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Efficacy and safety of local fibrinolytic therapy in intracranial hemorrhages: A systematic review and meta-analysis of randomised controlled trials

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1. Background

Stroke is the second leading cause of mortality and third leading cause of disability worldwide, accounting for 12% of the total deaths.[1] Hemorrhagic strokes alone account for 10–20% of all strokes with intracerebral haemorrhage (ICH) having a high case fatality rate of up to 48%.[1,2] Despite the recently published data, there is no standard protocol for treating these patients.[3–5] Two large trials (STICH and STICH II) comparing early surgery vs initial conservative/medical treatment for spontaneous ICH did not find a significant difference in the clincal outcome.[6,7] Hence, there is a paradigm shift to focus on minimally invasive techniques like the endoscopic evacuation of the hematoma and direct administration of fibrinolytics into the hematoma through an externally placed drain.[8,9] The efficacy of such procedures in improving the clinical outcome still remains urcertain.[10]

In CLEAR III trial, direct administration of alteplase through EVD for IVH showed a faster clearance of blood from the ventricle with decreased incidence of hydrocephalus.[11] Similalry, other studies foused on direct administration of fibrinolytics into the clot for ICH, also concluded that there is a decrease in mortality but it led to more survivors with a severe disabilities.[12,13] However, such intervention has also been attributed to cause an increased risk of ventriculitis and new haemorrhages.[13,14]

In 2020, Van Solinge et al[15] published the only systematic review on fibrinolytic therapy for IVH by including both RCTs and observational studies. That study concluded that the mortality was less (relative risk-RR 0.58 with 95% CI 047–0.72) in the intervention arm and time-to-clearance of the blood is quicker (median difference of 4.05 days; 95% CI - 5.52–2.57). Although, there was no difference in good clincal outcome but an increase in the risk of new ICH was reported (RR 1.67 with 95% CI 1.01–2.74). This review is limited due to inclusion of observational studies that may have contaminated the quality of results synthesis. To mitigate this shortcoming, we only included RCTs in this review that are published both on ICH and IVH, regarding the direct administration of intra-hematoma fibrinolytics.

2. Statement of objective

To quantify the effectiveness and safety of intra-hematoma fibrinolytics therapy in patients with spontaneous supratentorial ICH and IVH.

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3. Methodology

Systematic review reporting has been conducted in compliance with updated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines 2020 checklist.[16]

4. Eligibility (inclusion/exclusion) criteria

All registered RCTs (irrespective of the publication status) published in English language on direct intra-clot fibrinolytics administration in the treatment of ICH or/and IVH were included and these have reported at least mortality or functional outcome. The participants were people of all ages and had the intervention arm with administration of fibrinolytics directly into the clot while control arm had different comparators as below;

- Intra hematoma fibrinolytics vs standard medical treatment for ICH
- Intra hematoma fibrinolytics vs open craniotomy for ICH evacuation
- Intra hematoma fibrinolytics vs EVD alone for IVH
- Intra hematoma fibrinolytics vs EVD with saline administration for IVH.
- Minimally invasive hematoma evacuation with Intra hematoma fibrinolytics administration vs standard medical treatment.

Hemorrhages due to vascular malformation/intracranial aneurysms were excluded.

5. Information sources and search strategy

The electronic databases searched for relevant studies, included Medline, Embase, Cochrane Central Register of Controlled Trials, CINAHL, Web of Science and Scopus. In addition to the manual search of reference lists of all relevant articles, we also included the pertinent ongoing clincal trials that were registered in World Health Organization Clinical Trials Registry Platform (ICTRP), Clinicaltrials.gov and EU Clinical Trials Register.

Initially, a search question was formulated into search concepts for participants intervention, comparators, outcome, and type of study (PICOS framework). All the possible synonyms of each search concept were then listed as search terms. Corresponding controlled vocabularies were identified for search terms in the databases, where available. Finally, database-specific search options (truncation, proximity searching, etc.) and appropriate Boolean operators were used to form the final search strategy (Appendix 1). In order to increase the sensitivity of the search, only the search terms for participants, intervention and type of study were used in the final search strategy in most of the databases. Since there were many study results (>26,000) retrieved in Scopus, search terms for primary outcomes of interest were also included in the search strategy.

6. Selection and data extraction process

After running the search in each database separately, the results were collated and duplicates were removed. The title and abstract of all the results were then screened for selection criteria. If the studies met the inclusion criteria or when there was doubt, the full text of the studies was examined. Study selection and data extraction were done through an online tool (Eppi reviewer™ https://eppi.ioe.ac.uk/) and analysed with review manager (Revman 5.4), a Cochrane's bespoke software for writing systematic reviews. The following data were collected from the included studies.

- •Type of study design, first author name, dates, and countries of study
- •Number randomised to each group
- Details of intervention, including the name of the fibrinolytics used, dose and method of its use, methods of evacuation of the hematoma before administering the fibrinolytics, details of the standard medical or surgical treatment, etc.
- •Primary and secondary outcomes of interest to this systematic review.

7. Data items for outcome measures

7.1. Primary outcomes

- •Mortality at the end of the follow-up period
- •The functional outcome as measured by a modified Rankin scale (mRS) or Glasgow outcome scale (GOS)/its extended version (GOS-E) at the end of the follow-up period. Dichotomised mRS and GOS/GOS-E were used to categorise the outcomes into either favourable or unfavourable outcome.

7.2. Secondary outcomes

- New intracranial haemorrhage
- •CNS infections/Ventriculitis
- •Time-to-clearance of clot
- •Shunt-dependent hydrocephalus

8. Risk of bias assessment

The risk of bias of each included study was assessed by the Cochrane risk-of-bias tool for randomised trials (RoB).[17] Modified Rankin Scale was used as an outcome to assess the risk of bias and if the studies have not measured mRS, then either GOS/GOS-E or mortality was used for assessing risk of bias. In addition, the reporting bias were analysed through a funnel plot with symmetry in these plots projecting the publication bias.

9. Measurement of treatment effect

All the raw data were collected based on intention-to-treat analysis. For binary outcome variables, unadjusted odds ratios (OR) and 95% Confidence intervals (CI) were calculated from the raw data presented in the study. For continuous outcome variable, standardised mean difference and 95% CI were calculated.

10. Synthesis methods

Studies with missing outcome data were excluded from the meta-analysis. Extracted data were stored in the study laptop and analysed with Stata statistical software, and summary estimates (odds ratio with 95% confidence interval) were computed. The point estimates of the outcome data were summarised along with the effect of missing data, bias and confounding on the outcome in all the included studies.

11. Reporting bias assessment and heterogeneity

The missing outcome data for all the included studies were analysed in the risk of bias assessment. The authors of the included studies were contacted for some missing outcome data where applicable. The heterogeneity of the data was analysed using the I2 statistics. A value of >50% was considered high heterogeneity, and the data were analysed by the Random-effects model. The data were analysed by a fixed effect model if there was no heterogeneity in the data. If there was heterogeneity in data, it was critically evaluated to explore the reasons for such differences between the studies.

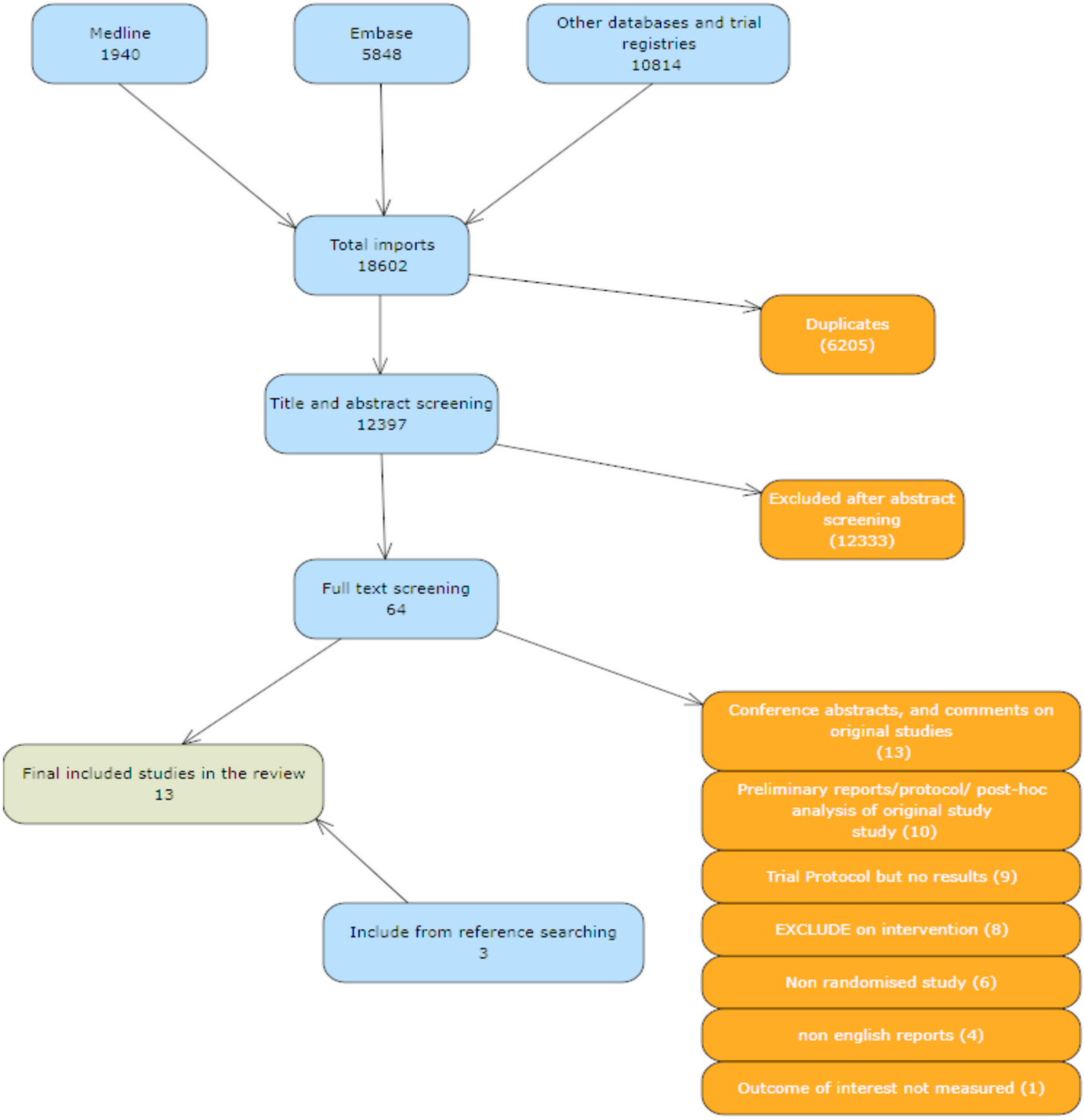

Fig. 1. PRISMA Flowchart of search strategy.

12. Results

12.1. Study selection

The complete search strategy identified 18,601 records and 77 records were filtered for full-text review that were narrowed down to 10 studies as per selection criteria. References searching yielded further 3 studies leading to a total of 13 studies (Figure-1).[11,18–29] Nine clinical trial protocols were published in various clinical trial registries, of which four were published after 2017 but no study results available for any of these ongoing trials until the period of search for this review (January 1991 till June 2022).[8–10,30–35] All the principal investigators were contacted via email published for the details of these ongoing trials but details remained inaccessible.

12.2. Study characteristics

All the included studies were parallel-group RCTs and there are three multinational, multicenter trials.[11,19,27] Five out of 13 studies were conducted in multiple centres, 3 of which were in China, one each in the USA and Netherland.[18,22–24,28] All the other studies were conducted in a single centre, one each in Turkey, UK, USA, Italy and

Table 1
Characteristics of the studies.

Short Title	Participants	Intervention arm	Control arm	Outcomes[a]
Akdemir et al[29] (1995)	**Setting** IVH Region/country Turkey Cause and location of ICH Primary supratentorial including anticoagulants induced. the control group includes aneurysm	EVD + fibrinolytics **Number randomised**- 7 **Fibrinolytics dose and protocol** Urokinase- 5000 IU of 50,000 IU/5 ml solution -infused twice a day followed by 15 min of drain clamping. **Number completed follow up**- 7	EVD alone **Number randomised**- 9. **Control intervention protocol** Continuous drainage of CSF through EVD **Number completed follow up**-9.	**Study's primary outcome**- Functional outcome measured by GOS **Study's secondary outcome**- late hydrocephalus
Hanley et al[27] (2016)	**Setting** ICH Region/country Multinational Cause and location of ICH Supratentorial ICH ICH volume >20 ml	MIS + fibrinolytics with EVD **Fibrinolytics dose and protocol:** "Alteplase- 0·3 mg in 1 mL or 1·0 mg in 1 mL every 8 h, for up to nine doses. All doses were followed by a 3 mL saline flush with closure of EVD system for 1 h" [Page- 1230] **Number randomised**: 54 **Number completed follow up**: 52.	Standard medical treatment **Number randomised:** 42 **Number completed follow up**: 38 **Control intervention protocol**: Patients allocated to the standard medical care group underwent standard care according to the American heart association guidelines for non-traumatic ICH	**primary outcome** •Mortality at 30 days • Bacterial brain infection at 30 days •symptomatic bleeding within 72 h after the last dose **secondary outcome** •clot size reduction •mRS at 180 days
Hanley et al[11] (2017)	**Setting** IVH Region/country Multinational Cause and location of ICH/IVHSupratentorial ICH/IVH ICH volume <30 ml	EVD + fibrinolytics **Number randomised:** 249 **Fibrinolytic used and dose:** 1 mg alteplase every 8 h, up to 12 doses followed by a 3 mL saline flush with closure of EVD system for 1 h. **Number completed follow up**: 246	EVD + saline **Control intervention protocol** 0.9% saline injection every 8 h, up to 12 doses followed by a 3 mL saline flush with closure of EVD system for 1 h. **Number randomised**: 251 **Number completed follow up**: 245	**Study's primary outcome** functional outcome measured by dichotomised mRS at 180 days. **Study's Important secondary Outcome** •Bacterial brain infection •symptomatic bleeding •All-cause mortality •Amount of residual blood
Hanley et al[19] (2019)	**Setting** ICH Region/country Multinational Cause and location of ICH/IVH IVH with or without Supratentorial ICH ICH volume >30 ml	MIS + fibrinolytics with EVD **Number randomised**: 250 **Fibrinolytics dose and protocol**: Injecting "alteplase directly into the clot through the catheter, at 1·0 mg in 1 mL followed by 3 mL flush every 8 h, for up to nine doses" "All doses were followed by a 3 mL flush of preservative-free normal saline, and the system was closed for 1 h "[Page- 1023] **Number completed follow up**: 250	Standard medical treatment **Number randomised**: 249 **Control intervention protocol**: Participants were treated according to "American Heart Association and European Stroke Organisation recommendations for treatment of non-traumatic spontaneous intracerebral haemorrhage medical care group had follow-up CT scans and other monitoring assessments on the same schedule as those in the intervention group" [Page 1024] **Number completed follow up:** 249	**Study's primary outcome:** mRS (0 to 3) at 365 days **Study's Important secondary outcome**: •Dichotomised eGOS 365 days •All-cause mortality 365 •Clot resolution rate
Zhou et al[24] (2011)	**Setting** ICH Region/country China- Multicentre Cause and location of ICH Hypertensive supratentorial ICH ICH volume 30–100 ml	Stereotactic aspiration + fibrinolytics **Number randomised**: 90 **Fibrinolytics dose and protocol**: 20,000U to 40,000U urokinase in 2–3 ml of saline injected in to the clot 3–5 times/day for 2–4 days **Number completed follow up**: 90	Standard craniotomy **Number randomised**: 78 **Control intervention protocol**: Traditional large craniotomy and evacuation of the hematoma **Number completed follow up**: 78	**Study's outcomes:** Mortality rate Functional status measured by -Glasgow outcome scale. Activities of daily living at 365 days measured by •Barthel index •Rankin scale (mRS 0–5)
King et al[26] (2012)	**Setting** IVH Region/country Singapore Cause and location of ICH/IVH IVH with or without Supratentorial ICH ICH volume <30 ml	EVD + fibrinolytics **Number randomised**: 7 **Fibrinolytics dose and protocol** 25,000 U of urokinase injection into the clot once in 12 h for 3 days followed by closure of EVD for 1 h **Number completed follow up**: 7	EVD + saline **Number randomised:** 9 **Control intervention protocol** same volume of saline injection via EVD **Number completed follow up**: 9	**Study's primary outcome:** •Length of ICU stay. •VP shunt rate •Rate of ventriculitis **Study's secondary outcome** Functional outcome

(*continued on next page*)

Table 1 (*continued*)

Short Title	Participants	Intervention arm	Control arm	Outcomes[a]
				measured by •NIHSS •mRS and survival at 6 months
Luciano et al[20] (1997)	**Setting** Premature IVH Region/country Italy Cause and location of ICH/IVH Premature IVH of preterm	EVD + fibrinolytics **Number randomised**: 6 **Fibrinolytics dose and protocol**: Continuous infusion of "Streptokinase (made with 12 ml of glucose saline), over 96 h at a dosage of 20,000 U/day (in- fusion rate 0.5 ml/h). CSF drainage through the catheter was per formed several times each day as required to maintain a normal ICP. The amount of drained CSF was in no case less than 12 ml/day, equal to the amount of fluid infused into the ventricle." [page: 73] **Number completed follow up**: 6	Standard medical treatment **Number randomised**: 6 **Control intervention protocol**: infants were "treated with diuretics (furosemide 2 mg/kg/day) only or subjected to ventriculostomy through the anterior fontanel for CSF drainage if raised ICP was observed." [page: 74] Number completed follow up: 6	**Study's primary outcome:** VP shunt rate **Study's secondary outcome:** •Concentration of fibrin degradation products in CSF •Mortality
Naff et al[21] (2004)	**Setting** IVH Region/country USA Cause and location of ICH Hypertensive supratentorial ICH ICH volume <30 ml	EVD + fibrinolytics **Number randomised**: 7 **Fibrinolytics dose and protocol**: Injection of "urokinase (25,000 international units [IU]) in 1 ml of normal saline solution every 12 h" "After each injection, the IVC was closed for 1 h" "injections continued every 12 h until EVD was discontinued, according to prespecified criteria, i.e., the patient tolerated 24 h of IVC closure with no sustained elevation of intracranial pressure above 15 mm Hg" [Page-578] **Number completed follow up**: 7	EVD + saline **Number randomised**: 5 **Control intervention protocol**: "1-ml placebo injections of normal saline solution every 12 h" "injections continued every 12 h until EVD was discontinued, according to prespecified criteria, i.e., the patient tolerated 24 h of IVC closure with no sustained elevation of intracranial pressure above 15 mm Hg." [Page-578] **Number completed follow up**: five	**Study's outcome** clot resolution rate
Naff et al[22] (2011)	**Setting** IVH Region/country USA- Multicentre Cause and location of ICH Supratentorial ICH ICH volume <30 ml	EVD + fibrinolytics **Number randomised**: 26 **Fibrinolytics dose and protocol**: "3 mg/3 mL of rtPA" "administration was continued every 12 h until CT evidence of clot resolution was sufficient to remove the catheter (at a minimum the opening of the third and fourth ventricles) or until a safety end point (symptomatic bleeding, infection, or death) occurred, whichever came first" [page- 3010] **Number completed follow up**: 26	EVD + saline **Number randomised**: 22 **Control intervention protocol**: "3 mL of normal saline" "administration was continued every 12 h until CT evidence of clot resolution was sufficient to remove the catheter (at a minimum the opening of the third and fourth ventricles) or until a safety end point (symptomatic bleeding, infection, or death) occurred, whichever came first" [page- 3010] **Number completed follow up**: 22	**Study's primary outcome** •Mortality •Ventriculitis • Rebleeding at 30 days **Study's secondary outcome** rate of clot lysis
Teernstra et al[28] 2003	**Setting** ICH Region/country Netherlands- Multicentre Cause and location of ICH Primary supratentorial ICH including anticoagulants induced ICH volume >10 ml	Stereotactic aspiration + fibrinolytics **Number randomised**: 36 **Fibrinolytics dose and protocol**: "5000 IU of urokinase dissolved in 1 mL NaCl 0.9% was injected via the catheter, which was subsequently flushed with 1 mL NaCl 0.9%, after which it was clamped" "This evacuation and urokinase injection procedure was performed eight times at 6-h intervals over a period of 48 h, before the catheter was removed." [Page- 969] **Number completed follow up**: 36	Standard medical treatment **Number randomised**: 35 **Control intervention protocol**: "nonsurgical group received standard supportive medical care "[Page- 969] **Number completed follow up**: 34	**Study's primary outcome** Mortality at 6 months **Study's secondary outcome**: •Reduction of ICH volume •Functional outcome measured by mRS
Sun et al[18] (2010)	**Setting** ICH Region/country China- Multicentre Cause and location of ICH Basal ganglia ICH ICH volume 30–80 ml	Stereotactic aspiration + fibrinolytics **Number randomised**: 159 **Fibrinolytics dose and protocol**: Injection of urokinase (10,000–50,000 U) into the clot, 3–4 times in the first 24 h and 2–3 times in the second 24 h. **Number completed follow up**: 136	Standard craniotomy **Number randomised**: 145 **Control intervention protocol** Craniotomy with bone flap diameter of 3 cm and evacuation of the hematoma **Number completed follow up**: 108	**Study's outcome** Death at 90 days Disability assessed by • mRS at day 14 • BI at day 90

(*continued on next page*)

Table 1 (*continued*)

Short Title	Participants	Intervention arm	Control arm	Outcomes[a]
Wang et al[23] (2009)	**Setting** ICH Region/country China- Multicentre Cause and location of ICH Basal ganglia ICH ICH volume 25–40 ml	Stereotactic aspiration + fibrinolytics **Number randomised**: 195 **Fibrinolytics dose and protocol** Injection of urokinase (10,000–50,000 U) into the clot for 3–5 days **Number completed follow up**: 185	Standard medical treatment **Number randomised**: 182″ **Number completed follow up**: 167	**Study's outcome** Death at 90 days Disability assessed by •mRS at day 14 •BI at day 90
Whitelaw et al[25] 2007	**Setting** Premature IVH Region/country UK Cause and location of ICH Premature IVH of preterm	EVD + fibrinolytics **Number randomised**: 39 **Fibrinolytics dose and protocol**: "rTPA 0.5 mg/kg was injected intraventricularly. After 8 h, artificial CSF with 10 mg of vancomycin and 5 mg/500 mL intrathecal gentamicin was infused at 20 mL/h into the right frontal ventricular catheter with a pressure transducer on the in-going line. Simultaneously, fluid was allowed to drain from the left occipital ventricular catheter, the height of the drainage reservoir being raised or lowered to maintain the ICP below 7 mm Hg. It was usually necessary to drain 60 to 100 mL/24 h more than the infused volume to maintain normal pressure" [Page 1073] **Number completed follow up**: 39	Standard medical treatment **Number randomised**: 38 **Control intervention protocol** "The infant was observed for daily for raised ICP" "Suspected raised ICP or excessive head expansion prompted a lumbar puncture (LP) with the object of removing 10 to 20 mL/kg over 10 to 20 min" "When >2 LPs were necessary or when the LP failed to drain enough to normalize head growth to <2 mm/day, a ventricular reservoir was indicated" [Page-1073] **Number completed follow up**: 38	**Study's primary outcome** •Composite outcome of VP shunt + death at 6 months •Disability measured by Bailey's score of Infant development at 2 years. **Study's secondary outcome** Secondary IVH

[a] Functional outcome scales have been dichomatized as favourable vs unfavourable for mrS (0–3 vs 4–5), GOS (good recovery-moderate disability vs severe disability to death and GOS-e (upper good recovery to upper severe disability vs lower severe disability to death).

Singapore.[20,21,25,26,29] Six out of 13 studies were conducted on patients with ICH[18,19,23,24,27,28] and the rest were conducted on patients with IVH causing obstructive hydrocephalus. Two studies out of 13 were conducted on neonates.[20,25] There were two studies conducted on patients with basal ganglia ICH[18,23] while the rest of the studies included patients with both lobar and deep supratentorial ICH/IVH.

12.3. Results of individual studies

Intraventricular hemorrhage studies involved only one type of intervention: administering fibrinolytics into the clot in the ventricle via external ventricular drain (EVD), though the choice of fibrinolytics, its dosage and protocol varied among them. Intracerberal hemorrhages studies involved two types of procedures before administering fibrinolytics into the clot. Hence there were five different sets of intervention and comparators in the included studies. For primary outcome, all-cause mortality and functional outcome with dichomatized mRS and GOS/eGOS has been anlysed while secodanry outcomes including new ICH, CNS infections, shunt-dependent hydrocephalus and time-to-clot resolution have also been assessed in each individual study (Table-1).

12.4. Risk of bias in studies

Modified Rankin Sscale was used as an outcome of interest for risk-of-bias (ROB) assessment in 6 out of 13 studies[11,18,19,23,27,28] while GOS was used in Akdemir et al study.[29] For the rest of the studies, mortality was used to assess ROB (Fig. 2). There were no imbalances in the baseline characteristics reported in all but one trial.[28] In Teernstra et al study,[28] there were significant differences in volume and location of ICH between the intervention and the control arms. The ICH was large and mostly were lobar (vs deep) in the intervention arm. Because the mRS was available only for six studies, publication bias could not be assessed with the funnel plot.

13. Results of data synthesis

The effects were pooled for different intervention and comparator sets for meta-analysis, using Revman 5 software tool (https://revman.cochrane.org).

13.1. Primary outcomes

All the included studies reported mortality at the end of follow up (Fig. 3). In pooled analysis for IVH patients, fibrinolysis vs saline for IVH showed a reduction in the risk of death in the fibrinolysis arm [RR-0.63 (0.46, 0.85) p = 0.003]. CLEAR III trial[11] was the largest trial with a significant decrease in the treatment arm's mortality [RR-0.64 (0.46, 0.88) p = 0.006]. All the other trials showed statistically significant results but had wide confidence intervals due to the small sample size. In newborns with IVH, fibrinolysis vs EVD alone [RR-0.43 (0.12, 1.51) p = 0.19] and fibrinolysis vs standard care [0.65 (0.20, 2.15) p = 0.48] showed nonsignificant reduction in the risk of mortality.[20,25] In pooled analysis of ICH patients, a reduction in the risk of death in the intervention arm was noticed in fibrinolysis vs standard craniotomy [0.60 (0.40, 0.89) p = 0.01][18,24] and fibrinolysis vs standard medical treatment [RR-0.83 (0.65, 1.05) p = 0.12].[19,23,27,28] The largest trial in this domain was MISTIE III trial that also showed comparable statistically significant results [RR-0.77 (0.55, 1.08) p = 0.07].[27]

Six out of 13 studies measured outcome by dichotomized mRS (Fig. 4). In the CLEAR III trial[11] (fibrinolysis vs saline for IVH), thw results were statistically nonsignicant for the good functional outcome [RR-1.07 (0.88, 1.30) p = 0.48]. For fibrinolysis vs standard medical treatment for ICH, the proportion of people with the favourable outcome is greater in the fibrinolysis arm [RR-1.20 (1.00, 1.44) p = 0.05].[19,23,27,28] In the CLEAR III trial (fibrinolysis vs saline for IVH),[11] the proportion of people with favourable outcomes measured by GOS-E is also more in the fibrinolysis arm [RR-1.24 (0.97, 1.59) p = 0.08]. In the Akdemir study[29] of neonates, there was statistically nonsignificant

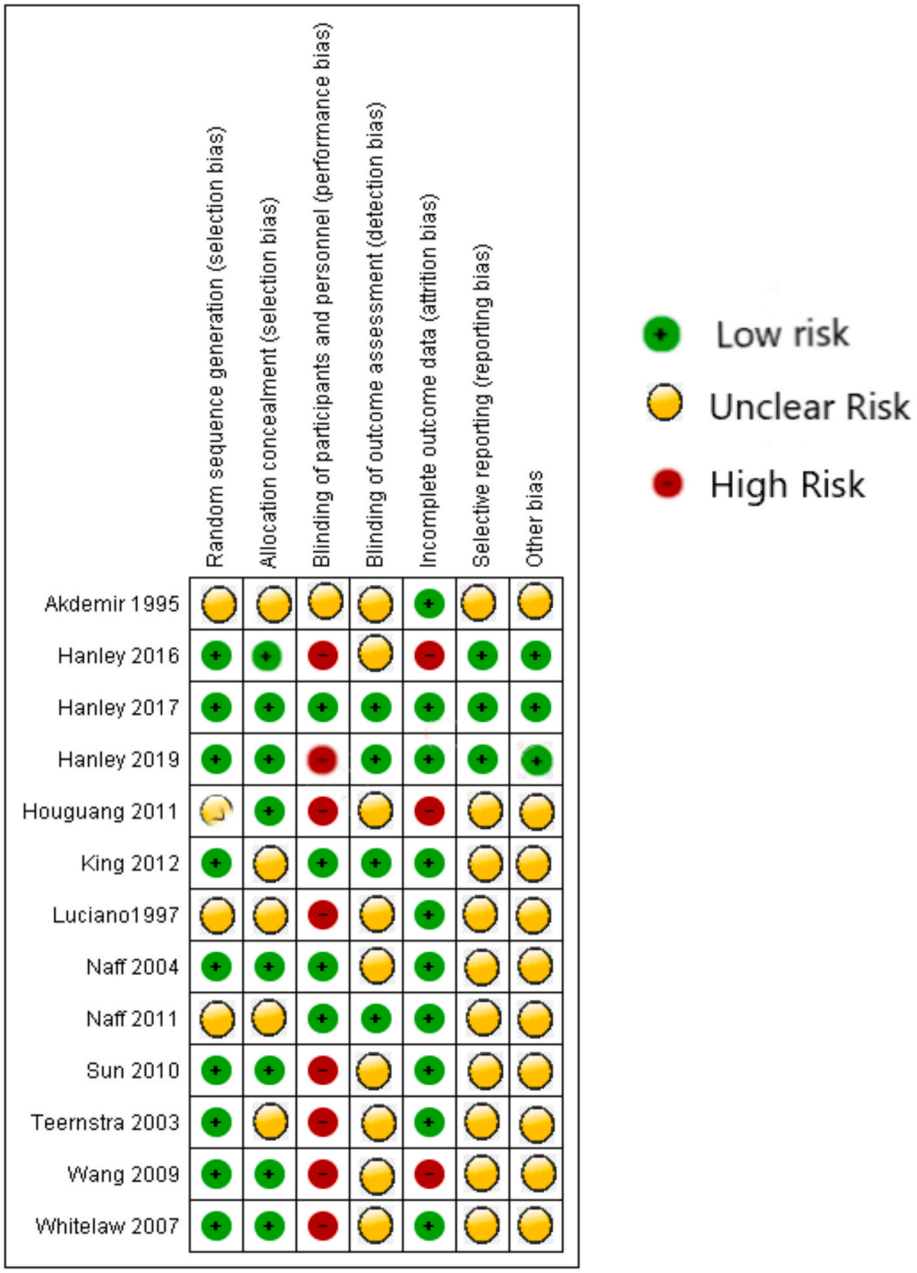

Fig. 2. Overview of Risk of Bias assessment.

difference in the good functional outcome measured by GOS between the study arms comparing fibrinolysis vs EVD alone in IVH [RR-3.21 (0.87, 11.90) p = 0.08] and CI was wide due to small sample size (Fig. 5).

13.2. Secondary outcomes

For CNS infections/ventriculitis (Fig. 6), fibrinolysis vs saline in IVH showed reduced risk of ventriculitis in fibrinolysis arm [RR-0.59 (0.35, 1.00) p = 0.05] but for fibrinolysis vs standard medical treatment in ICH, the risk of brain infections between the study arms remained nonsignificant [RR-1.34 (0.24, 7.49) p = 0.74].[11,22,26] While for the risk of developing new hemorrhages (Fig. 7), there was nonsignificant difference in the risk of any new bleeding in the fibrinolysis vs saline in IVH [RR-1.36 (0.44, 4.23) p = 0.60] but a higher risk of new bleeding in fibrinolysis arm was noted both in Whitelaw study[25] of fibrinolysis vs standard care in neonates in IVH [RR-4.22 (1.31, 13.65) p = 0.02] and fibrinolysis vs standard medical treatment for ICH [RR-2.27 (1.23, 4.19) p = 0.009].[23,27] However, for fibrinolysis vs standard craniotomy in patients with ICH, there was significant reduction in the risk of bleeding in the fibrinolysis arm [RR-0.48 (0.30, 0.78) p = 0.003].[18,24]

For shunt-dependent hydrocephalus (Fig. 8), in fibrinolysis vs saline for IVH, the results were statistically nonsignificant between the study arms [RR-1.10 (0.77, 1.59) p = 0.59][11,22,26] while in Akedemir study (fibrinolysis vs EVD alone for IVH), a higher risk of shunt dependent hydrocephalus in the fibrinolysis arm [RR-3.21 (0.87, 11.90) p = 0.08] was found.[29] Finally, in time-to-clot resolution results synthesis (Fig. 9), there was a greater daily percentage reduction of clot size in the fibrinolysis arm [SMD-0.93 days (0.39 days, 1.47 days) p = 0.0008] in fibrinolysis vs saline for IVH.[21,22] MISTIE III (fibrinolysis vs standard medical treatment for ICH) trial also reported a greater daily percentage reduction of clot size in the fibrinolysis arm [SMD-3.69% (3.40%, 3.97%) p = 0.00001].[19] In CLEAR III trial, time-to-open the third and fourth ventricle was measured and in the fibrinolysis arm, there was a

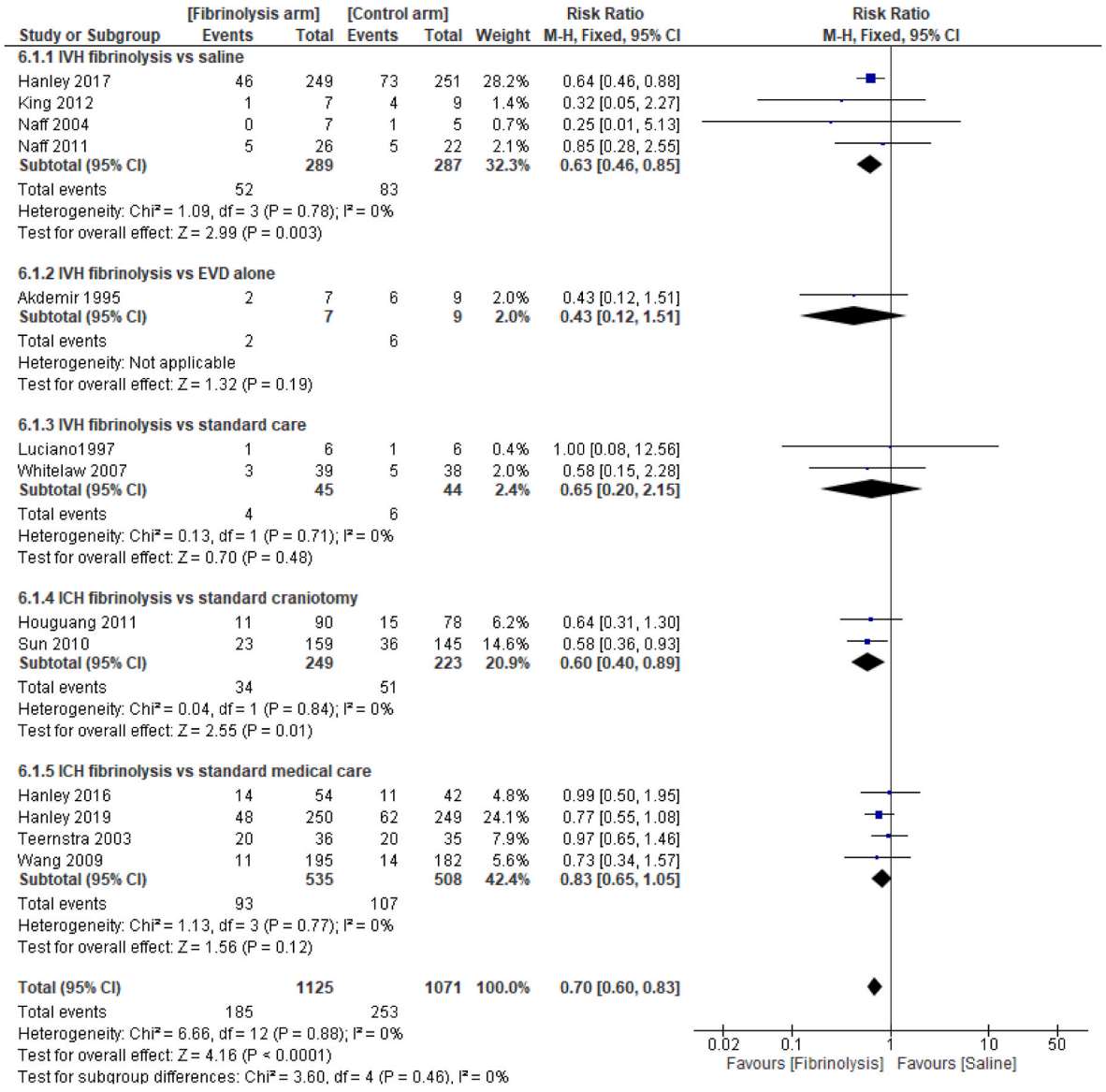

Fig. 3. Forest plot for mortality.

faster clearing of the blood with third and fourth ventricle opened sooner compared to the saline arm [SMD-0.35 days (0.17 days, 0.53 days) p = 0.0001].[11] Similalry, in Teernstra et al SICHPA trial and King et al study (fibrinolysis vs standard medical treatment for ICH), there was a greater significant reduction in clot size after starting treatment in the fibrinolysis arm [SMD-0.59 ml (0.11 ml, 1.06 ml) p = 0.05] and (SMD- 1.11 ml [0.03 ml, 2.20 ml] p = 0.01) respectively.[26,28]

14. Discussion

Fibrinolytics are traditionally used in the treatment of ischemic strokes and acute coronary syndrome for intravascular clot lysis.[1,2,36] Since the beginning of the 21st century, many retrospective and prospective non-randomised studies have shown the beneficial role of local fibrinolytics in ICH and IVH.[37–40] In the last decade, a few multicenter RCTs, especially CLEAR III and MISTIE III trials, have explored the use of local fibrinolytics in this population.[11,19]

15. Effect of intervention

Although, mortality was reported in all the included studies but the time point at which it was measured varies significantly between the studies from 30 days to 2 years. Overall there is a trend towards reduced mortality in the fibrinolysis arm in all the included studies with the most significant decrease in CLEAR III (fibrinolysis vs saline for IVH) and Sun et al (fibrinolysis vs standard craniotomy for ICH) trials.[11,18] Six studies that used mRS for functional outcome, including CLEAR III[11] and MISTIE III,[19] showed no significant difference in favourable outcome between the fibrinolysis vs the control arm with dichomotized mRS in pooled analysis. Similarly, 2 studies that used GOS for clincal outcome, also did not show a difference in good outcome between the study arms.[11,29] All the studies that measured the clot resolution (6 out of 13) have shown a faster clot resolution in the fibrinolysis arm with a greater magnitude in the studies involving IVH than in those of ICH.[11,19,21,22] This is possibly due to natural CSF circulation in the ventricles that aids faster clot resolution in IVH than ICH, where the clot is in the closed space.

Overall, there were more infections in the studies (7 out of 13) involving IVH compared to ICH but there was an overall trend towards decreased infection in fibrinolysis arm in IVH.[11,22,26] In the CLEAR III trial,[11] ventriculitis was significantly less in the fibrinolysis arm. This may be due to the faster resolution of the clot in the fibrinolysis arm,

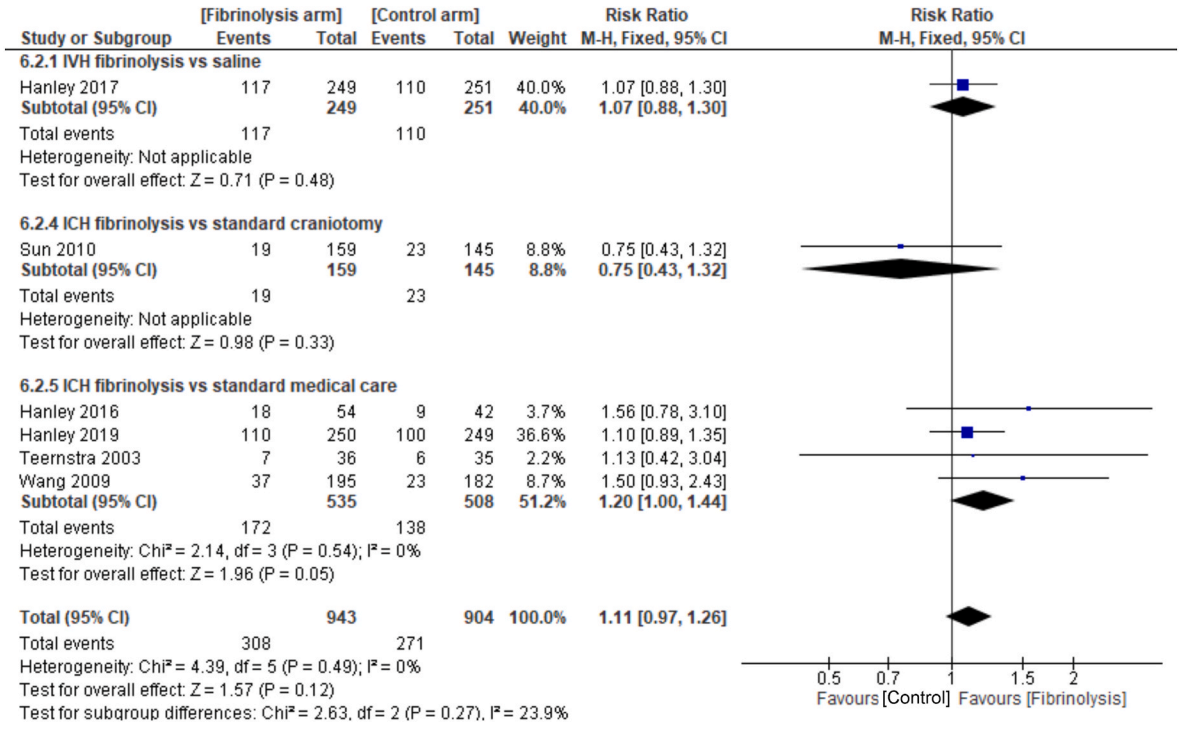

Fig. 4. Forest plot for mRS.

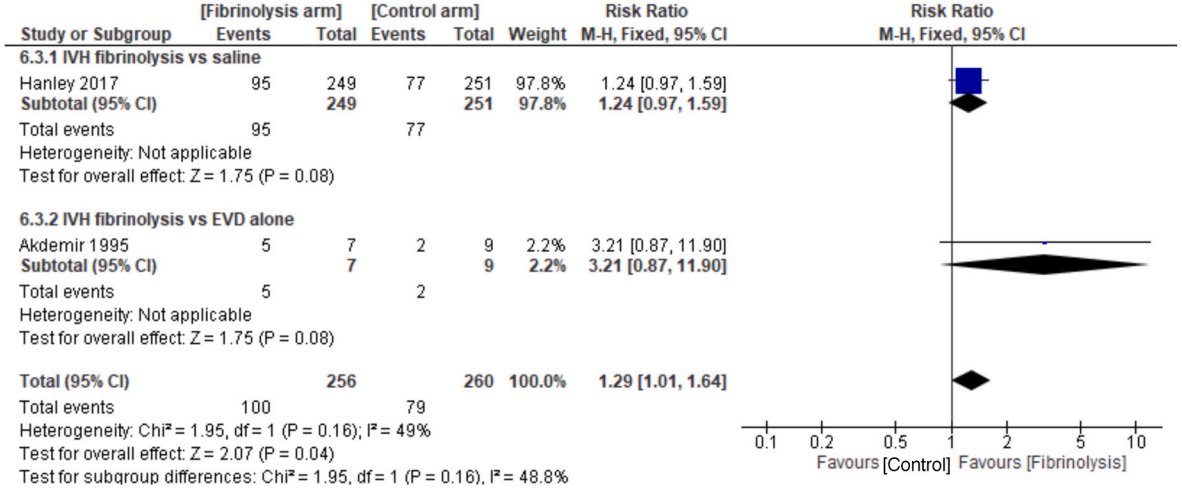

Fig. 5. Forest plot for GOS.

which led to faster removal of EVD in this group, reducing the risk of infection in these patients. In studies involving ICH, there was no difference in the infection between the study arms. As the incidence of infection in this population with ICH is generally low compared to IVH, the studies may not be sufficiently powered to deduce any minor differences in the infection rate, if at all. For development new bleeds, as a whole (after excluding the studies that tested ICH fibrinolysis vs standard craniotomy), there was a trend towards an increase in the new bleeds in the fibrinolysis arm but the heterogeneity was significant (I^2 = 75%). In CLEAR III,[11] Naff et al,[22] and MISTIE III[19] trials also reported no difference for symptomatic new bleeds between the study arms. Finally, there was no difference in the risk of shunt dependent hydrocephalus between the study arms in any of the studies.[11,22,26]

15.1. Quality of evidence

There were significant variations in the ICH volumes, intervention arm, comparater sets, the choice of fibrinolytics, their dosage, and protocols of administration. While the earlier studies used Streptokinase and urokinase, the later studies used Alteplase for fibrinolysis. The studies were also carried out in different settings, diverse populations, different eligibility criteria clincal outcomes and had varied objectives. In the studies involving ICH, fibrinolysis vs standard medical care, the main aim was to determine whether local fibrinolysis is better than medical treatment in moderate volume ICH. However, in the studies of ICH for fibrinolysis vs standard craniotomy, the aim was to check whether fibrinolysis is better than craniotomy in reducing ICP and improving outcome in large volume ICH. In the studies testing ICH fibrinolysis in neonates, the main aim was to study the shunt dependency between the intervention arms. Moreover, each study used

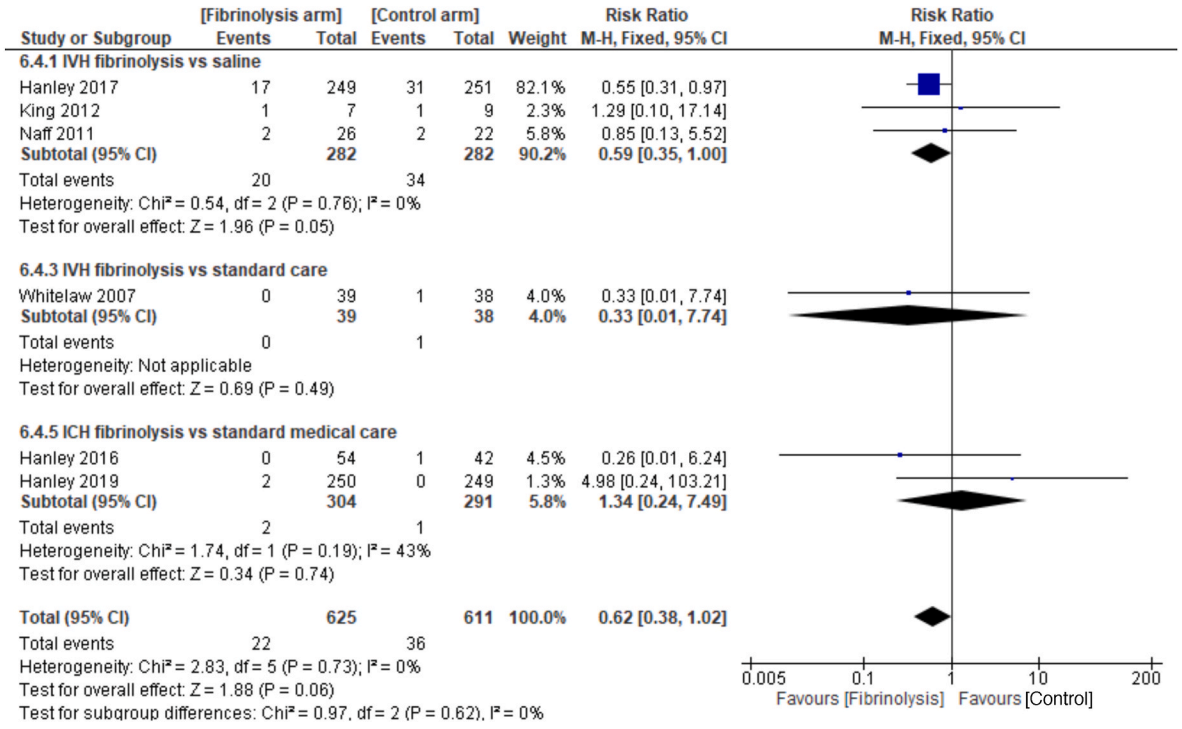

Fig. 6. Forest plot for CNS infection.

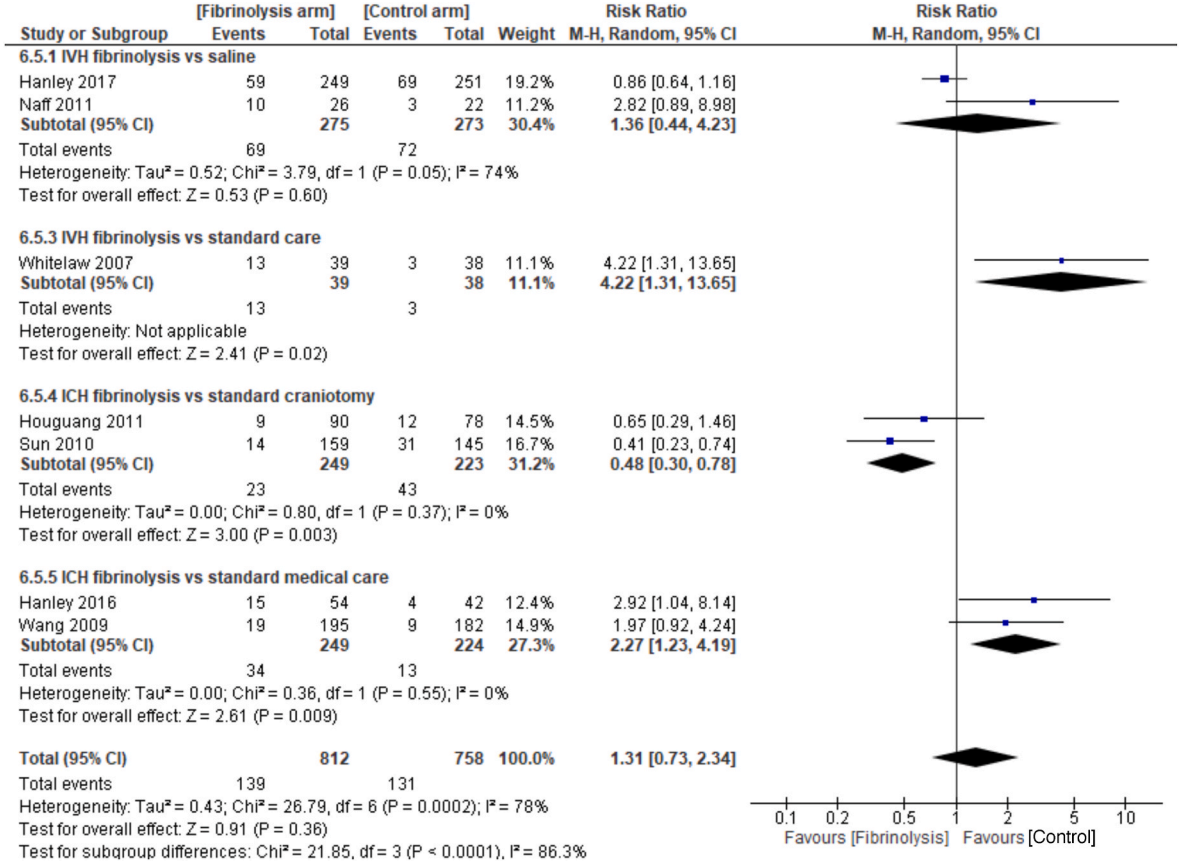

Fig. 7. Forest plot for new intracranial hemorrhages.

different primary outcome measures, and many of the studies were phase II or preliminary studies with a small sample size. Considering all these factors, the study results cannot be generalised to the entire population. Among all the included studies, only CLEAR III and MISTIE III trials showed no significant biases. Due to the nature of the intervention and control arms, the participants and providers could not be

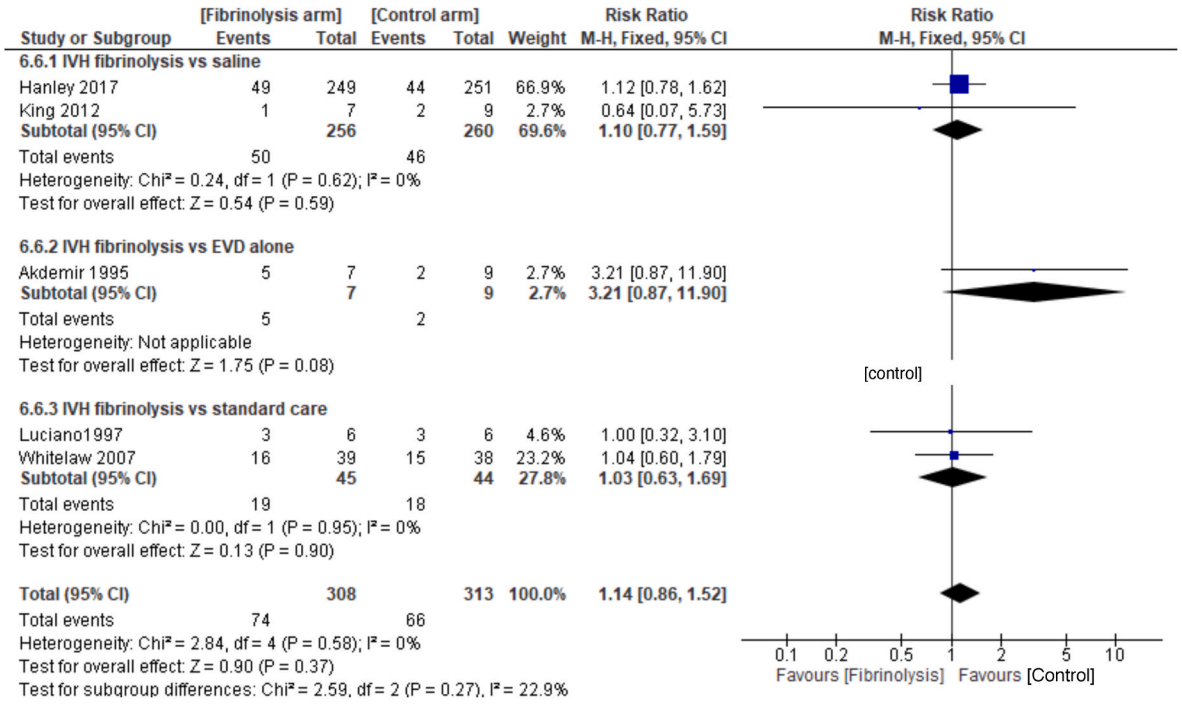

Fig. 8. Forest plot for shunt dependent hydrocephalus.

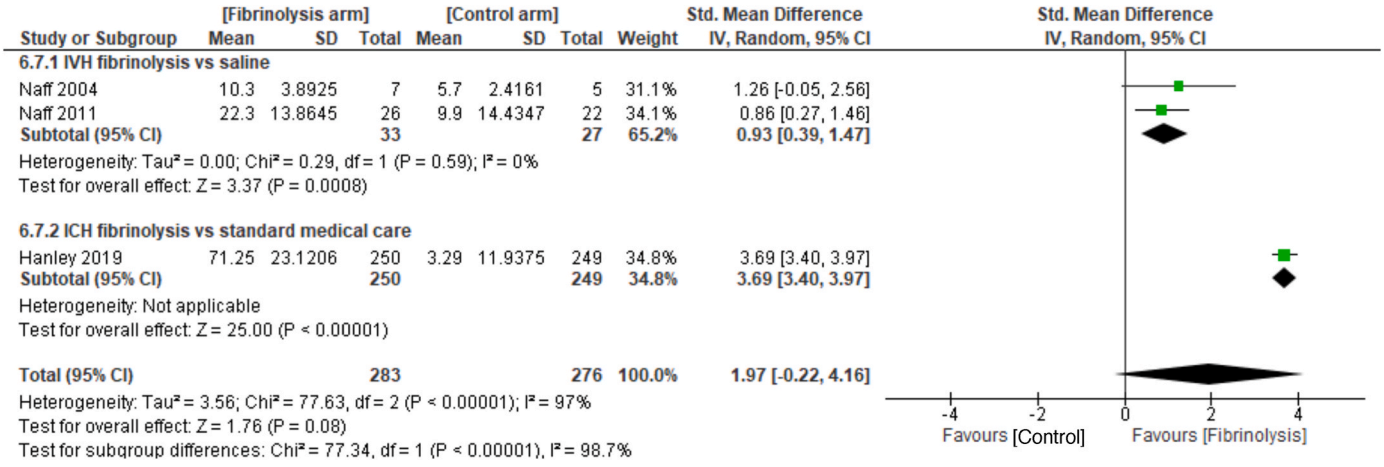

Fig. 9. Forest plot for Daily clot resolution rate.

blinded in the MISTIE III trial. All the other included studies have high risk or unclear risks of bias in more than two domains. Especially in studies done before 2000, the study reports were preliminary and did not include a detailed methodology.[20,29]

15.2. Potential biases in the review process

The strengths of review are its robust search strategy that it would not have missed out on any potentially eligible study and inclusion of RCTs only in review process. In terms of limitations, there were a few trial protocols published but the study results were unavaible up to date of conduct of this review period. Not including those unpublished studies carries a risk of selection bias in this review. Evaluating the funnel plot for mortality for all the studies, it was evident that there was asymmetry in the plot with a relative scarcity of small studies with negative results (those studies that showed increased mortality in the intervention arm).

15.3. Comparative analysis with published studies and reviews

Over the past three decades, there are quite a few observational studies published with focus on local fibrinolytics therapy in ICH or IVH including few systematic reviews.[41–43] Predominently, the aims of all these studies and reviews, were to evaluate whether a quicker and complete clearance of the blood clots will improve clincal outcomes. To the best of our knowledge, this is the first review that has analysed the RCTs alone to study the effect of local fibrinolytics in all types of supratentorial intracranial haemorrhages including both ICH and IVH.

Guo et al[41] did a network meta-analysis on different interventions on spontaneous ICH. The author included RCTs published in all the surgical modalities used for the treatment of ICH. This meta-analysis also included ten trials that used minimally invasive stereotactic puncture (MIPS) therapy in ICH. In our review, four of these trials were excluded [34–37] as per selection criteria.[42–45] Kim et al[42] and Zuccarello et al[43] studies were excluded because participants in the intervention arm were given local fibrinolytic therapy only when there was residual clot after

aspiration. Hattori et al[44] study was not included because the intervention involved stereotactic aspiration of the clot without local fibrinolytic administration while Ge et al[45] study was excluded because participants in the control arm were also given local fibrinolytic therapy for a residual clot Analogous to results of our review, Guo et al[41] also found a decreased risk of mortality and increased risk of recurrent bleeding in the intervention arm in the MIPS group while on the contrary to our review, the author showed a better functional outcome in the intervention arm in the MIPS group. This is possibly because, the studies were included based on different intervention definitions (MIPS with or without local fibrinolytic therapy).

Similar to our review, Van Solinge et al[15] also found a decreased risk of mortality and infection, faster clot resolution in the intervention arm (EVD + fibrinolytics), but no difference in functional outcome between the study arms. However, on the contrary, they reported decreased shunt dependency in the intervention arm. This is because more observational studies included in their review that has reported decreased shunt dependency in the intervention arm.

16. Conclusions

The local fibrinolytic therapy in ICH and IVH improves the clot resolution rate and decreases the risk of mortality with no significant impact on clincal outcome. Although there is an increased trend for new hemorrhages with local fibrinolytic therapy, but there is no significant risk of these being symptomatic. In patients with IVH, local fibrinolytic therapy decreases the risk of ventriculitis, but there is no significant difference in the shunt-dependent hydrocephalus. Overall, local fibrinolytic therapy in ICH and IVH appears to be safe and effective in decreasing mortality, but there is no substantial gain in functional outcome. Further studies are required to consolidate evidence for any concrete recommendations.

CRediT authorship contribution statement

Arun Babu Rajeswaran: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Arshad Ali:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis. **Saleh Safi:** Validation, Software, Resources, Methodology, Data curation. **Ahmed Eid Abdulghani Saleh:** Validation, Software, Resources, Project administration, Methodology, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.wnsx.2024.100316.

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Abreviations

GOS: Glasgow outcome score
GOS-E−: Glasgow outcome score extended
mRS: modified Rankin scale
BI: Barthel's index
CT: Computed Tomography
IVH: Intraventricular hemorrhage
ICH: Intracerebral haemorrhage
RCT: Randomised Controlled Trial
EVD: External Ventricular Drain
LP: Lumbar Puncture
VP shunt: Ventriculoperitoneal shunt
CI: Confidence Interval
CSF: Cerebero spinal Fluid
ICP: Intra Cranial Pressure