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Treatment of Intraventricular Hemorrhage with External Ventricular Drainage and Fibrinolysis: A Comprehensive Systematic Review and Meta-Analysis of Complications and Outcome

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Key words

- Catheter occlusion
- External ventricular drainage
- Functional outcome
- Intraventricular fibrinolysis
- Intraventricular hemorrhage
- Mortality
- Shunt dependency
- Ventriculitis
- Ventriculostomy

Abbreviations and Acronyms

CI: Condfidence interval
CSF: Cerebrospinal fluid
EVD: External ventricular drain
GRADE: Guidance to assess the overall risk of bias, inconsistency, imprecision, indirectness, and publication bias
ICH: Intracerebral hemorrgahe
ICP: Intracerebral preassure
IVF: Intraventricular fibrinolysis
IVH: Intraventricular hemorrhage
OR: Odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Metaanalyses
SAH: Subarachnoid hemorrhage
VC: Ventricular catheter

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BACKGROUND: **External ventricular drainage (EVD) is a key factor in the treatment of intraventricular hemorrhage (IVH) but associated with risks and complications. Intraventricular fibrinolysis (IVF) has been proposed to improve clinical outcome and reduce complications of EVD treatment. The following review and metaanalysis provides a comprehensive evaluation of IVH treatment with external ventricular drainage (EVD) and intraventricular fibrinolysis (IVF) with regards to complications and clinical outcomes.**

METHODS: **The PRISMA guidelines were followed preparing this review. Studies included in the meta-analysis were compared using forest plots and the related odds ratios.**

RESULTS: **After a literature search, 980 articles were identified and 65 and underwent full-text review. Forty-two articles were included in the review and meta-analysis. We found that bolted and antibiotic-coated catheters were superior to tunnelled/uncoated catheters ($P < 0.001$) and antibiotic- vs. silver-impregnated catheters ($P < 0.001$]) in preventing infection. Shunt dependency was related to the volume of blood in the ventricles but unaffected by IVF ($P = 0.98$). IVF promoted hematoma clearance, decreased mortality (22.4% vs. 40.9% with IVF vs. no IVF, respectively, $P < 0.00001$), improved good functional outcomes (47.2% [IVF] vs. 38.3% [no IVF], $P = 0.03$), and reduced the rate of catheter occlusion from 37.3% without IVF to 10.6% with IVF ($P = 0.0003$).**

CONCLUSIONS: **We present evidence and best practice recommendations for the treatment of IVH with EVD and intraventricular fibrinolysis. Our analysis further provides a comprehensive quantitative reference of the most relevant clinical endpoints for future studies on novel IVH technologies and treatments.**

INTRODUCTION

Hemorrhagic stroke is a life-threatening condition with significant morbidity and mortality.[1] Intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) account for the majority of hemorrhagic strokes.[2] Secondary extension of the hemorrhage into the cerebral ventricles or primary intraventricular hemorrhage (IVH) has been consistently demonstrated as an independent predictor of poor outcome.[1,2] IVH increases the intracerebral pressure (ICP), which causes compression of the brain parenchyma by mass effect and induces secondary edema. These conditions can be complicated by obstructive hydrocephalus caused by cerebrospinal fluid (CSF) malabsorption or direct occlusion of CSF pathways.[1]

The treatment goals in IVH are to: 1) prevent further bleeding, 2) evacuate the hematoma and reduce any mass effect, and 3) maintain normal ICP in order to preserve cerebral perfusion pressure and reduce the risk of secondary brain injury. Comprehensive care includes monitoring of the ICP, cerebral perfusion pressure and hemodynamic function.[3]

CSF drainage is a key factor in maintaining acceptable ICP (<20 mmHg), routinely measured using parenchymous or ventricular sensors. External ventricular drainage (EVD) is facilitated through a ventricular catheter inserted into the lateral

Table 1. GRADE Score

Bibliography: Winkler et al.,[13] Wang et al.,[14] Nilsson et al.,[15] Akdemir et al.,[16] Gubucz et al.,[17] Hanley et al.,[18] Tung et al.,[19] Coplin et al.,[20] Ducruet et al.,[21] Huttner et al.,[22] Staykov et al.,[23] and Torres et al.[24]

Certainty Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants Studies	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**	**Without Coating/IVF**	**With Coating/ IVF**	**Relative Effect (95% CI)**	**Risk with Uncoated**	**Risk difference with Catheters be Coated**
Antibiotic coated versus uncoated catheters											
3566; 2 RCTs, 1 observational	not serious	not serious	not serious	not serious	none	⊕ ⊕ ⊕ ⊕ High	231/1802 (12.8%)	56/1764 (3.2%)	**OR 0.23** (0.17 to 0.32)	128 per 1.000	**95 fewer per 1.000** (from 104 fewer to 85 fewer)
Antibiotic coated versus silver impregnated catheters											
2060; 2 RCTs, 1 observational	not serious	not serious	not serious	not serious	none	⊕ ⊕ ⊕ ⊕ High	40/296 (13.5%)	56/1764 (3.2%)	**OR 0.3** (0.18 to 0.46)	135 per 1.000	**93 fewer per 1.000** (from 108 fewer to 68 fewer)
Silver impregnated catheters versus uncoated catheters											
2098; 2 RCTs, 1 observational	not serious	not serious	not serious	not serious	none	©©©© High	231/1802 (12.8%)	40/296 (13.5%)	**OR 0.81** (0.54 to 12.2)	128 per 1.000	**23 fewer per 1.000** (from 56 fewer to 512 more)
IVF versus EVD alone											
768; 3 RCTs, 6 observational	serious	serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	©©©◯ Moderate	43/383 (11.2%)	31/385 (8.1%)	**OR 0.69** (0.42 to 1.11)	112 per 1.000	**32 fewer per 1.000** (from 62 fewer to 11 more)

Catheter Occlusion and IVF Treatment

Bibliography: Kramer et al.,[25] Torres et al.,[24] Findley et al.,[26] Coplin et al.,[20] and Huttner et al.[22]

Certainty Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies) Follow-Up	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**	**EVD Alone**	**With IVF**	**Relative Effect (95% CI)**	**Risk with EVD Alone for Catheter Occlusion**	**Risk Difference with IVF for Catheter Occlusion**
Catheter occlusion											
154; 1 RCT, 4 observational	serious	not serious	not serious	not serious	none	©©©◯ Moderate	26/69 (37.7%)	9/85 (10.6%)	**OR 0.20** (0.08 to 0.48)	377 per 1.000	**269 fewer per 1.000** (from 331 fewer to 152 fewer)

Shunt Dependency and IVF Treatment

Bibliography: Gluski et al.,[27] Catapano et al.,[28] Kuo et al.,[29] Zacharia et al.,[30] Akdemir et al.,[16] Gubucz et al.,[17] Hanley et al.,[18] Naff et al.,[31] Staykov et al.,[23] Tung et al.,[19] Coplin et al.,[20] Ducruet et al.,[21] Huttneret al.[22]

Certainty Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies) Follow-Up	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**	**EVD Alone**	**With IVF**	**Relative Effect (95% CI)**	**Risk with EVD Alone for Shunt Dependency**	**Risk Difference with IVF for Shunt Dependency**
Shunt dependency											
709; 4 RCTs, 9 observational	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	⊕⊕⊕⊕ High	62/344 (18.0%)	64/365 (17.5%)	**OR 0.99** (0.68 to 1.46)	180 per 1.000	**1 fewer per 1.000** (from 50 fewer to 63 more)

Good Functional Outcome and IVF Treatment

Bibliography: Hanley et al.,[18] Kramer et al.,[25] Tung et al.,[19] Loung et al.,[33] Staykov et al.,[23] and Torres et al.[24]

Certainty Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies) Follow-Up	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**	**EVD Alone**	**With IVF**	**Relative Effect (95% CI)**	**Risk with EVD Alone for Death**	**Risk Difference with IVF for Death**
Good functional outcome											
680; 3 RCTs, 3 observational	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	129/337 (38.3%o)	162/343 (47.2 %)	**OR 1.40** (1.03 to 1.91)	383 per 1.000	**82 more per 1.000** (from 7 more to 159 more)

Mortality Rate and IVF Treatment

Bibliography: Akdemir et al.,[16] Gubucz et al.,[17] Hanley et al.,[18] Naff et al.,[30] Tung et al.,[19] Coplin et al.,[20] Ducruet et al.,[21] Huttner et al.,[22] Litrico et al.,[32] Loung et al.,[31] and Staykov et al.[23]

Certainty Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies) Follow-Up	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**	**EVD Alone**	**With IVF**	**Relative Effect (95% CI)**	**Risk with EVD Alone for Good Functional outcome**	**Risk Difference with IVF for Good Functional Outcome**
Mortality rate											
805; 5 RCTs, 6 observational	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	165/403 (40.9%)	90/402 (22.4%)	**OR 0.39** (0.29 to 0.54)	409 per 1.000	**197 fewer per 1.000** (from 242 fewer to 137 fewer)

Quality assessment of included studies divided in outcome measures. Quality of all included studies was assessed by 2 reviewers. Conflicts were solved by a third reviewer.
IVF, intraventricular fibrinolysis; CI, confidence interval; OR, odds ratio.

ventricle.[4] Treatment is associated with complications including misplacement, malpositioning, neuroinfection, and catheter occlusion, for example, due to blood clots or debris.[2]

IVH treatment in general is a well-evaluated topic with several reviews[5-7] published 15–25 year ago, while more recent reviews have focused exclusively on intraventricular fibrinolysis (IVF) treatment.[8-12] However, no systematic review or meta-analysis to date has presented current knowledge on all potential EVD-related complications in IVH patients with and without IVF treatment. The aim of the present systematic review and meta-analysis was to perform an extensive evaluation of EVD treatment in IVH patients, quantifying complication rates, and clinical outcomes. We assessed the effects of IVF in conjunction with EVD treatment and provide a comprehensive overview of historical data for future studies on IVH and EVD therapy. Our study further outlines the effects of current best practice to be considered in clinical treatment.

METHODS

We conducted a systematic review and meta-analysis on patients with IVH (primary or secondary) treated with EVD. The review and meta-analysis was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). No limitation was applied regarding time of publication. PubMed, Embase, and Cochrane databases were searched using the search terms: “intraventricular hemorrhage” and/or “bleeding” and/or “hematoma” and/or “IVH AND external ventricular drainage ”and/or “ventriculostomy”.

Criteria for Assessing Quality

The evidence quality was assessed and rated by 2 investigators (MHJ, RM) using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach. We used detailed GRADE guidance to assess the overall risk of bias, inconsistency, imprecision, indirectness, and publication bias and summarized the results in an evidence profile (Table 1 and Supplementary Table 1). Conflicts were solved by a third investigator (ARK).

Table 2. Pooled Estimates

	AB Coating	Silver	Uncoated	IVF	No IVF	
Catheter Related Infections	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	***P*-Value**
	4.3% (2.4—7.6)	13.4% (7.9—22.0)	16.1% (10.1—24.7)	8.1% (5.7—11.3)	12.8% (8.8—18.2)	AB versus uncoated: $P < 0.001$
						AB versus silver: $P < 0.001$
						Silver versus uncoated: $P = 0.31$
						IVF versus EVD alone: $P = 0.12$
Shunt dependency				17.5% (9.0—23.8)	14.9% (9.6—22.3)	IVF versus EVD alone $P = 0.98$
Catheter occlusions				10.6% (7.1—11.9)	37.7% (25.2—43.1)	IVF versus EVD alone: $P = 0.0003$
Mortality rate (30 days)				22.4% (17.7—29.8)	40.9% (37.7—62.3)	IVF versus EVD alone: $P < 0.00001$
Good functional outcome (90 days)				47.2% (42.2—52.6)	38.3% (32.9—44.8)	IVF versus EVD alone: $P = 0.03$

Catheter Related Infections, Shunt Dependency, Catheter Occlusions, Mortality Rates, and Good Functional Outcome.
IVF, intraventricular fibrinolysis; EVD, External ventricular drainage; RCT, randomized controlled trial; CI, confidence interval.

Eligibility Criteria

The inclusion criteria for the review and meta-analysis were.

- Full text articles with original data.
- Studies evaluating an adult patient population (>18 years) with primary or secondary IVH treated with external ventriculostomy.
- Studies evaluating catheter occlusions, infection rates, shunt dependency, alteplase, clearance of IVH, EVD complications, functional outcome, and/or mortality.

Spin-off articles from larger studies were included only if new data were presented. Studies evaluating the treatment of neonates or children (<18 years) with IVH were excluded, as were reviews, meta-analyses, animal studies, published abstracts, and non-English language studies. Studies evaluating only endoscopic treatment of IVH, third ventriculostomies, or treatment with lumbar catheters were also excluded.

Study Selection

Initially, one investigator (MHJ) screened all titles and abstracts. Two independent investigators (MHJ, RM) screened the full text of eligible studies. Disagreements were resolved via consensus and by consulting a third author (ARK). Data extraction was performed by one investigator (MHJ).

Data Synthesis and Statistical Analysis

Studies included in the meta-analysis were compared using forest plots and the related odds ratios (ORs). In the absence of significant heterogeneity, studies were pooled using the Mantel-Haenszel (M-H) fixed-effects model. Otherwise, the studies were pooled using a Mantel-Haenszel random-effects model. Pooled ORs were reported with 95% confidence intervals (CIs). Studies in the meta-analysis were separated into observational studies and randomized trials. These analyses were conducted using RevMan 5.0 software. For the meta-analysis of single proportions, we applied a random intercept logistic regression model allowing individual participant data always to be extracted for binary data. This analysis was conducted in STATA 17 (StataCorp, College Station, Texas, USA). In the estimated risk assumptions, the number of patients in each study was applied in the analysis for a weighted result. The GRADE system does not take this into account, and therefore, results in Table 1 differs from Table 2 for some results.

RESULTS

Study Selection

We identified 980 studies by PubMed search and 49 duplicates were removed. The titles and abstracts of the remaining 932 articles were screened. We selected 65 studies for full text review. During full text review, 3 articles were found eligible for inclusion based on their reference lists. Fifty articles underwent secondary full-text review. Eight articles were excluded due to irrelevant endpoints. In total, 42 articles were included in the review and meta-analysis (Figure 1).

Risk of Bias and Quality Assessment

The overall risk of bias was very low for randomized controlled trials (RCTs) and moderate to very low for observational studies. The nature of the trial interventions precluded blinding of patients and their physicians; random sequence generation, and blinding of outcome assessment were considered as low-risk items across trials. The GRADE summary findings for selected outcomes and interventions are shown in Table 1, while an overall quality assessment of all individual studies is shown in Supplementary Table 1.

General Observations

Acute hydrocephalus requiring EVD treatment was seen in 38% (range, 25.2%—58.6%) of the cases with severe IVH.[34-36] Most patients in need of acute EVD treatment had a pan-ventricular hemorrhage with a Graeb score above 3.[37] The distribution pattern of ventricular blood affected the severity of the IVH and the incidence of acute hydrocephalus.[29,34-36] A Graeb score >5, non-lobar ICH <30 ml, and Glasgow Coma Scale <8 were independent predictors of EVD

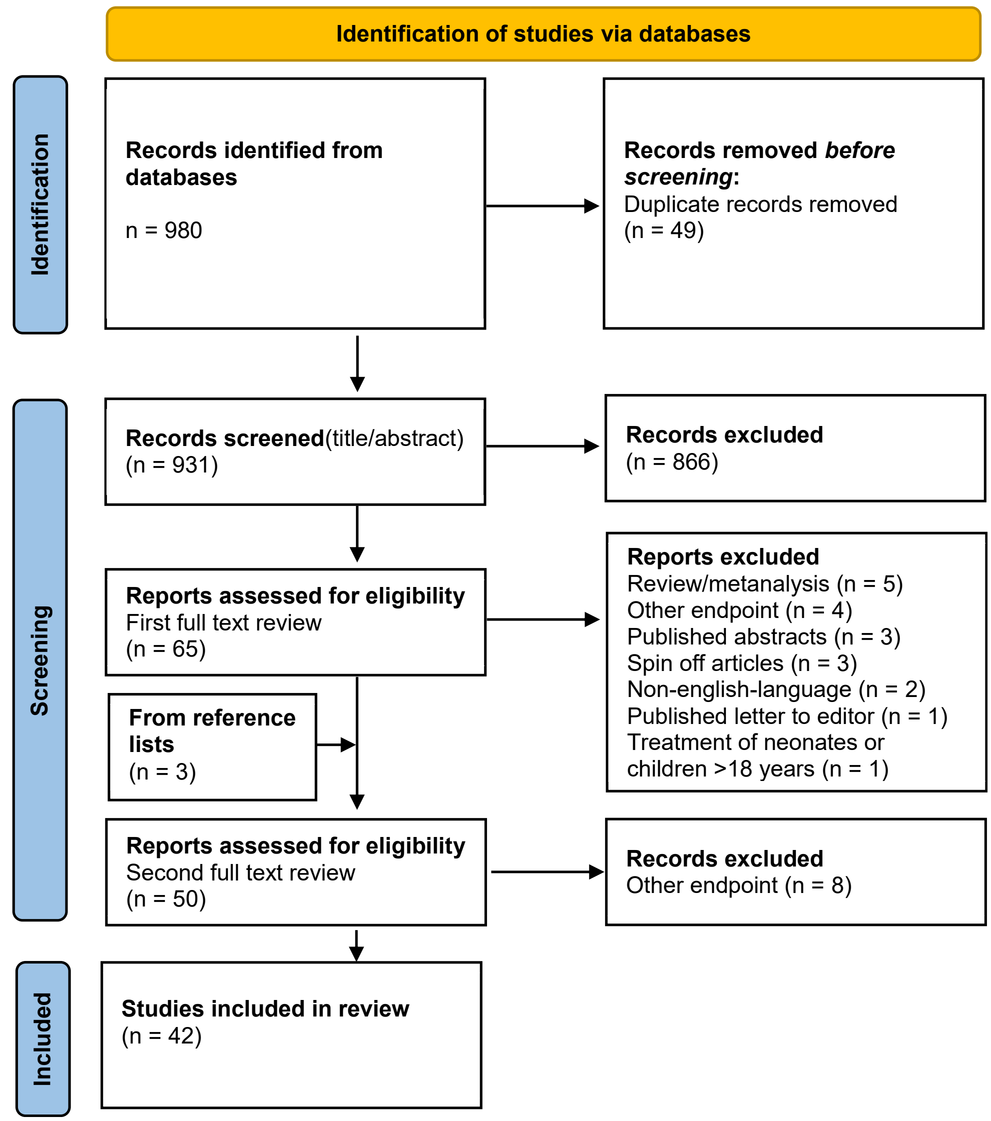

Figure 1. PRISMA flow diagram showing the study selection process.

placement for acute hydrocephalus in IVH patients.[36]

Catheter-Related Infections

The mean infection rate in patients treated with EVD (without IVF) was 12.8% (95% CI, 8.8–18.2; ICC = 0.07, Table 2).[13,15,38-40] The key risk factors associated with increased rates of infection/ventriculitis were surgical tunneling of EVDs, CSF leakage, long treatment duration, and use of catheters not coated with antibiotics (ABs).[38]

Catheter Coating. The infection rate was significantly lower for AB-coated catheters (estimated risk, 4.3%; 95% CI, 2.4–7.6; ICC = 0.6 [GRADE: 3.2%]) than for uncoated catheters (estimated risk, 16.1%; 95% CI, 10.1–24.7; ICC = 0.06 [GRADE: 12.8%]) (OR = 0.23; 95% CI, 0.17–0.32; $P < 0.001$, GRADE: high)[13,15,38,41,42] (Table 2).

Similar results were observed when comparing the infection rates of AB-coated catheters (estimated risk, 4.3%; 95% CI, 2.4–7.6; ICC = 0.6 [GRADE: 3.2%]) with silver impregnated catheters (estimated risk 13.4%, 95%CI, 7.9–22.0; ICC 0.06 [GRADE: 13.5%]) corresponding to an OR of 0.3; 95%CI, 0.18–0.46; $P < 0.001$, GRADE: high)[13,15,42] (Tables 1 and 2). On the contrary, no significant preventive effect of silver impregnated coating could be documented compared to uncoated catheters (OR of infection = 0.81; 95% CI, 0.54–12.2; $P = 0.31$, GRADE: high)[13,15,42] (Tables 1 and 2).

CSF Leakage and Bolted Versus Tunneled EVDs. A single observational study reported complications (ventriculitis,

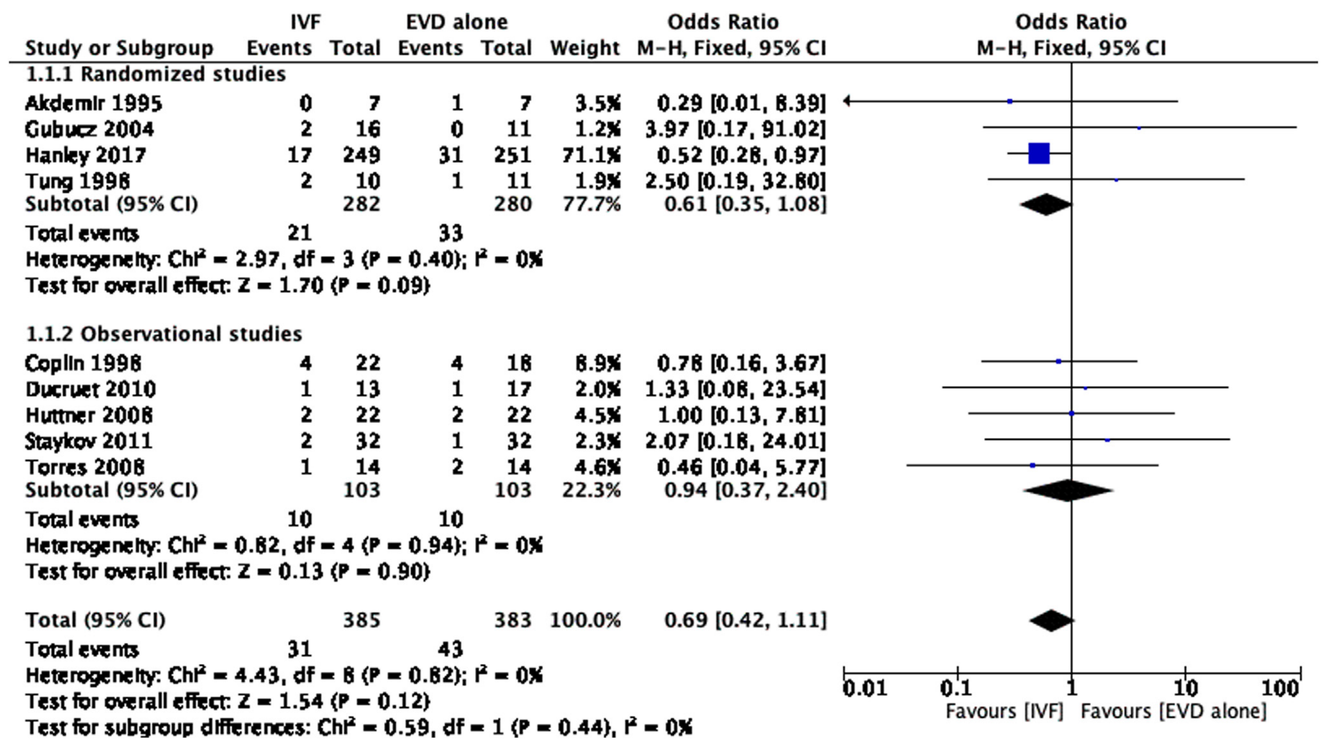

Figure 2. Pooled ORs of ventriculitis comparing intraventricular fibrinolysis with EVD alone. IVF, intraventricular fibrinolysis; EVD alone, external ventricular drainage alone; OR, odds ratio; CI, confidence interval.

misplacement, leakage, catheter displacement, disconnection of the tube systems, and hemorrhages following the EVD placement procedure) in 59.4% of tunneled catheters and 17.6% of bolt-connected catheters ($P = 0.007$).[40] Tunneling increased the risk of CSF leakage by 36% compared with 3.2% for bolted catheters.[38] Among patients with CSF leakage for >1 day, 21.1% experienced ventriculitis, while a duration of CSF leakage <1 day was not associated with infection.[38,40]

Duration of EVD Treatment. Ventriculitis was most often observed at 5–7 days after EVD placement.[38] In one observational study, the overall infection rate was found to be 27.5% in patients treated with EVD for more than 5 days.[14] A life table analysis of the day of infection revealed an infection rate of 6% by day 5, 13% by day 10, 17% by day 15, 21% by day 20, 29% by day 25, 36% by day 30, and 46% above 30 days. Correlation between duration of EVD treatment and infection rate was especially distinct for patients above 65 years of age treated with EVD for more than 6 days ($P < 0.05$).[43] The results were based on 3 observational studies (GRADE: low).

IVF and Risk of Ventriculitis. Comparing 9 studies (RCTs and observational) evaluating ventriculitis in IVF treatment compared with EVD alone (768 patients), we observed a tendency towards a reduced risk in the IVF group, although this difference was not significant (OR = 0.69; 95% CI, 0.42–1.11; $P = 0.12$, GRADE: moderate) (Figure 2 and Tables 1 and 2). Similar findings applied to RCTs alone (OR = 0.61; 95% CI, 0.35–1.08; $P = 0.09$, GRADE: high) (Figure 2).

Shunt Dependency

The overall rate of shunt dependency in patients treated with EVD without IVF was 14.9% (95% CI, 9.6–22.3; ICC = 0.14) (Table 2).[27-29,30,34]

The IVH score was significantly associated with shunt dependency (IVH score: 15.7 [20.1 mL] versus IVH score 12.4 [11.0 mL]; $P = 0.02$).[29] Other positively correlated factors included thalamic primary hematoma,[30,44] intraventricular casting (69/272 [47.3%] versus 26/55 [25.4%]; $P < 0.001$) and ICP >25 mmHg for 2 or more episodes within 24 hours.[30,45] In the CLEAR III (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III) RCT,[44,46] permanent CSF shunting was observed in 18% of the total patient population (500 patients). A higher risk of permanent CSF shunting was also associated with Afro-American ethnicity (OR = 1.98; 95% CI, 1.18–3.34), long duration of EVD treatment (OR = 1.10; 95% CI, 1.05–1.15), placement of more than one EVD (OR = 1.93; 95% CI, 1.13–3.31), high daily CSF drainage (OR = 1.07 per 10 mL; 95% CI, 1.04–1.10), and intracranial pressure >30 mm Hg (OR = 1.70; 95% CI, 1.09–2.88).

IVF and Shunt Dependency. Our meta-analysis showed that shunt dependency was not reduced by IVF treatment compared with EVD alone (OR = 0.99; 95% CI, 0.68–1.46; $P = 0.98$, GRADE:

Study or Subgroup	IVF Events	IVF Total	EVD alone Events	EVD alone Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Randomized studies						
Akdemir 1995	1	7	3	7	5.0%	0.22 [0.02, 2.97]
Gubucz 2004	1	16	2	11	4.3%	0.30 [0.02, 3.80]
Hanley 2017	46	249	44	251	69.2%	1.07 [0.68, 1.68]
Naff 2004	0	6	1	7	2.5%	0.33 [0.01, 9.79]
Staykov 2011	3	10	3	11	3.9%	1.14 [0.17, 7.60]
Subtotal (95% CI)		288		287	84.8%	0.96 [0.63, 1.46]
Total events	51		53			
Heterogeneity: Chi² = 2.64, df = 4 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
2.1.2 Observational studies						
Coplin 1998	4	22	2	18	3.5%	1.78 [0.29, 11.04]
Ducruet 2010	5	33	1	17	2.2%	2.86 [0.31, 26.66]
Huttner 2008	4	22	6	22	9.5%	0.59 [0.14, 2.48]
Subtotal (95% CI)		77		57	15.2%	1.19 [0.46, 3.09]
Total events	13		9			
Heterogeneity: Chi² = 1.69, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		365		344	100.0%	0.99 [0.68, 1.46]
Total events	64		62			
Heterogeneity: Chi² = 4.40, df = 7 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%						

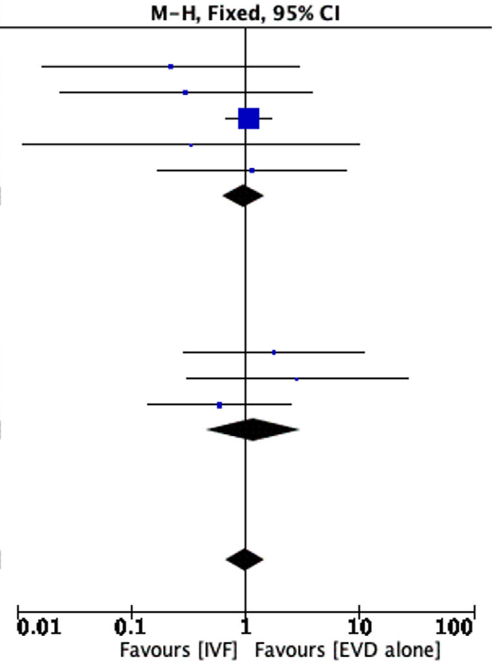

Figure 3. Pooled ORs of permanent CSF shunting comparing intraventricular fibrinolysis with EVD alone. IVF, intraventricular fibrinolysis; EVD alone, external ventricular drainage alone; OR, odds ratio; CI, confidence interval; CSF, cerebral spinal fluid.

high) (Figure 3 and Table 1) (the mean shunt dependency rate in IVF-treated patients: 17.5% [range: 0%–38.5%]).

Catheter Occlusions

The overall estimated rate of catheter occlusion (drainage stop) was 26.4%, 95% CI, 15.0–42.1; ICC = 0.06 for patients treated with EVD and no IVF (Table 2).[18]

Higher risks of occlusion were observed in patients with casting ventricles than in patients with no casting (38.8% vs. 23.1%; P = 0.003).[28,36] Furthermore, patients with catheter occlusions had significantly more blood in the ventricular system (49.2 vs. 27.2 cc; P = 0.01).[36] Small catheter lumen (1.5 mm inner diameter) was associated with a 5.8 times higher risk of temporary occlusions than large catheters (2.3 mm inner diameter) (P = 0.01).[47] Similarly, permanent occlusions and catheter replacements were 2.2 times more frequent for small catheters than for large catheters (P = 0.04).[47] Importantly, larger catheters did not increase the risk of catheter-related hemorrhage (8.7% small diameter vs. 7.1% large diameter [P = 1]).[47]

IVF and Catheter Occlusions. Five studies (1 RCT and 4 observational) evaluated catheter occlusions for EVD with IVF versus EVD alone. Our meta-analysis showed that IVF significantly reduced the risk of having at least one catheter occlusion from 37.3% without IVF to 10.6% with IVF (OR: 0.20; 95% CI, 0.08–0.48; P = 0.0003, GRADE: moderate) (Figure 4 and Table 1).

Clearance of Blood

IVH clot resolution follows first-order kinetics. Urokinase reduced clot half-life by 44.6% compared with placebo (4.69 days with IVF vs. 8.48 days without IVF).[31] In accordance with this, the CLEAR III trial showed a significantly decreased IVH volume in the alteplase group compared with the saline group at the end of treatment (5.9 mL vs. 11.5 mL; P < 0.0001).[18] Use of IVF for intraventricular clot clearance significantly increased the amount of hemoglobin in drained CSF (P = 0.01) with a peak effect on day 2.[48] Complete clot resolution evaluated using serial computed tomography scans was reduced by 3 days in the urokinase-treated group relative to placebo (7.3 days vs. 10.3 days; P = 0.035).[48,49] Computed tomography-based IVH volumes were significantly lower at days 7, 10, and 11 (P = 0.01–0.02) high-dose IVF (4 mg alteplase every 12 hours) than with low-dose IVF (1 mg every 8 hours). However, this effect did not apply to the third (P = 0.41) and fourth (P = 0.16) ventricles. Furthermore, a significant decrease in ICH volumes was seen when administering IVF to patients with breakthrough ICH (91.7% reduction in the IVF group compared with 68% in the control group (EVD alone), P < 0.01).[50]

Functional Outcome and Mortality

In 6 studies (3 RCTs and 3 observational), the overall mean 30-day mortality rate was 50% (95% CI, 37.7–62.3; ICC = 0.16) for patients treated with EVD compared with 36.4% (range 31%–43.1%) for IVH patients with no indication for EVD treatment.[35,36] The mean rate of good functional outcome (modified Rankin Scale [mRS] 3 or below) was 23.9% (95% CI, 10.7–44.8; ICC = 0.2) in EVD-treated patients.[18,22,24,51,52] In comparison, an

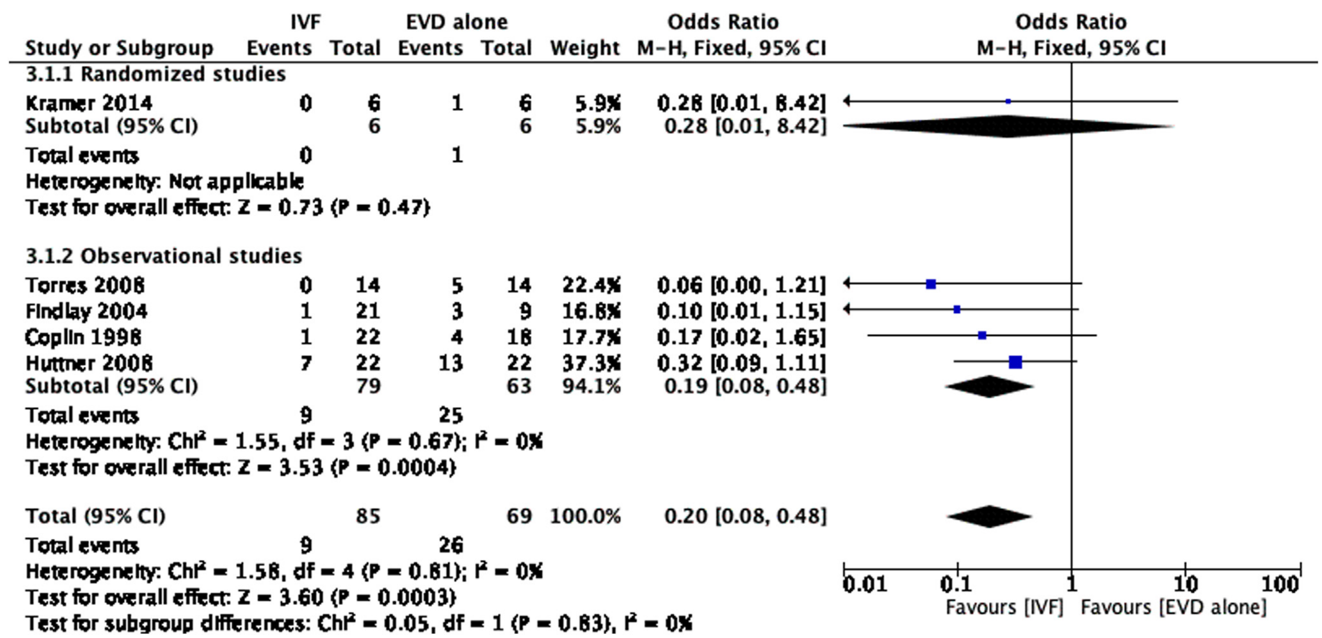

Figure 4. Pooled ORs of catheter occlusions comparing intraventricular fibrinolysis with EVD alone. IVF, intraventricular fibrinolysis; EVD alone, external ventricular drainage alone; OR, odds ratio; CI, confidence interval.

observational prospective cohort study by Hwang et al.[53] showed that EVD-treated IVH patients had similar mortality rates and functional outcomes as those who did not receive EVD, despite having a significantly worse prognosis at admission.[54] This similarly suggests that EVD treatment can improve the outcome for the most severely injured IVH patients.

Functional Outcome and Mortality in IVF Treatment. Thirteen studies presented information on all-cause mortality. Meta-analysis evaluating 5 RCTs and 6 observational studies showed a highly significant reduction of the absolute mortality rate from 40.9% without IVF to 22.4% (range: 0%–45.5%) with IVF, corresponding to an overall pooled OR for mortality of 0.39 (95% CI, 0.29–0.54; $P < 0.00001$) in favor of IVF treatment (GRADE: high, Figure 5, Table 1). Similar results were observed when evaluating RCT studies alone (pooled OR = 0.43; 95% CI, 0.29–0.64), 5 RCT studies included) (Figure 5).

Seven studies presented data on >90-day functional outcome. Of these, 3 were RCTs (Figure 6). Good clinical outcome was defined as a mRS of 3 or below. The pooled OR was 1.40 (95% CI, 1.03–1.91; $P = 0.03$) in favor of IVF (GRADE: high, Table 1). The mean rate of good functional outcome after 30 days was 47.2% (95% CI, 42.2–52.6) in the IVF group compared with 23.9 (95% CI, 32.9%–44.8%) without IVF (Table 2).

DISCUSSION

EVD treatment is often indicated for IVH patients due to acute hydrocephalus and elevated ICP. However, EVD insertion is associated with complications, for example, risk of infection, occlusion, and iatrogenic hemorrhage. In this review and meta-analysis, we evaluated best practice EVD treatment in IVH patients and provided an aggregated analysis of common clinical safety and efficacy endpoints for future reference.

In this review and meta-analysis we have aimed to present clear and tangible clinical recommendations based on GRADE quality assessments. Our review and meta-analysis provides new evidence to support the use of IVF for improved functional outcome in IVH patients, which is still a controversial subject. The review focusses exclusively on IVH treatment and presents a comprehensive synthesis of a homogeneous and structured data pool with focus on several relevant clinical endpoints. This is contrary to previous reviews and meta-analyses, which have focused on EVD treatment in general (inhomogeneous indications) or isolated clinical endpoints. It is our hope that this paper would guide and align clinical practice in EVD treatment in IVH patients.

Key Learnings and Best Practice Recommendations

Catheter Occlusions. We found that large-lumen catheters (inner diameter of 2.3 mm [compared to 1.5 mm]) reduce the risk of catheter occlusion in IVH patients with casting ventricles[47] (GRADE: moderate), and should arguably be used for patients with high Graeb score (≥5). As a novel observation, we also found that IVF treatment significantly reduced the risk of catheter occlusion (10.6% vs. 37.7%; $P = 0.0003$) compared with EVD alone, and hence the need for counteracting interventions such as catheter replacement surgery or saline injections. We find that there is sufficient evidence to recommend IVF

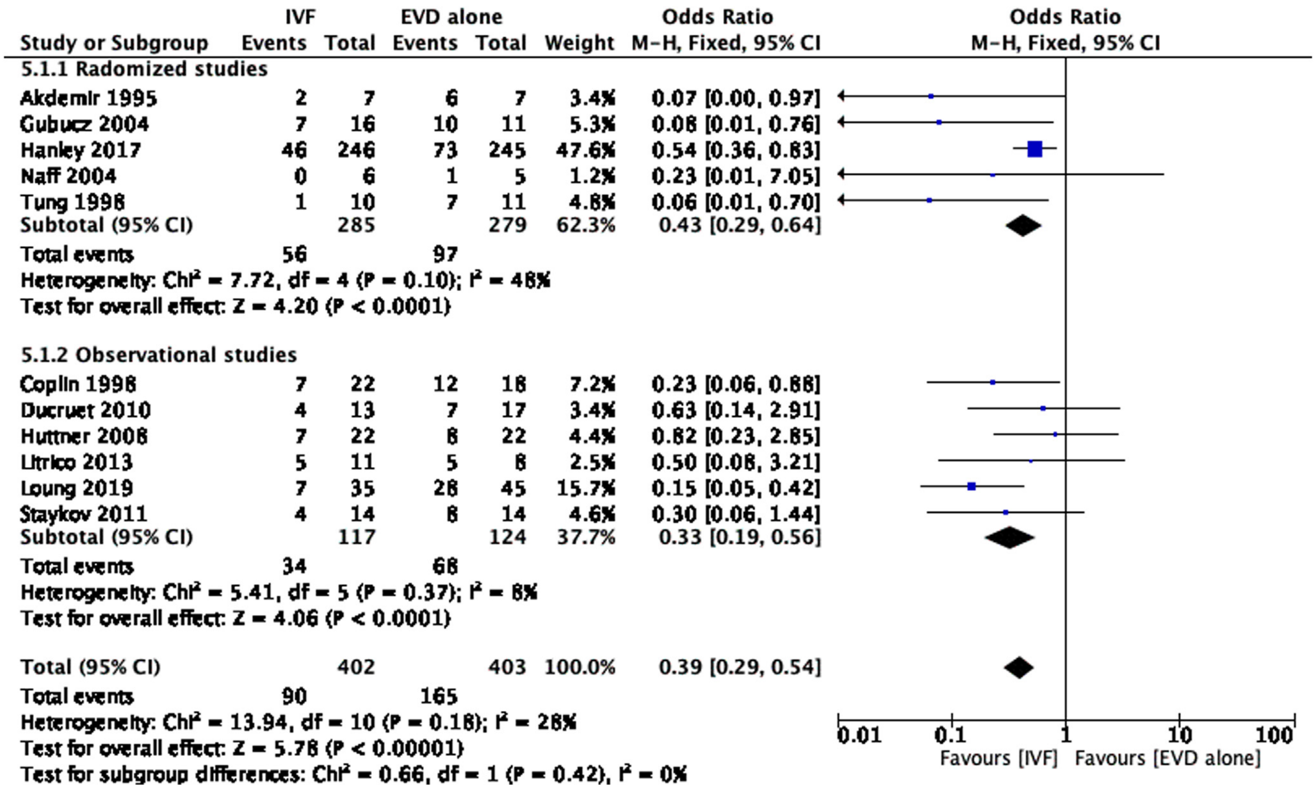

Figure 5. Pooled ORs of mortality comparing intraventricular fibrinolysis with EVD alone. IVF, intraventricular fibrinolysis; EVD alone, external ventricular drainage alone; OR, odds ratio; CI, confidence interval.

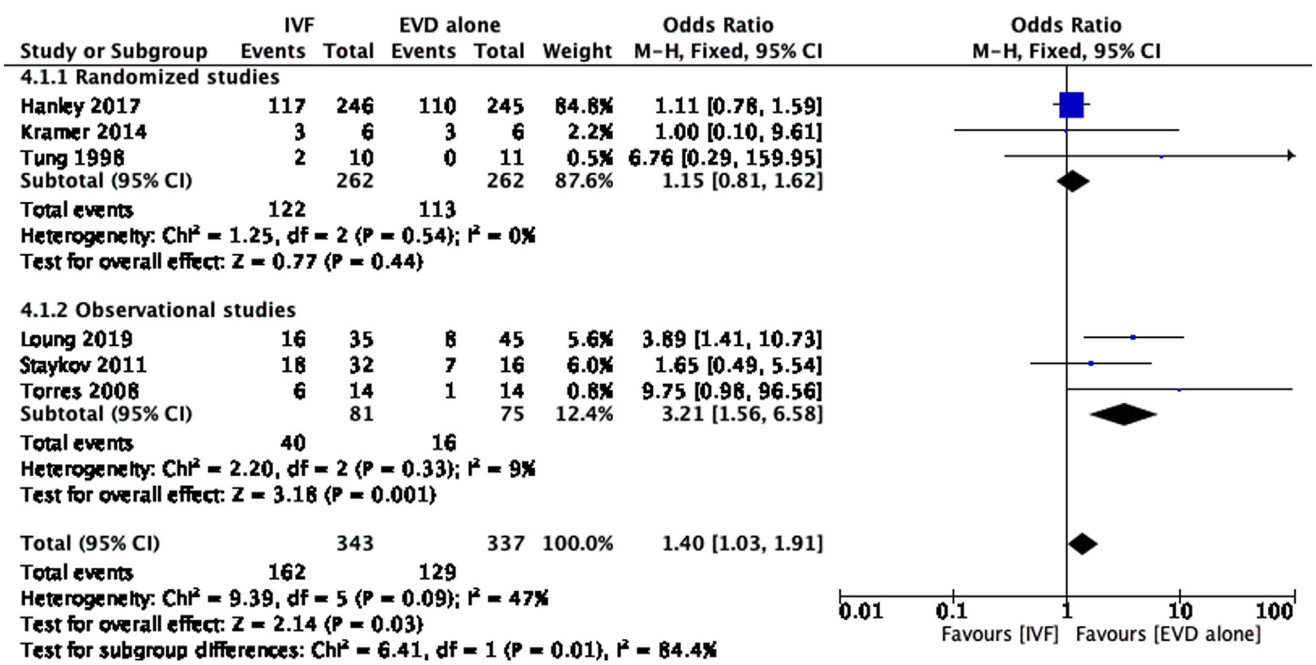

Figure 6. Pooled ORs of functional outcome >90 days comparing intraventricular fibrinolysis with EVD alone. IVF, intraventricular fibrinolysis; EVD alone, external ventricular drainage alone; OR, odds ratio; CI, confidence interval.

treatment based on this indication alone (GRADE: high), particularly in cases of high risk of occlusion and critical indication for CSF drainage.

CNS Infection. We found that AB coating of catheters was significantly associated with a reduced risk of CNS infection compared with uncoated catheters (OR = 0.23; 95% CI, 0.17–0.32; P < 0.001). This supports the findings of a previous meta-analysis by Wang et al. (2013) comparing uncoated catheters for arbitrary EVD indications with clindamycin/rifampin-impregnated catheters (OR = 0.27; 95% CI = 0.10–0.73; P < 0.05) and minocycline/rifampin-impregnated catheters (OR = 0.11; 95% CI = 0.06–0.21; P < 0.05),[42] respectively.

As a novel finding, our meta-analysis and review further documented that AB coated catheters are superior to silver-impregnated (OR = 0.3; 95% CI, 0.18–0.46; P < 0.001) in terms of reducing the risk of CNS infection, while similar advantages could not be documented for silver-impregnated catheters compared to uncoated catheters (OR = 0.81; 95% CI, 0.54–12.2; P = 0.31).[13,15,38,42,55,56]

In summary, we therefore, recommend that AB coated catheters should be used when possible in the treatment of IVH (GRADE: high).

Catheters should be removed as soon as clinically possible and preferably before 5 days of treatment (GRADE: low). Leakage should be prevented and handled immediately (<1 day) to avoid infection.[14] IVF seems to reduce risk of ventriculitis, presumably due to shorter EVD treatment time and fewer catheter changes, although this effect was not significant.[18,57]

Furthermore, we found that bolted catheters were superior to tunneled catheters in preventing CSF leakage and infection. Tunneling was associated with increased risk of CSF leakage (36%) compared to bolted catheters (3.2%). Further, CSF leakage for >1 day increased risks of ventriculitis compared to <1 day of leakage (21.1% vs. no observed infections).[38] In support of this observation, a recent meta-analysis by Garg et al. found that bolted EVDs were associated with significantly lower risk of catheter-related infections for arbitrary indications (M-H OR: −0.60; 95% CI, 0.39–0.94; P = 0.026). Bolted EVDs were also associated with a reduced risk of EVD malfunction (drainage stop and leakage) (M-H OR: −0.31; 95% CI, 0.16–0.58; P = 0.0003), accidental disconnection (M-H OR: −0.09; 95% CI, 0.03–0.26; P < 0.0001), and catheter misplacements (MH OR: −1.65; 95% CI, 1.14–2.40; P = 0.008) compared with tunneled EVDs.[12]

In summary, we therefore recommend to use bolted EVDs when possible and resolve observed leakage swiftly (GRADE moderate).

Functional Outcome and Mortality. As a highly important finding, we observed that IVF significantly reduces mortality (30-day mortality rate 22.4% vs. 40.9%, OR: 0.39 [95% CI, 0.29–0.54; P < 0.00001]) and improved functional outcome (OR for good functional outcome = 1.40 [95% CI, 1.03–1.91; P = 0.03) compared with no IVF. Based on these findings we strongly recommend that IVF is implemented in the treatment of IVH when CSF drainage is indicated (GRADE: high).

These conclusions are consistent with a recent meta-analysis by Kuramatsu et al. describing the same significant effect with a shift toward improved outcome across the entire range of the mRS estimates and reduced mortality for patients treated with IVF (good functional outcome OR = 1.75 [95% CI, 1.39–2.17] and mortality OR = 0.47 [95% CI, 0.35–0.64]).[11] Other meta-analyses found similar tendencies, although the effects on functional outcome in IVF treated patients were not significant (OR: 1.41 (95% CI: 0.98–2.03).[8,9]

Shunt Dependency. Our literature review revealed no significant evidence for interventions to reduce the risk of shunt dependency, which occurred in approximately 15% of patients with standard EVD. However, acute hydrocephalus was related to pan-ventricular hemorrhage (Graeb score >3) and hematoma location in the third and fourth ventricles.[29,30,36,44] Likewise, shunt dependency was correlated with high IVH volume and casting ventricles.[29,30,36,44] IVF did not reduce the risk of shunt dependency compared with no IVF treatment (OR: 0.99; 95% CI, 0.68–1.46; P = 0.98, GRADE: high), as also observed in a meta-analysis from Solinge et al.[8] (OR: 0.93 and 95% CI: 0.70–1.22).

Clearance of Blood. IVF increased the clearance of IVH.[18,31,48] High-dose IVF (4 mg/12 hours) was favorable compared with low-dose (1 mg/8 hours) and accelerated clearance in the lateral ventricles but not in the third and fourth ventricles.[58] In accordance, Solinge et al. also found accelerated hematoma clearance of the lateral ventricles in IVF treated patients (median difference of days = − 4.05 days; 95% CI: −5.52 to −2.57).[8] Doses of tPA (Tissue plasminogen activator) administrated varied between 1 and 6 mg/day. No dose-related adverse events were reported.[8] Based on these observations IVH could potentially be a cost-effective treatment reducing the ICU length of stay in addition to clinical benefits described above.

EVD in IVH Patients in Comparison with Other Indications for EVD

Our review and meta-analysis was based on studies investigating EVD treatment in IVH patients. Other conditions, such as SAH, traumatic brain injury and bacterial meningitis are also treated with EVD.[2] Overall, our findings in IVH patients were comparable to other patient categories. EVD-associated infections were seen in 22% of patients with arbitrary indications for EVD treatment[2,59] compared with 12.8% in our analysis for patients not treated with IVF. Furthermore, AB coating was shown to reduce the risk of infection by 50%[2,60] (we found infection rate in AB-coated catheters to be 4.3% compared to 16.1% for uncoated catheters [P < 0.001]). Temporary occlusion rates (at least one) were reported in 41% of cases, while permanent occlusions were observed in 19%–54%,[47,61,62] compared to an overall occlusion rate of 26.6% in our study, although greatly reduced by IVF. Aten et al.[62] also found that the risk of infection was 29% for patients who experienced an EVD replacement compared with 6% for those who did not have the catheter replaced.[62] For shunt dependency in SAH patients, a review and meta-analysis by Wilson et al. showed that 15.8% of the patients needed permanent CFS drainage,[63,64] which was similar to our findings in IVH patients with an overall shunt dependency of 14.9%.

Future Perspectives

Significant improvement in treatment of IVH has been lacking in recent years. Innovations in IVH treatment are currently being tested and carry significant potential for further improvement, for example, the Integra Surgiscope, an aspiration-irrigation system for minimally invasive clot removal[65] and the Artemis evacuator, an ultrasonic irrigation-aspiration device. Both technologies are based on the rationale that fast hematoma evacuation may reduce mortality and improve functional outcome. Furthermore, new catheter technologies are emerging, such as the IRRAflow technology, which is a dual-lumen catheter with an automatic, closed system for irrigation and aspiration.[65] Additionally, the CerebroFlo is an endexo technology, featuring a permanent additive to the catheter design that reduces fibrinogen and platelet activation.[65] Future trials will shed light on the potential benefit of these techniques.

This review and meta-analysis serves as a reference of historical data for future studies on the subject.

Risk of Bias and Limitations

It is our opinion that the risk of publication bias is highest in the included observational studies, for which the treatment effect could be overestimated. However, no publication bias is assumed in RCT studies. Furthermore, since general agreement on the usage of outcome measures in the individual studies is wanted, no overall presentation of the results in relevant meta-analyses is possible.

CONCLUSIONS

Our review and meta-analysis provides clear best practice recommendations for EVD treatment in IVH patients. Bolted, AB-coated, large-lumen catheters are superior to tunneled, uncoated, and small-lumen catheters. Catheters should be removed as soon as clinically possible and preferably not be left for more than 5 days. IVF treatment is strongly recommended to improve blood clearance, survival rates, and functional outcome, while simultaneously reducing the risk of catheter occlusions.

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SUPPLEMENTARY DATA

Supplementary Table 1. Quality Assessment of the Included Studies

Study	Design	No. of Patients Included for Analysis	Blinding of Participants and Personnel	Complete/Incomplete Outcome Measures	Minimization of Selection Bias	Control of Confounding Factors
Akdemir; 1995[16]	RCT	16	Low	Low	Low	Low
Asaad; 2019[40]	Prospective cohort study Cohort study	46	Low	High	Low	Low
Bota; 2005[66]	Prospective cohort study Cohort study	638	Low	Low	Low	Low
Catapano; 2021[28]	Retrospective cohort study	561	Low	High	High	High
Coplin; 1998[20]	Retrospective cohort study	40	Low	Low	Low	High
Ducruet; 2010[21]	Retrospective cohort study	30	Low	Low	Low	Low
Findlay; 1993[67]	Prospective cohort study	10	Low	Low	High	High
Findlay; 2004[26]	Prospective cohort study	30	Low	High	high	High
Gilard; 2017[47]	Retrospective cohort study	74	Low	Low	High	Low
Gluski; 2021[27]	Retrospective cohort study	560	Low	Low	Low	Low
Gubucz; 2004[17]	RCT	27	High	Low	Low	Low
Hanley; 2017[18]	RCT	500	High	High	High	High
Herrick; 2014[36]	Retrospective cohort study	183	Low	Low	High	Low
Hughes; 2015[37]	Retrospective cohort study	105	Low	Low	High	Low
Huttner; 2008[22]	Case-control	44	Low	Low	High	Low
Hwang; 2012[53]	Prospective cohort study	142	Low	Low	High	Low
King; 2012[48]	RCT	16	High	High	High	High
Kirmani; 2015[14]	Retrospective cohort study	130	Low	Low	Low	Low
Kuo; 2018[29]	Retrospective cohort study	72	Low	Low	Low	Low
Kramer; 2014[25]	RCT	77	High	High	High	Low

Continues

Supplementary Table 1. Continued

Study	Design	No. of Patients Included for Analysis	Blinding of Participants and Personnel	Complete/Incomplete Outcome Measures	Minimization of Selection Bias	Control of Confounding Factors
Krel; 2019[58]	Retrospective cohort study	22	Low	Low	High	High
Lajcak; 2013[57]	Retrospective cohort study	403	Low	Low	High	Low
Lemcke; 2012[68]	Prospective cohort study	95	Low	Low	Low	Low
Litrico; 2013[32]	RCT	19	High	High	Low	Low
Luong; 2019[33]	Prospective cohort study	80	Low	Low	High	High
Lovasik; 2016[35]	Retrospective cohort study	563	Low	High	High	Low
Miller; 2008[45]	Retrospective cohort study	213	Low	Low	Low	Low
Murthy; 2017[44]	RCT	500	High	High	High	High
Naff; 2000[49]	RCT	20	High	High	High	High
Naff; 2004[31]	RCT	12	High	High	High	High
Nilsson; 2018[15]	Retrospective cohort study	296	Low	Low	High	High
Park; 2018[38]	Prospective cohort study	52	Low	Low	High	Low
Roeder; 2019[34]	Retrospective cohort study	1112	Low	Low	Low	Low
Staub-Bartelt; 2021[50]	Retrospective cohort study	36	Low	Low	Low	Low
Staykov; 2011[23]	Retrospective cohort study	48	Low	Low	High	Low
Torres; 2008[24]	Prospective cohort study	28	Low	Low	Low	Low
Tung; 1998[19]	Retrospective cohort study	21	Low	Low	Low	Low
Wang; 2013[42]	RCT	401	High	High	High	Low
Winkler; 2013[13]	RCT	61	Low	High	Low	Low
Yasar; 2020[43]	Retrospective cohort study	47	Low	Low	High	High
Zacharia; 2012[30]	Retrospective cohort study	210	Low	Low	Low	Low
Zheng; 2018[39]	Retrospective cohort study	84	Low	Low	High	High

RCT, randomized controlled trial.

Supplementary Table 2. Overview—All Included Studies in the Review and Meta-Analysis

Study	Study	Total No. of Patients	Study Subject and Outcome Measures	Included in Review and/or Meta-Analysis	Study Results
Akdemir; 1995[16]	Akdemir 1995 (18)	16	Urokinase	Meta-analysis	IVF decreased in-hospital mortality, shunt dependence, and improved functional outcome and ventricular clearance, but did not reach statistical significance.
			Mortality		
			Shunt dependency		
			Clearance of blood		
Asaad; 2019[40]	Asaad 2019 (10)	46	Bolted EVD	Review	Bolted EVDs have significant fewer complications than tunneled EVD.
			Tunneled EVD		
			Infection		
			CSF leak		
			Occlusions		
			Displacement		
Bota; 2005[66]	Bota 2005 (50)	638	Infection	Review	Ventriculostomy related infections was associated with length of ICU stay
Catapano; 2021[28]	Catapano 2021 (27)	561	rtPA	Review	Ventricular casting increases the risk of chronic hydrocephalus and shunt dependency. Risk was found decreased when rtPA was applied.
			Shunt dependency		
Coplin; 1998[20]	Coplin 1998 (51)	40		Meta-analysis	IVF increased ventricular clearance. No significant difference in functional outcome or shunt dependence.
			Urokinase		
			Functional outcome		
			Mortality		
			Shunt dependency		
			Infection		
Ducruet; 2010[21]	Ducruet 2010 (52)	30		Meta-analysis	rTPA increases hematoma removal. However, rtPA might worsen peripheral hematoma edema.
			rtPA		
			Functional outcome		
Findlay; 1993[67]	Findlay 1993 (53)	10	rtPA	Review	rtPA increases drainage output and lowers ICP.
Findlay; 2004[17]	Findlay 2004 (33)	30	rtPA	Review	rtPA lowers the risk of occlusions due to blot clots
			Clearance		
			Catheter replacement		
			Shunt dependency		
Gilard; 2017[47]	Gilard 2017 (29)	74	Occlusion	Review	Risk of catheter occlusion was decreased in patient treated with a large catheter.
			Hematoma related to EVD placement		
			Infection		
			Shunt dependency		
			Functional outcome		

Continues

Supplementary Table 2. Continued

Study	Study	Total No. of Patients	Study Subject and Outcome Measures	Included in Review and/or Meta-Analysis	Study Results
Gluski; 2021[27]	Gluski 2021 (21)	560	Acute hydrocephalus	Review	Bleed characteristics affect the incidence of acute hydrocephalus. It did not affect the rate of shunt dependency.
			Shunt dependency		
			Functional outcome		
Gubucz; 2004[17]	Gubucz 2004 (17)	27	Urokinase	Review and meta-analysis	Urokinase is safe to use. Earlier mobilization, decrease in no. of infections.
			Mortality		
			Functional outcome		
			Infection		
Hanley; 2017[18]	Hanley 2017 (15)	500	Alteplase	Review and meta-analysis	Alteplase improved mortality rates but did not substantially improve functional outcome.
			Functional outcome		
			Mortality		
			Shunt dependency		
			Infection		
Herrick; 2014[36]	Herrick 2014 (25)	183	Mortality	Review	EVD placement is associated with reduced mortality and short-term outcome.
			Functional outcome		
Hughes; 2015[37]	Hughes 2015 (20)	105	Duration of EVD treatment	Review	The mean CSF drainage time was 17 days (range: 26 days). After that either the EVD is removed, or the patient is having a permanent VP shunt placed.
Huttner; 2008[22]	Huttner 2008 (54)	44	Intraventricular fibrinolysis	Meta-analysis	IVF increased ventricular clearance. No significant difference in functional outcome or shunt dependence.
			Clearance of blood		
			Functional outcome		
			Shunt dependency		
Hwang; 2012[53]	Hwang 2012 (42)	142	Functional outcome	Review	EVD insertion was not associated with increased functional outcome, but the EVD group had similar mortality rates and functional outcome as those who did not receive an EVD, despite having a significantly worse prognosis at admission.
			Mortality		
King; 2012[48]	King 2012 (35)	16	Urokinase	Review and meta-analysis	Administration of IV significantly fastened the rate of disappearance of the IVH measured on serially obtained CT scans. Further, IVF significantly increased the concentration of Hb in the CSF drained.
			Shunt dependency		
			Infection		
			Functional outcome		
			Mortality		
Kirmani; 2015[14]	(14)	130	Mortality	Review	Exponential increase of infections was seen after 5 days of EVD treatment.
			Infection		
			Catheter replacements		

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Supplementary Table 2. Continued

Study	Study	Total No. of Patients	Study Subject and Outcome Measures	Included in Review and/or Meta-Analysis	Study Results
Kuo; 2018[29]	Kuo 2018 (22)	72	Hydrocephalus	Review	The distribution pattern of blood in the ventricles affected the severity of the IVH and the incidence of acute hydrocephalus.
Kramer; 2014[25]	Kramer 2014 (55)	77	Alteplase Clearance of blood Shunt dependency Functional outcome	Meta-analysis	tPA accelerated clearance of blood especially when administrated early.
Krel; 2019[58]	Krel 2019 (16)	22	rtPA Duration of EVD treatment Shunt dependency Infection	Review	Higher rates of ventriculitis (18%) compared to the literature in rtPA treated patients.
Lajcak; 2013[57]	Lajcak 2013 (11)	403	Infection	Meta-analysis	Silver-impregnated catheters lowered the infection rate significantly compared to nonimpregnation.
Lemcke; 2012[68]	Lemcke 2012 (12)	95	Infection	Review	Antibiotic and silver-impregnated catheters reduces risks of infection
Litrico; 2013[32]	Litrico 2013 (56)	19	rtPA Clearance of blood Mortality rate	Meta-analysis	Significantly increased clearance of blood in the rtPA treated group.
Luong; 2019[33]	Luong 2019 (57)	80	rtPA Mortality Functional outcome	Meta-analysis	rtPA lowered the mortality rates and improved functional outcome at 1 month.
Lovasik; 2016[35]	Lovasik 2016 (24)	563	Functional outcome Mortality	Review	A trend toward decrease in mortality was seen in the group treated with an EVD and increase in functional outcome
Miller; 2008[45]	Miller 2008 (26)	213	Shunt dependency	Review	Age, low Glasgow Coma Scale score, elevated CSF protein, CSF erythrocyte count, ventriculitis, and duration of EVD were independent predictors of permanent shunting
Murthy; 2017[44]	Murthy 2017 (30)	500	Alteplase Shunt dependency	Review	Permanent CSF shunting was found in 18% of the patients
Naff; 2000[49]	Naff 2000 (36)	20	Clearance of blood	Review	Urokinase may significantly improve 30-day survival rate in IVH patients
Naff; 2004[31]	Naff 2004 (34)	12	Urokinase Safety Clearance	Review and meta-analysis	Urokinase speeds resolution of blood compared with EVD alone
Nilsson; 2018[15]	Nilsson 2018 (9)	296	Infection	Review	Silver-impregnated catheters did not decrease rate of ventriculitis
Park; 2018[38]	Park 2018 (7)	52	Infection	Review	CSF leak increases risk of infection.
Roeder; 2019[34]	Roeder 2019 (23)	1112	Functional outcome Mortality	Review	Small amounts of intraventricular blood was not associated with increased risk of hydrocephalus and poor outcome

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Supplementary Table 2. Continued

Study	Study	Total No. of Patients	Study Subject and Outcome Measures	Included in Review and/or Meta-Analysis	Study Results
Staub-Bartelt; 2021[50]	Staub-Bartelt 2021 (38)	36	Intraventricular fibrinolysis	Review	A significant decrease in ICH volumes were found when IVF was applied in the ventricles system for patient with ICH with breakthrough
			Volumetrics of IVH		
Staykov; 2011[23]	Staykov 2011 (37)	48	Intraventricular fibrinolysis	Review and meta-analysis	IVF decreased shunt dependency.
			Shunt dependency		
			Clearance of blood		
			Infection		
			Mortality		
Torres; 2008[24]	Torres 2008 (40)	28	Intraventricular fibrinolysis	Meta-analysis	IVF decreased in-hospital mortality, improved functional outcome, but did not reach statistical significance.
			Mortality		
			Functional outcome		
Tung; 1998[19]	Tung 1998 (58)	21	Intraventricular fibrinolysis	Meta-analysis	IVF decreased in-hospital mortality and shunt dependence, improved functional outcome, increased meningitis, but did not reach statistical significance.
			Mortality		
			Functional outcome		
			Shunt dependency		
			Infection		
Wang; 2013[42]	Wang 2012 (59)	401	Urokinase	Review	EVD + urokinase is preferred treatment in IVH
			Functional outcome		
Winkler; 2013[13]	Winkler 2013 (6)	61	Infection	Review	No difference in infection rate between silver impregnated and antibiotic coated catheters
Yasar; 2020[43]	Yasar 2020 (5)	47	Infection	Review	Duration of EVD treatment was statistically significant correlated with the infection rate especially for patients above 65 treated with EVD for more than 6 days
Zacharia; 2012[30]	Zacharia 2012 (28)	210	Shunt dependency	Review	Given the anatomical relationship of thalamic hemorrhages to the third ventricle and the foramen of Monro, it is intuitive that hematoma formation in this location more easily results in obstruction of CSF flow independent of IVH volume than in hemorrhages occurring in other locations
Zheng; 2018[39]	Zheng 2018 (8)	84	Urokinase	Review	High Graeb score is associated with higher risk of ventriculitis
			Infection		
			Tunneling		

IVF, intraventricular fibrinolysis; EVD, External ventricular drainage; RCT, randomized controlled trial; ICH, Intracerebral hemorrhage; rtPA, recombinant tissue plasminogen activator; ICP, intracerebral pressure; ICU, intensive care unit; VP, ventriculoperitoneal; CSF, cerebrospinal fluid; CT, computed tomography; Hb, hemoglobin.