subgroup analysis between the 2 agents due to unavailability of urokinase in the United States, 11 of the 14 additional studies we included in our analysis utilized alteplase as the fibrinolytic agent of choice. Despite the large increase in studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IVF patients</th>
<th>Control patients</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 Randomized Clinical Trials</td>
<td>Kramer et al, 2014</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>5.8%</td>
<td>1.00 (0.32, 3.10)</td>
</tr>
<tr>
<td></td>
<td>Linco et al, 2012</td>
<td>4</td>
<td>11</td>
<td>2</td>
<td>8</td>
<td>3.6%</td>
<td>1.45 (0.35, 6.09)</td>
</tr>
<tr>
<td></td>
<td>Naft et al, 2011</td>
<td>13</td>
<td>26</td>
<td>6</td>
<td>22</td>
<td>12.2%</td>
<td>1.83 (0.84, 4.01)</td>
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<tr>
<td></td>
<td>Tung et al, 1998</td>
<td>2</td>
<td>10</td>
<td>0</td>
<td>11</td>
<td>0.9%</td>
<td>5.45 (0.29, 101.55)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>53</td>
<td>47</td>
<td>22.5%</td>
<td>1.57</td>
<td>0.89, 2.80</td>
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<tr>
<td>Total events</td>
<td>22</td>
<td>11</td>
<td>22</td>
<td>11</td>
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<tr>
<td>Heterogeneity: Tau^2 = 0.00; CH^2 = 1.47, df = 3 (P = 0.69); I^2 = 0%</td>
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<td>Test for overall effect: Z = 1.55 (P = 0.12)</td>
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<tr>
<td>2.1.2 Prospective Cohort studies</td>
<td>Akdemir et al, 1995</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td>9</td>
<td>1.6%</td>
<td>2.57 (0.29, 22.93)</td>
</tr>
<tr>
<td></td>
<td>Dunavov et al, 2011</td>
<td>28</td>
<td>48</td>
<td>13</td>
<td>49</td>
<td>27.2%</td>
<td>2.20 (1.30, 3.71)</td>
</tr>
<tr>
<td></td>
<td>Varelas et al, 2005</td>
<td>4</td>
<td>10</td>
<td>3</td>
<td>10</td>
<td>5.1%</td>
<td>1.33 (0.40, 4.49)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>65</td>
<td>68</td>
<td>33.9%</td>
<td>2.05</td>
<td>1.28, 3.29</td>
<td></td>
<td></td>
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<tr>
<td>Total events</td>
<td>34</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td></td>
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<tr>
<td>Heterogeneity: Tau^2 = 0.00; CH^2 = 0.59, df = 2 (P = 0.74); I^2 = 0%</td>
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<tr>
<td>Test for overall effect: Z = 3.01 (P = 0.003)</td>
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<tr>
<td>2.1.3 Retrospective Cohort studies</td>
<td>Coplin et al, 1998</td>
<td>8</td>
<td>22</td>
<td>4</td>
<td>18</td>
<td>7.1%</td>
<td>1.64 (0.59, 4.56)</td>
</tr>
<tr>
<td></td>
<td>Findlay et al, 2004</td>
<td>9</td>
<td>21</td>
<td>4</td>
<td>9</td>
<td>9.6%</td>
<td>0.96 (0.40, 2.33)</td>
</tr>
<tr>
<td></td>
<td>Hailivi et al, 2011</td>
<td>2</td>
<td>18</td>
<td>1</td>
<td>11</td>
<td>1.4%</td>
<td>1.22 (0.12, 11.95)</td>
</tr>
<tr>
<td></td>
<td>Hutner et al, 2007</td>
<td>10</td>
<td>22</td>
<td>9</td>
<td>22</td>
<td>16.2%</td>
<td>1.11 (0.56, 2.19)</td>
</tr>
<tr>
<td></td>
<td>Rainov et al, 1995</td>
<td>15</td>
<td>16</td>
<td>2</td>
<td>5</td>
<td>6.4%</td>
<td>2.34 (0.80, 6.91)</td>
</tr>
<tr>
<td></td>
<td>Todo et al, 1991</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>1.0%</td>
<td>9.43 (0.85, 137.77)</td>
</tr>
<tr>
<td></td>
<td>Torres et al, 2008</td>
<td>6</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>1.9%</td>
<td>6.00 (0.83, 43.59)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>119</td>
<td>84</td>
<td>43.6%</td>
<td>1.46</td>
<td>0.96, 2.22</td>
<td></td>
<td></td>
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<tr>
<td>Total events</td>
<td>55</td>
<td>21</td>
<td>21</td>
<td>21</td>
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<tr>
<td>Heterogeneity: Tau^2 = 0.01; CH^2 = 6.09, df = 6 (P = 0.41); I^2 = 1%</td>
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<td>Test for overall effect: Z = 1.77 (P = 0.08)</td>
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<tr>
<td>Total (95% CI)</td>
<td>237</td>
<td>199</td>
<td>100.0%</td>
<td>1.66</td>
<td>1.27, 2.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>111</td>
<td>49</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: Tau^2 = 0.00; CH^2 = 9.37, df = 13 (P = 0.74); I^2 = 0%</td>
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<tr>
<td>Test for subgroup differences: CH^2 = 1.18, df = 2 (P = 0.55), I^2 = 0%</td>
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<tr>
<td>Test for overall effect: Z = 3.65 (P = 0.0003)</td>
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</table>

Figure 3. Forest plot of all studies with their respective relative risk (RR) and 95% confidence interval (CI), events (good functional outcome), and overall RR. IVF indicates intraventricular fibrinolysis.
utilizing alteplase, we observed similar benefits in terms of mortality and good functional outcome as previous studies. Recently, Hanley33 added further evidence to the safety of alteplase when used for IVF in IVH. They investigated the potential neurotoxicity of the agent and found enhanced lysis of intraventricular blood clots and no significant impact on perihematomal edema.37 We were unable to include perihematomal edema as an endpoint in our study due to insufficient data available to perform a meta-analysis. Another retrospective study assessed safety by evaluating the rates of EVD tract hemorrhage in those receiving IVF and described methods to place ventricular catheters that may reduce complications.38 Although this study provided useful information, more research is needed on the impact of IVF on bleeding complications related to placement of EVDs.

**Limitations and Strengths**

A meta-analysis is only as robust as the quality of articles from which it is derived. The majority of studies included in this analysis are grade II and III levels of evidence. There was also considerable heterogeneity among patient populations, length of follow-up, and conditions (e.g., ICH and subarachnoid hemorrhage) responsible for creating IVH. The sparse amount of studies on this topic restricts us to include articles with heterogeneous patient populations, dosing regimens, and follow-up lengths. These limitations should be carefully considered before generalizing these results to specific patient populations. The sensitivity analysis of only RCTs revealed a trend toward decreased mortality, but no statistical difference ($P = 0.05$). Although RCTs represent the highest level of evidence for this subject, the lack of statistical significance observed with regard to some endpoints may be due to limited sample size and does not reflect the lack of association. These small RCTs, which may have more appropriately been called randomized pilot studies, warrant inclusion of other observational studies. Due to the inclusion of both RCTs and observational studies, there is the potential that results may have been influenced by publication bias or smaller studies having lower

### Figure 4.

Forest plot of all studies with their respective relative risk (RR) and 95% confidence interval (CI), events (ventriculitis), and overall RR. IVF indicates intraventricular fibrinolysis.
Intra ventricular Fibrinolysis in IVH

methodological qualities. However, no evidence of heterogeneity across different type of studies was found through a robust evaluation using 2 statistical tests with no evidence of publication bias.

A multinational, RCT (Clot Lysis Evaluating Accelerated Resolution of IVH [CLEAR-III]) recently began enrollment with the goal of enrolling 500 patients. Although the results of the CLEAR-III study should be the highest quality evidence on the benefits and complications of IVF, it will likely be several years before results are published. We think our study provides the largest and most comprehensive analysis of the existing published literature and will hopefully aid clinicians in making the most informed decision about the use of IVF in patients with IVH. Our study also clearly demonstrates the need for further prospective studies and provides information that may aid in proper utilization of this strategy in existing clinical practice. It establishes that the efficacy of IVF use in IVH is promising and may have an impact on outcomes, such as mortality and functional outcome. Moreover, we report valuable safety data and demonstrated a decreased requirement for permanent cerebral spinal fluid shunting in those treated with IVF. Nonetheless, our analysis lends further support to the need to test the role of IVF in an efficacy trial and is not sufficient to substitute for data from a large, randomized, controlled clinical trial.

Conclusions

In our analysis, the use of IVF significantly decreased mortality, improved functional outcomes, and decreased shunt dependence in IVH. It was not associated with increased rates of ventriculitis or rehemorrhage. Current RCTs are underpowered to provide recommendations about the use of IVF in IVH. These studies do not necessarily reflect the lack of association between IVF and improved outcomes, but rather inadequate sample sizes.

Disclosures

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Khan et al  Intraventricular Fibrinolysis in IVH  2669

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/07/22/STROKEAHA.114.005990.DC1

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SUPPLEMENTAL MATERIAL

Title: Fibrinolysis for Intraventricular Hemorrhage: An Updated Meta-Analysis and Systematic Review of the Literature


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Online Supplement Figure Legends
1. Funnel plot showing symmetrical distribution of studies indicating absence of publication bias

Online Supplemental Data Tables
1. List of included articles, characteristics, conclusions.

Key words: intracerebral hemorrhage, meta-analysis, fibrinolysis

Subject codes: [43] Acute Intracerebral Hemorrhage, [54] Emergency Treatment of Stroke, [74] Stroke Treatment Other - Medical

Running Title: Intraventricular Fibrinolysis in IVH
Supplemental Methods

Search Strategy - The systematic search strategy involved a query through multiple electronic databases and bibliographies of relevant articles. In March and April of 2014, we electronically searched PubMed/MEDLINE, Clinicaltrials.gov, The Cochrane Library, Web of Knowledge, and Scopus to find articles (excluding so-called grey literature) with no time-frame or language restrictions. The following terms in various combinations were used: “fibrinolysis”, “tissue plasminogen activator”, “urokinase”, “streptokinase”, “tPA”, and “intraventricular hemorrhage”. Two researchers (NK and SLL) conducted independent literature searches. If there was any question as to the eligibility of an article, consensus was reached through discussion with the senior author (AA). When necessary, additional contact was made with the authors of the included articles to confirm data.

Statistical Analyses - A random effects meta-analysis was performed on the selected studies. In contrast to a fixed effects model, this method does not assume that the relative risk is the same across studies and yields a more conservative estimate of effect. For each study, the numbers of primary or secondary outcomes in patients treated with IVF and in the controls were identified and a risk ratio (RR) was calculated. We used a continuity correction of 0.5, as appropriate for studies with a zero cell. In cases of two or more zero cells, the assumption of continuity correction was not used and the corresponding point estimates were designated as "not estimable". The overall RR for all pooled studies was computed using the method of DerSimonian and Laird. We also conducted subgroup analyses separately for each of the previously defined secondary endpoints. The mixed-effects model was used to calculate both the pooled point estimate in each subgroup and the overall estimates. According to the mixed-effects model, we used a random effects model (DerSimonian, Laird) to combine studies within each subgroup and a fixed effect model (Mantel–Haenszel method) to combine subgroups and estimate the overall effect. We assumed the study-to-study variance (tau-squared) to be the same for all subgroups. Tau-squared was first computed within subgroups and then pooled across subgroups. The equivalent z test was performed for each pooled odds ratio (OR); p < 0.05 was considered statistically significant.

Heterogeneity between studies was assessed by the Cochran Q and I² statistic. Heterogeneity was considered as statistically significant when the p-value derived from Cochran Q was < 0.1. For the qualitative interpretation of heterogeneity, I² values of at least 50% are usually considered to represent substantial heterogeneity, while values of at least 75% indicated considerable heterogeneity.

Evidence of publication bias was determined using Egger’s formal statistical test. Given that the Cochrane Handbook for Systematic Reviews of Interventions dictates as a rule of thumb that tests for funnel plot asymmetry should be used only when there are at least ten studies included in the meta-analysis, we performed the Egger’s test only in the case of nine or more studies. For the interpretation of Egger’s test, statistical significance was defined as p<0.1. Publication bias (i.e. assessment of bias across studies) was also graphically evaluated using a funnel plot. Statistical analyses were conducted using Review Manager (RevMan) Version 5.2 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and Comprehensive Meta-analysis Version 2 software (Borenstein M, Hedges L, Higgins J, Rothstein H, Biostat, Englewood NJ, 2005).
<table>
<thead>
<tr>
<th>Author</th>
<th>Grade of Evidence †</th>
<th>Study Type</th>
<th>Included Population</th>
<th>Excluded Population</th>
<th>Fibrinolytic Agent &amp; Dosage</th>
<th>Mortality</th>
<th>Good Functional Outcome (GFO)</th>
<th>Ventriculitis</th>
<th>Shunt requirement</th>
<th>Re-hemorrhage</th>
<th>Fibrinolytic complications</th>
<th>Author’s Conclusion</th>
<th>Length of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Todo (1991)</td>
<td>3</td>
<td>Retrospective Cohort Study</td>
<td>Severe IVH due to any cause</td>
<td>None listed</td>
<td>UPA, 10,000 – 12,000 units once or twice daily</td>
<td>F: 0/6: C: 3/5</td>
<td>F: 5/6: C: 0/5</td>
<td>F: 0/6: C: 0/5</td>
<td>F: 2/6: C: 2/2</td>
<td>F: 0/6: C: 0/5</td>
<td>None</td>
<td>UPA improves prognosis of severe IVH</td>
<td>NR</td>
</tr>
<tr>
<td>Rainov (1995)</td>
<td>3</td>
<td>Retrospective Cohort Study</td>
<td>Severe ICH with predominantly IVH</td>
<td>None listed</td>
<td>UPA, 10,000 units twice daily</td>
<td>F: 0/16: C: 1/5</td>
<td>F: 15/16: C: 2/5</td>
<td>F: 0/16: C: 0/5</td>
<td>F: 1/16: C: 2/5</td>
<td>NR</td>
<td>Profuse sweating and headache at &gt;10 mL infusion</td>
<td>UPA is safe, effective and may be used in almost all IVH</td>
<td>1 year</td>
</tr>
<tr>
<td>Akdemir (1995)</td>
<td>3</td>
<td>Prospective, Randomized Cohort Study</td>
<td>Severe IVH</td>
<td>None listed</td>
<td>UPA, 5,000 – 50,000 units twice daily</td>
<td>F: 2/7: C: 6/9</td>
<td>F: 2/7: C: 1/9</td>
<td>F: 0/7: C: 1/9</td>
<td>NR</td>
<td>NR</td>
<td>None</td>
<td>UPA is safe and effective for treatment of IVH</td>
<td>NR</td>
</tr>
<tr>
<td>Coplin (1998)</td>
<td>3</td>
<td>Retrospective Cohort Study</td>
<td>Spontaneous IVH</td>
<td>None listed</td>
<td>UPA, 10,000 units twice daily</td>
<td>F: 7/22: C: 12/18</td>
<td>F: 8/22: C: 4/18</td>
<td>NR</td>
<td>F: 4/22: C: 2/18</td>
<td>F: 1/22: C: 0/18</td>
<td>No significant increase over control group</td>
<td>UPA therapy decreases morality in IVH</td>
<td>NR</td>
</tr>
<tr>
<td>Tung (1998)</td>
<td>2</td>
<td>Randomized Controlled Trial</td>
<td>IVH with HCP</td>
<td>Hemorrhage associated with AVM or aneurysm, parenchymal clots</td>
<td>UPA, 50,000 units twice daily</td>
<td>F: 1/10: C: 7/11</td>
<td>F: 2/10: C: 0/11</td>
<td>F: 2/10: C: 1/11</td>
<td>F: 3/10: C: 3/11</td>
<td>F: 0/10: C: 0/11</td>
<td>Increased ventriculitis</td>
<td>UPA was associated with lower mortality and shunt requirement</td>
<td>3 months</td>
</tr>
<tr>
<td>Tush (1999)</td>
<td>3</td>
<td>Retrospective Cohort Study</td>
<td>IVH</td>
<td>None listed</td>
<td>UPA, 5,000 – 10,000 units once or twice daily</td>
<td>F: 1/5: C: 2/4</td>
<td>NR</td>
<td>F: 2/5: C: 0/4</td>
<td>F: 0/5: C: 1/4</td>
<td>F: 1/5: C: 0/4</td>
<td>Increase in CSF infections</td>
<td>UPA trended towards improved acute neurological recovery, worsened long-term neurological outcomes, decreased shunt requirements, and increased CSF infection rate</td>
<td>NR</td>
</tr>
<tr>
<td>Naff (2000)</td>
<td>2</td>
<td>Randomized Controlled Trial</td>
<td>IVH with or without ICH</td>
<td>Hemorrhage associated with AVM or aneurysm, pregnancy, age &lt;18 years</td>
<td>UPA, 5,000 – 25,000 units twice daily</td>
<td>F: 3/12: C: 1/8</td>
<td>NR</td>
<td>F: 0/10: C: 0/8</td>
<td>NR</td>
<td>F: 1/12: C: 0/8</td>
<td>None</td>
<td>Low dose UPA in IVH is safe and may reduce mortality</td>
<td>30 days</td>
</tr>
<tr>
<td>Naff (2004)</td>
<td>2</td>
<td>Randomized Controlled Trial</td>
<td>Spontaneous supratentorial ICH &lt; 30 mL with IVH causing obstructive HCP</td>
<td>Coagulopathy, age &lt; 18 years, untreated AVM or aneurysm, pregnancy</td>
<td>UPA, 25,000 units twice daily</td>
<td>F: 0/6: C: 1/5</td>
<td>NR</td>
<td>F: 0/7: C: 1/5</td>
<td>NR</td>
<td>F: 0/7: C: 1/5</td>
<td>None</td>
<td>UPA speeds resolution of IVH</td>
<td>NR</td>
</tr>
<tr>
<td>Gubuz (2004)</td>
<td>3</td>
<td>Prospective, Randomized Cohort Study</td>
<td>Hypertension-related supratentorial ICH with IVH</td>
<td>None listed</td>
<td>UPA (Not available)</td>
<td>F: 5/16: C: 6/11</td>
<td>NR</td>
<td>NR</td>
<td>F: 0/16: C: 0/11</td>
<td>None</td>
<td>UPA is safe</td>
<td>30 days / 1 year</td>
<td></td>
</tr>
<tr>
<td>Varelis (2005)</td>
<td>3</td>
<td>Prospective Cohort Study</td>
<td>Aneurysmal SAH with IVH</td>
<td>None listed</td>
<td>tPA, 2mg once to twice daily</td>
<td>F: 1/10: C: 4/10</td>
<td>F: 4/10: C: 3/10</td>
<td>F: 0/10: C: 0/10</td>
<td>F: 2/9: C: 5/6</td>
<td>F: 0/10: C: 0/10</td>
<td>No significant increase over control group</td>
<td>IPA administration is feasible without complications after SAH and may be associated with better outcomes</td>
<td>NR</td>
</tr>
<tr>
<td>Author</td>
<td>Grade of Evidence</td>
<td>Study Type</td>
<td>Included Population</td>
<td>Excluded Population</td>
<td>Fibrinolytic Agent &amp; dosage</td>
<td>Mortality</td>
<td>Good Functional Outcome (GFO)</td>
<td>Ventricularis</td>
<td>Shunt requirement</td>
<td>Re-hemorrhage complications</td>
<td>Author’s Conclusion</td>
<td>Length of follow-up</td>
<td></td>
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</tr>
<tr>
<td>Ramakrishnan (2010)</td>
<td>3 Selection:***</td>
<td>Retrospective Cohort Study</td>
<td>Primary IVH or Aneurysmal SAH with IVH and at least a Hunt &amp; Hess Grade of 3</td>
<td>Coagulopathy, those whose aneurysms were not treated within 48 hours</td>
<td>tPA 5mg daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>IA and not associated with ICH volume</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Torres (2008)</td>
<td>3 Selection:***</td>
<td>Retrospective Cohort Study</td>
<td>Primary supratentorial ICH with IVH without operative intervention</td>
<td>Hemorrhage associated with AVM or aneurysm</td>
<td>tPA 1 or 3mg twice daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>UPA is safe and effective in prevention of EVD blockage and facilitates rapid clearance of IVH</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Dunatov (2011)</td>
<td>3 Selection:***</td>
<td>Prospective Cohort Study</td>
<td>ICH and IVH in those who presented within 6 hours of onset</td>
<td>Previously known AVM or aneurysm, traumatic or pontine ICH, coagulopathy, acute renal failure or MI, history of CHF, ICH score 1 and 5, pregnancy or lactation</td>
<td>tPA 1mg twice daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>IA and not associated with ICH volume</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Hallett (2011)</td>
<td>3 Selection:***</td>
<td>Retrospective Cohort Study</td>
<td>ICH with IVH</td>
<td>Hemorrhage associated with AVM or other secondary etiologies</td>
<td>tPA 1-2mg daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>IA is safe and may lead to better outcomes</td>
<td>Discharge</td>
<td></td>
</tr>
<tr>
<td>Naff (2011)</td>
<td>2 JADAD 4/5</td>
<td>Randomized Controlled Trial</td>
<td>Aged 18-75 years with supratentorial ICH &lt;30mL</td>
<td>Hemorrhage associated with AVM, aneurysm, or tumor; Infarctional or subarachnoid location, pregnancy, coagulopathy</td>
<td>tPA 3mg twice daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>IA and not associated with ICH volume</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>King (2012)</td>
<td>2 JADAD 5/5</td>
<td>Randomized Controlled Trial</td>
<td>Aged 16 - 75 years with supratentorial ICH &lt;30 mL and IVH of any volume</td>
<td>Hemorrhage associated with AVM, aneurysm, or trauma; Infarctional or subarachnoid location, coagulopathy, no history of hypertension</td>
<td>UPA 25,000 units twice daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Treatment with UPA is safe and more effective than EVD alone</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Litracco (2012)</td>
<td>2 JADAD 3/5</td>
<td>Randomized Controlled Trial</td>
<td>Aneurysmal SAH with severe ICH causing 3rd and 4th ventricle</td>
<td>Age &lt; 18 years, multiple ruptured aneurysms, coagulopathy, pregnant</td>
<td>tPA 3mg twice daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>IA and not associated with ICH volume</td>
<td>1 year</td>
<td></td>
</tr>
<tr>
<td>Ziai (2013)</td>
<td>3 Selection:***</td>
<td>Retrospective Cohort Study</td>
<td>Spontaneous R II H &lt;40mL and secondary IVH causing acute obstructive HCP</td>
<td>None listed</td>
<td>tPA 4mg twice daily, then changed to 1mg three times daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>IA is safe and not associated with ICH volume</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Hollingsworth (2013)</td>
<td>2 JADAD 2/5</td>
<td>Randomized Controlled Trial</td>
<td>Spontaneous ICH &lt;50mL and secondary IVH causing acute obstructive HCP</td>
<td>Hemorrhage associated with AVM or aneurysm, posterior fossa location; severe complicating illness, active internal bleeding, heparin use, coagulopathy, pregnancy, age &lt; 18 years</td>
<td>tPA 0.3mg twice daily, 1mg twice daily, 1mg three times daily</td>
<td>NR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>IA is safe and not associated with ICH volume</td>
<td>Discharge or 30 days</td>
<td></td>
</tr>
</tbody>
</table>

**Evidence Grade:**
- 1: Insufficient
- 2: Low
- 3: Moderate
- 4: High
- 5: Very high
<table>
<thead>
<tr>
<th>Author</th>
<th>Grade of Evidence †</th>
<th>Study Type</th>
<th>Included Population</th>
<th>Excluded Population</th>
<th>Fibrinolytic Agent &amp; dosage</th>
<th>Mortality</th>
<th>Good Functional Outcome (GFO)</th>
<th>Ventriculitis</th>
<th>Shunt requirement</th>
<th>Re-hemorrhage</th>
<th>Fibrinolytic complications</th>
<th>Author’s Conclusion</th>
<th>Length of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabiano (2013)</td>
<td>3</td>
<td>Retrospective Cohort Study</td>
<td>Patients receiving ventricular tPA who developed a fever</td>
<td>None listed</td>
<td>tPA (Not reported)</td>
<td>NR</td>
<td>NR</td>
<td>F: 6/7</td>
<td>C: 4/86</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Increased ventriculitis risk with tPA administration NR</td>
</tr>
<tr>
<td>Kramer (2014)</td>
<td>2</td>
<td>Randomized Controlled Trial</td>
<td>Aged &gt; 18 years with aneurysmal SAH with IVH</td>
<td>Aneurysm unsecured, coagulopathy, active extracranial hemorrhage, pregnancy, tPA allergy</td>
<td>tPA 2mg twice daily</td>
<td>F: 1/6</td>
<td>C: 2/6</td>
<td>F: 3/6</td>
<td>C: 3/6</td>
<td>F: 1/6</td>
<td>F: 0/6</td>
<td>F: 2/6 C: 2/6</td>
<td>No significant increase over control group tPA accelerates clearance of SAH and IVH 6 months</td>
</tr>
</tbody>
</table>

AVM = arteriovenous malformation; C = control group; CHF = chronic heart failure; CSF = cerebrospinal fluid; EVD = extraventricular drain; F=Fibrinolytic group; HCP = hydrocephalus; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mg = milligrams, mL = milliliters; MI= myocardial infarction; NR = not reported; SAH = subarachnoid hemorrhage; tPA = alteplase; UPA = urokinase; † Grades of evidence were determined using OCEBM for all, Newcastle Ottawa Scale for Cohort Studies, and the JADAD scale for Randomized Controlled Trials.
Figure I

Figure Legend: Funnel plot showing symmetrical distribution of studies indicating absence of publication bias
Supplemental References


