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Analysis of Thrombolytic Agents in Intraventricular Hemorrhage: A Systematic Review and Meta-Analysis

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ABSTRACT

AIM: To determine the effectiveness of extraventricular drainage (EVD) combined with fibrinolytics in reducing morbidity and mortality rates associated with intraventricular cerebral hemorrhage (IVH).

MATERIAL and METHODS: A literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO registration number: CRD42022332152). Articles were selected from various sources, including PubMed, Trip Database, LILACS, Cochrane Library, and ScienceDirect. Clinical trials focusing on IVH treatment using EVD and/or fibrinolytics were considered. The Risk of Bias in Non-randomized Studies of Interventions (ROB 2) tool was employed for bias assessment. A fixed-effects regression model was used following heterogeneity analysis. Treatment effectiveness was evaluated based on mortality outcomes.

RESULTS: A total of 531 patients from four studies were included. The use of fibrinolytics significantly decreased IVH mortality compared with a placebo. The odds ratio (OR) for recombinant tissue plasminogen activator (rtPA) or alteplase was 0.54 [0.36; 0.82]. For urokinase (UK), the OR was 0.21 [0.03; 1.54], rendering it statistically non-significant. The overall OR was 0.52 [0.35; 0.78], and the heterogeneity I2 was 0% (indicating low heterogeneity).

CONCLUSION: While EVD alone is a common approach for managing hydrocephalus, its effectiveness is limited by potential blockages and infections. Combining EVD with UK or rtPA demonstrated improved patient outcomes. rtPA stands out as a reliable and effective option, while limited data are available regarding UK's effectiveness in reducing IVH mortality.

KEYWORDS: Intraventricular thrombolytic, Intraventricular hemorrhage, Thrombolytic therapy, Fibrinolytic therapy, Prognosis

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INTRODUCTION

Intraventricular hemorrhage (IVH) is associated with elevated morbidity and mortality rates in cerebrovascular accidents. Hemorrhages, including intracerebral (ICH), subarachnoid (SAH), and intraparenchymal hemorrhages, whether linked to hypertension, acute hydrocephalus, secondary brain injuries, or spontaneous primary intracerebral hematoma with ventricular involvement, contribute to deterioration of the health conditions of patients with IVH (5,12,24).

Various studies have reported on the application of extraventricular drainage or drain (EVD) for reducing mortality and enhancing the prognosis of patients with IVH. Particularly, the combination of EVD with ventricular fibrinolytic agents, namely, urokinase (UK) and recombinant tissue plasminogen activator (rtPA) or alteplase, has shown promising results in intraventricular fibrinolysis (IVF) compared with EVD alone for clot dissolution (12,14).

The primary objective of this study was to present a comprehensive summary of the efficacy of three IVH treatment modalities: EVD alone (without the use of any fibrinolytic drug), EVD associated with rtPA (EVD+rtPA), and EVD associated with UK (EVD+UK). This study was not limited to the use of only one type of thrombolytic or the use of rtPA and UK without differentiating between them and in relation to a placebo. The meta-analysis considered the distinct characteristics of each form of treatment and compared their outcomes.

MATERIAL and METHODS

This systematic review of the literature adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (22). A comprehensive bibliographic search was executed in databases including PubMed, Trip Database, LILACS, Cochrane Library, and ScienceDirect. Utilizing the descriptors "*Cerebral Intraventricular Hemorrhage*", "*Thrombolytic Therapy*" and "*Fibrinolytic Therapy*" using Boolean operators "AND" and "OR", the search aimed to address the guiding question of the research on the three forms of treatment for IVH, considering works published from January 2002 to January 2023, which resulted in the identification of 1406 articles (Figure 1).

Inclusion Criteria

The inclusion criteria were original works in English, Spanish, and Portuguese, including clinical trials (randomized and

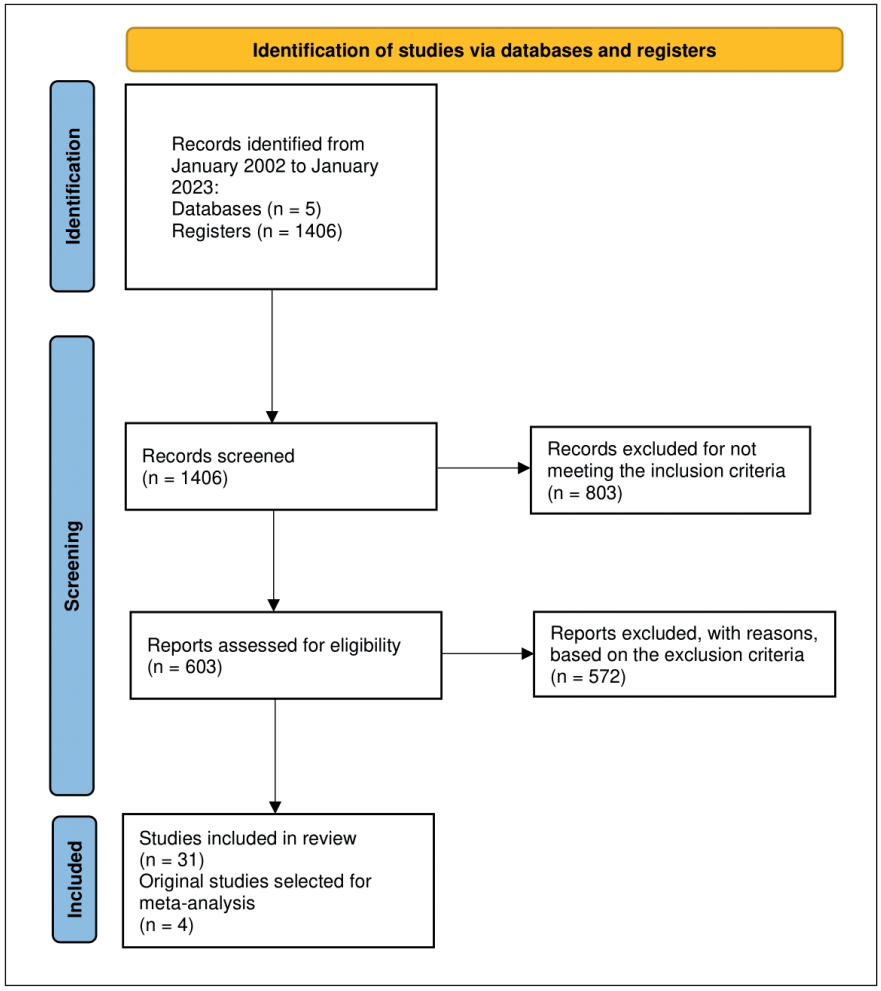

Figure 1: Representation of the identification, screening, eligibility and inclusion and exclusion criteria for the review.

non-randomized), meta-analyses, systematic reviews, and peer reviews. After evaluation, 603 works remained, and their abstracts were carefully reviewed.

Exclusion Criteria

Articles unrelated to the topic, unavailable in fulltext, duplicates, cohort studies, and case reports were excluded. Following the application of the inclusion and exclusion criteria, 31 relevant studies were identified and included.

Meta-Analysis

The studies were assessed for heterogeneity using appropriate measures, with the Higgins I2 measure determining the degree of variation in the association measure attributable to heterogeneity. The Cochran test was employed under the null hypothesis in the absence of heterogeneity. Data analysis was conducted using a fixed-effects regression model.

Odds ratio (OR) values and their corresponding 95% confidence intervals (95% CI) were calculated.

Forest and funnel plots were employed to evaluate publication bias, while subgroup analysis was conducted based on the type of drug used in each study. Statistical analyses were performed using RStudio Team (2015), an integrated development environment for the R programming language developed by RStudio, Inc., located in Boston, MA.

Data Validation

Data validation involved two authors discussing the selected works. In cases where a consensus was not reached, a third author was consulted. To analyze the risk of bias in intervention-type studies, the Cochrane Back Review Group (CBRG) guidelines were utilized.

RESULTS

The meta-analysis involved the evaluation of thrombolysis and mortality in patients undergoing treatment with EVD and fibrinolytics.

The characteristics of each study included in the meta-analysis (11,13,15,20) are presented in Table I.

After review, four publications were considered that reported mortality after thrombolysis, including 531 patients (Table I). Two were considered to have a low risk of bias, whereas two had some concerns (Figure 2).

Among the four studies, three (13,15,20) showed no significant difference between the control and experimental groups

Table I: Characteristics of the Studies Included in the Meta-Analysis

Study	Number of patients in group A (rtPA)	Number of patients in group B (UK)	Number of patients in group C (Placebo)	Mortality rate in group A	Mortality rate in group B	Mortality rate in group C
Hanley et al. (11)	246		245	19%		30%
Naff et al. (20)		7	5		0%	20%
Kramer et al. (15)	6		6	17%		33%
King et al. (13)		7	9		14%	44%

rtPA: *Recombinant tissue plasminogen activator or alteplase,* ***UK:*** *UROKINASE*

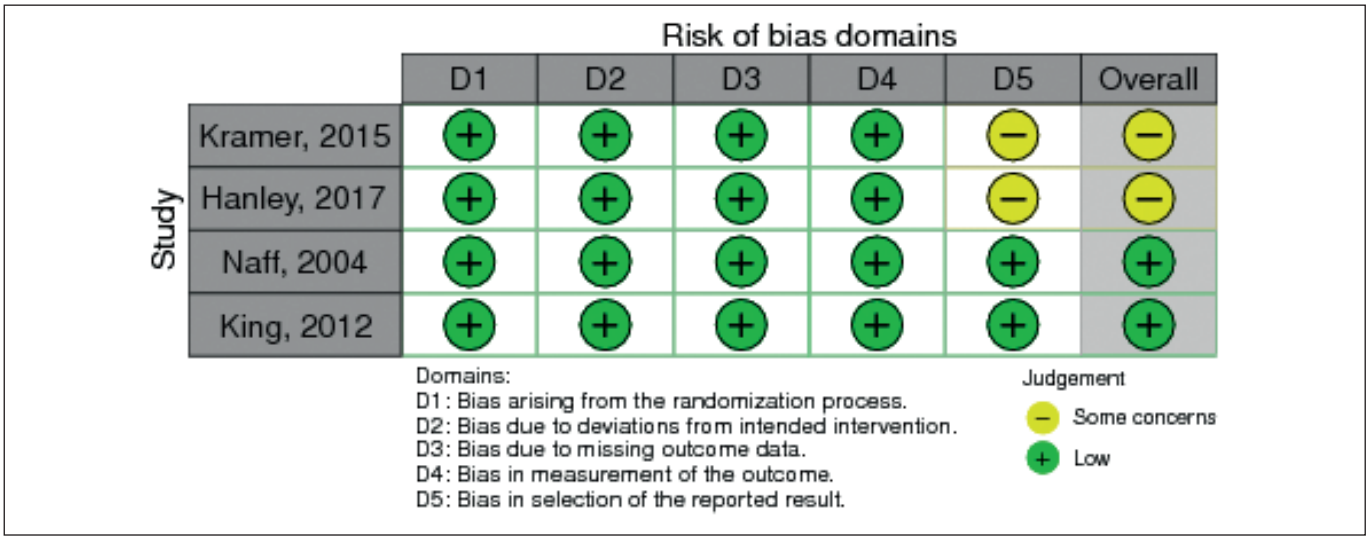

Figure 2: Risk of bias.

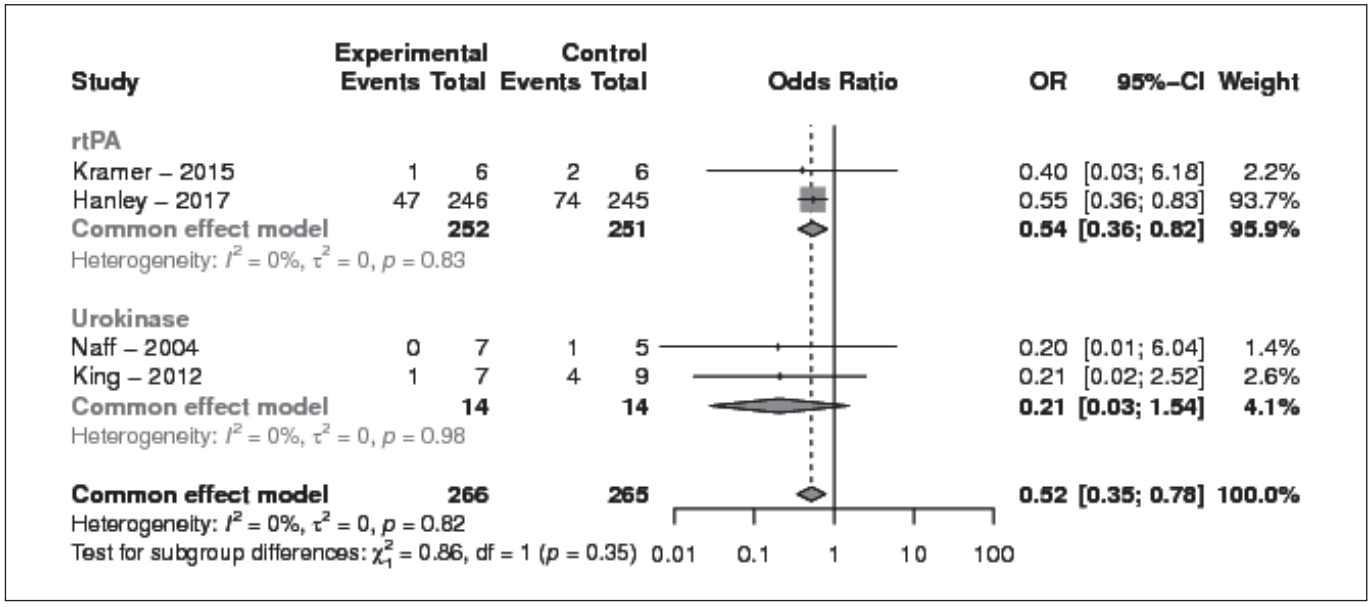

Figure 3: Forest plot of the publications analyzed in relation to mortality and thrombolytic agents used.

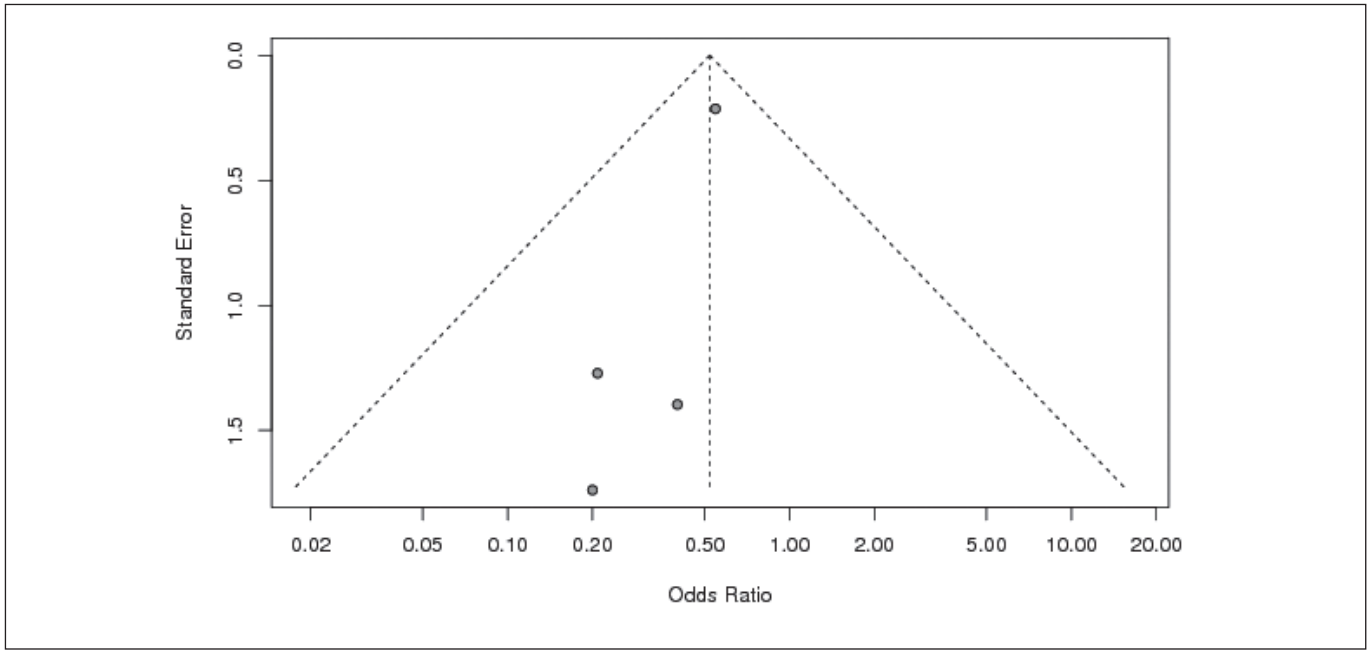

Figure 4: Publication bias for studies that assessed the different thrombolytics in intraventricular hemorrhage (IVH) treatment.

(Figure 3). However, our meta-analysis demonstrated a significant reduction in mortality in the thrombolytic group, with an OR of 0.52 [0.35; 0.78]. In the subgroup analysis for rtPA, the reduction was also significant, with an OR of 0.54 [0.36; 0.82]. Regarding UK, the OR was 0.21 [0.03; 1.54], rendering it not significant. The measure of heterogeneity, I2 (Higgins heterogeneity measure), was 0%, a value considered as low heterogeneity. According to Cochran's Q heterogeneity test, the sample evidence did not allow us to reject the null hypothesis of non-heterogeneity (p=0.82).

Publication bias was assessed using the funnel plot (Figure 4). The graph represents each study with the value of association and effect measures.

DISCUSSION

Initial description and general characteristics of the studies

The CLEAR III trial was a phase III, randomized, multicenter, double-blind, placebo-controlled trial designed to evaluate

accelerated resolution clot lysis in IVH. The study aimed to compare the use of EVD associated with intraventricular injection of rtPA using EVD and intraventricular injection of 0.9% saline solution (11,31).

Conducted across 73 locations in Brazil, Canada, Germany, Hungary, Israel, Spain, the United Kingdom, and the USA, the CLEAR III trial involved 500 randomized patients, with 249 in the rtPA group and 251 in the saline (placebo) group. Patients, aged 18–80 years, had a prior diagnosis of obstructive hydrocephalus and underwent EVD therapy. Inclusion criteria addressed symptom onset within 24 h before diagnostic computed tomography (CT), supratentorial ICH volume up to 30 mL, IVH obstructing the third and/or fourth ventricles, and clot stability on repeated CT scan at least 6 h after EVD placement (11,31).

For the study, participants received up to 12 doses of treatment containing 1 mg of rtPA or normal saline via EVD with an 8-h gap between doses. Investigators aimed to remove as much clot as possible until a satisfactory stopping point was reached: third and fourth ventricles open, 80% of clot resolution after stability, removal of IVH mass effect, or completion of 12 treatment doses (11,31).

In the meta-analysis by Shi et al., the efficacy and safety of intraventricular rtPA administration after aneurysmal SAH were evaluated. Studies were divided into an intervention group of rtPA with EVD and a control group with saline solution (placebo) plus EVD. In the primary outcome, analyzing 141 patients for good functional improvement at 3 or 6 months (defined as Modified Rankin Scale or mRS 0-3 and Glasgow Outcome Scale [GOS] 4-5), neither group showed statistically significant results. In secondary outcome analyses, there was a 42% reduction in angiographic vasospasm in the intervention group compared with that in the placebo group in a total of 167 patients. For acute obstructive hydrocephalus (217 patients), the rtPA group showed a tendency to decrease this type of hydrocephalus compared with the control group. The analysis of hemorrhage and mortality (involving 217 patients) did not reveal statistical significance between the groups (23).

On the topic of IVF in aneurysmal SAH, the FIVHeMA study is anticipated to be the first phase III, randomized clinical trial assessing the enhancement of EVD with IVF versus EVD alone in the treatment of aneurysmal SAH. This study suggests that involving 390 patients could result in a 10% increase in the rate associated with a good functional status (here defined only as mRS 0-3), shifting from 75% in the EVD alone group to 85% in the EVD plus IVF group. Given the lack of success in finding effective treatments in many other phase III studies, the impact of this study could be crucial in the scientific community, potentially identifying an effective neuroprotective treatment against aneurysmal SAH (8).

In the study by Naff et al., UK was the substance under analysis, and selected patients with ICH were divided into two groups: UK (intervention) and control (placebo; saline solution) groups. The clot half-life (time to reach 50% of the initial clot volume) was 88.9 and 132.3 h in females in the intervention and placebo groups, respectively. In males, the clot half-life in the intervention and placebo groups was 136.4 and 274.8 h, respectively. This difference in both sexes resulted from a deviation from the 1:1 proportion, and hence, the results were presented as expected for each sex. The mean time for the intraventricular clot to reach its half-life was shorter in the intervention group, with a reduction of 3.8 days, than in the placebo group (20).

EVD

IVH is associated with a poor prognosis in hemorrhagic stroke. Clinical management involves inserting a ventricular catheter to facilitate blood drainage. However, as this procedure did not demonstrate a reduction in morbidity and mortality, the administration of fibrinolytic agents via a ventricular drain has been proposed to enhance clot lysis and drainage volume. Trials comparing the use of thrombolytics to placebo or open-label control were analyzed, suggesting evidence that the use of thrombolytics may be safe and of therapeutic value. Larger, well-planned clinical trials are needed to confirm these findings (18,10).

EVD, commonly referred to as ventriculostomy catheters, are employed to manage acute hydrocephalus by temporarily draining cerebrospinal fluid (CSF) from the brain's ventricles. Despite its efficacy in treating acute hydrocephalus, the invasiveness of ventriculostomy exposes patients to potential risks, including ICH and infection. These risks often arise from catheter failures, particularly when there is an obstruction in the catheter's flow due to displacement, migration, tissue debris, or thrombus. Such obstructions can significantly increase treatment costs and pose an increased risk of patient mortality. To mitigate these challenges, suggestions have been made for improvements in clinical procedures, patient observation, and modifications to the catheter's geometry to reduce such complications (2,10).

Various factors related to EVD impact the treatment of IVH. In the CLEAR-IVH program, the ventricular regions associated with the best and worst prognoses and variations in intraventricular thrombolytic rtPA doses in IVH resolution were studied. In patients who received a placebo via EVD in the midline region of the ventricles, hemorrhage resolved more rapidly, albeit indifferently, than those who received a placebo in other ventricular regions (anterolateral and posterolateral). However, in the CLEAR III program, the use of EVD directly influenced the amount of hemorrhage removed from the ventricle and, in clinical practice, EVD demonstrated better safety regarding adherence in the midline opening of the ventricles. However, its performance in removing >80% of IVH was suboptimal (11,28,31).

Alteplase

In the central nervous system (CNS), only essential compounds for cellular metabolism can easily cross the blood–brain barrier. To overcome this challenge, devices were introduced to enable the direct administration of drugs into the CSF. rtPA is an example of such drugs, working to convert plasminogen into plasmin for fibrin degradation. The use of fibrinolytics through intraventricular devices is increasingly explored in studies on IVH, aiming to facilitate blood clot remov-

al, maintain intraventricular drain patency, reduce intracranial pressure, and improve overall outcomes. However, adverse effects, including bleeding around the EVD and neurotoxic effects leading to hemoglobin-induced neurotoxicity, have also been observed (7).

Studies related to the use of EVD combined with the injection of rtPA in stroke with IVH aimed to achieve better clinical results than intraventricular injection of normal saline solution (placebo) for treating this condition (Table II). In the CLEAR III trial, routine EVD with rtPA did not demonstrate functional improvements in patients with IVH, but it significantly reduced mortality within 180 days, and most survivors acquired serious disabilities. An association was observed between the amount of clot removal and improved odds of mRS ≤ 3. Although rtPA appeared safe compared with saline solution, several limitations exist in this trial (11,31).

Patients with non-traumatic IVH undergoing IVF experienced a lower risk of mortality and EVD obstruction, along with faster blood clearance from the third and fourth ventricles, than those receiving only EVD (3, 26). Administering rtPA every 8 hours at a dose of 1 mg has been shown to be safe and beneficial, particularly in patients with a significant intraventricular blood load exceeding 20 mL (1).

However, patients undergoing IVF showed a potential increase in the risk of symptomatic intracranial hemorrhage and decrease in the risk of ventriculitis, although more data are needed for a comprehensive understanding of these effects (26). The most concerning complication of IVF is rebleeding, leading to protocols requiring a demonstration of hematoma stability. Therefore, it is recommended that patients undergo vascular neuroimaging examination to rule out lesions that might increase the risk of hemorrhages (1).

Although treatment with rtPA efficiently dissolves blood clots in IVH, after the CLEAR III trial and related studies, some pathophysiological sequelae were noted. The cascade induced by treatment with rtPA can cause damage parallel to cure, affecting various brain barriers, the glymphatic system, and brain structures responsible for clearing CSF. Despite these considerations, the results of the CLEAR III trial were promising regarding mortality (4).

When summarizing the CLEAR-IVH study, the group using rtPA exhibited dose-dependent faster outcomes in the midline ventricles and anterolateral ventricles, respectively. However, in the posterolateral ventricles, the resolution of the problem was slower and independent of the dose (18).

In a study by Kramer et al., 77 randomly selected patients admitted to the ICU with SAH participated in a randomized placebo-controlled study. Among them, 48 received thrombolytic administration via an EVD, with six patients receiving rtPA by EVD, and none developed new ICH. Although intraventricular rtPA accelerated the clearance of SAH and IVH, especially when administered early, ideal doses and administrations remain unclear with insufficient data (16).

The administration of intraventricular rtPA induced an increase in proinflammatory cytokines in the CSF during the first 24 h of treatment, decreasing after this period, even with the continuity of administration. The observed inflammatory response was believed to be mainly attributed to the effects of fibrinolysis rather than the direct toxicity of the drug. This was supported by the finding that an increase in CSF cytokine concentrations within the first 24 h had a direct linear relationship with the peak level of CSF fibrin-derived product (D-dimer). Patients who underwent greater fibrinolysis and had more ventricular blood clearance exhibited a more prominent inflammatory response in the CSF. Thus, the use of intraventricular rtPA significantly reduced hemorrhage and hematoma in the affected regions, making its pharmacological benefit much greater than its deleterious effects. However, the very rapid release of this fibrinolytic may transiently increase and perpetuate the injury and local inflammation (15).

In a meta-analysis developed by a study of randomized clinical trials, the use of rtPA and UK in the IVH clinic was compared. The results showed that compared with the control group, UK had no effect on mortality, whereas rtPA was associated with a reduction in patient mortality. However, survivors had moderately severe or severe functional disability after follow-up, not increasing the proportion of survivors with good recovery. The analysis of adverse events found no association between IVF and the placement of a ventriculoperitoneal shunt. In addition, the probability of ventriculitis was relatively lower in the rtPA group, whereas in the UK group, there was no difference compared with the control group. Therefore, an increased risk for infections, rebleeds, or severe adverse effects was not reported. Therefore, the use of IVF in IVH seems safe (27).

In the clinical picture of ischemic stroke in patients with large vessel occlusion, endovascular thrombectomy is well recommended. However, reperfusion of the smaller arteries is challenging with the isolated thrombectomy process, requiring strategies such as the additional use of rtPA. The Mechanical Removal of Embolism in Cerebral Ischemia (MERCI) assay showed a recanalization rate of 46% from the MERCI device alone and 60.8% when combined with rtPA. However, alteplase efficiency is compromised by endogenous CNS factors. Due to this, methods for increasing rtPA resistance to inhibitors have been investigated, such as the bioengineering development of tenecteplase and use of a diabody, an antibody that targets two proteins, to block inhibitors of the fibrinolytic process. In patients with hemorrhagic stroke, tissue plasminogen activators reduce the deleterious consequences of IVH and are administered directly into the EVD to increase the volume drained and restore CSF circulation (25).

Spontaneous IVH (SIH) may be associated with high mortality and morbidity, including impaired consciousness, hydrocephalus, and cognitive problems. This condition can occur primarily or secondary to an ICH, and its most appropriate clinical management, as well as its specific treatment, are not well defined. In the CLEAR III study, patients with primary IVH and those with secondary IVH to ICH were compared in terms of mortality and response to intraventricular injection of alteplase to patients in the control group (that received common saline). rtPA was safe in both situations, with similar results for patients with primary and secondary IVH, in addition to a

Table II: Main Findings of the Studies

Study	Study design	Model used and intervention	Type of treatment	Main findings
Hanley et al. (11)	CT	500 patients; rtPA: 1 mg 8/8 h, maximum of 12 doses; P: saline.	EVD alone and EVD with rtPA	In the CLEAR III trial, irrigation of the ventricles with alteplase via a routine EVD did not improve functional outcomes in patients with intraventricular hemorrhage. Lethality within 180 days was significantly lower in the alteplase group; however, most of these survivors had severe disabilities.
Shi et al. (23)	MA	217 patients; rtPA: variable doses P: saline.	EVD alone and EVD with rtPA	rtPA reduced the incidence of angiographic vasospasm by 42%, but there was no statistically significant improvement in the functional capacity of the subjects.
Naff et al. (20)	CT	12 patients; UK: 25000 IU; P: saline.	EVD alone and EVD with UK	UK accelerated blood clot resolution.
Webb et al. (28)	CT	64 patients; rtPA: 0,3 mg, 1 mg or 3 mg twice a day; P: EVD alone.	EVD alone and EVD with rtPA	IVH was reduced more rapidly in all regions by increasing the dose of rtPA. rtPA accelerates intraventricular hemorrhage resolution. This effect is dose-dependent, greater in midline ventricles and lesser in posterolateral ventricles.
LaPointe and Haines (18)	SR	54 patients; UK: variable doses.	EVD with UK	Evidence suggests that UK may have therapeutic value and be quite safe in the treatment of IVH.
Haldrup et al. (10)	SR and MA	General approach between EVD and IVF	EVD alone and EVD with IVF	The study demonstrates the differences in the use of the EVD and also addresses IVF in general. Therefore, even with different ways of using the EVD, the use of IVF continued to be an effective alternative in reducing mortality and improving functional status.
Erdman et al. (7)	SR	76 patients; rtPA: 5 mg/day P: saline.	EVD alone and EVD with rtPA	Time with severe vasospasm and EVD were shorter in the rtPA group.
van Solinge et al. (26)	SR and MA	1020 patients; rtPA: 1 mg up to 4 mg; UK: 5000 IU to 50000 IU P: saline.	EVD alone, EVD with rtPA and EVD with UK.	Lower risk of mortality and EVD obstruction in non-traumatic IVH and higher blood clearance in the third and fourth ventricles compared to EVD alone.
Baker et al. (3)	SR and MA	1084 patients; rtPA: 1-4 mg, 1-3 times a day; UK: 5000-50000 IU, 1-2 times a day.	EVD with rtPA and EVD with UK.	In the treatment of hypertensive IVH using in vitro fertilization, patients had a better chance of survival.
Kramer et al. (16)	CT	12 patients; rtPA: 2 mg 12/12h, maximum of 5 doses; P: saline.	EVD alone and EVD with rtPA.	rtPA accelerated intracranial blood clearance. CSF (cerebrospinal fluid) drainage volume in the 48 hours after drug administration was slightly higher in patients treated with rtPA, but the difference was not statistically significant.
Kramer et al. (15)	CT	12 patients; rtPA: 2 mg 12/12h, maximum of 5 doses; P: saline.	EVD alone and EVD with rtPA.	Results show that intraventricular administration of rtPA induces a transient increase in CSF inflammatory cytokines, which appears to be largely related to the extent of fibrinolysis. If this inflammatory response is detrimental, pharmacological strategies aimed at attenuating inflammation induced by the release of blood breakdown products may have a therapeutic benefit if combined with intraventricular fibrinolysis.

Table II: Cont.

Study	Study design	Model used and intervention	Type of treatment	Main findings
Wang et al. (27)	MA	607 patients; rtPA: 1 mg to 3 mg every 8 hours or every 12 hours UK: 02 IU 12/12h P: saline.	EVD alone, EVD with rtPA and EVD with UK.	Most patients with IVH are unlikely to benefit from functional recovery. Although the use of IVF (intraventricular fibrinolytics) is safe, its benefits are limited to a reduction in mortality at the expense of increasing the number of survivors with moderately severe injuries to severe disability.
Nelson et al. (21)	PR	46 patients; rtPA: 1 mg, 8/8h; P: saline.	EVD alone and EVD with rtPA.	In the evaluation of patients with primary IVH, the results were similar in the two groups.
Gaberel et al. (9)	CT	54 mice rtPA: 1 mg every 30min, maximum of 3 doses UK: 10 IU every 30min, maximum of 3 doses P: saline.	Saline injection, rtPA injection and UK injection.	UK significantly improved neurologic outcome and treatments with rtPA or UK reduced post-IVH ventricular volumes when compared with saline. UK exhibits a safer profile than rtPA after IVH regarding to secondary inflammatory processes and neurotoxicity.
Du et al. (6)	CT	47 patients UK: 20000 IU every 12h.	Unilateral EVD and bilateral EVD, both with UK.	In patients with severe IVH, some evidence was obtained in support of the use of bilateral EVD because it could significantly accelerate IVH elimination without any major side effects.
King et al. (13)	CT	16 patients UK: 25000 IU every 12h for 3 days P: saline.	EVD alone and EVD with UK.	The difference between the two groups was significant with an overall average increase in CSF hemoglobin (Hb) concentration of 0.57 g/dL (190%) for UK-treated patients compared to the placebo group. Complete clot resolution was estimated at 7.3 days for the group treated with UK and 10.3 days for the placebo group. The estimated half-life for clot resolution, which was the time required for 50% of the clot to resolve, was 2.3 days for the UK group and 4.6 days for the placebo group. There was also a tendency towards lower mortality for UK-treated patients (14%) compared to the placebo group (44%) at six months, so that the cumulative survival in the UK-treated group was 86% and 56 % in the placebo group, respectively.
Yang et al. (29)	CT	60 patients Group A: 20000 IU of UK in 5 ml of saline solution every 8h Group B: 20000 IU of UK every 6h.	Bilateral EVD (Group A) and Ommaya reservoir-associated EVD (Group B).	The length of conventional EVD catheter was 7 (5 to 9) days in group A and 5 (4 to 6) days in group B. The total drainage time was 7 (5 to 9) days in group A and 9 (8 to 11) days in group B. 2 out of 29 (6.90%) patients developed ventriculitis in group B compared to 3 out of 22 (13.64%) patients in group A. No patient had hydrocephalus in group B, but five patients in group A had it. 1 out of 29 (3.4%) patients in group B died in the hospital compared with 6 out of 22 (27.3%) patients in group A.
Li et al. (19)	MA	810 patients rtPA: variable doses UK: variable doses P: EVD alone. EVD alone, EVD with rtPA and EVD with UK	EVD isolado, EVD com rtPA e EVD com UK.	RtPA and UK groups improved survival of patients with IVH and did not increase the risk of intracranial rebleeding compared to the placebo group. From the best to the worst outcome, in terms of survival and prognosis, it was obtained by UK, rtPA and EVD alone, respectively.

CT: *Clinical trial,* ***MA:*** *Meta-analysis,* ***SR:*** *Systematic review,* ***PR:*** *Peer review,* ***P:*** *placebo,* ***rtpa:*** *recombinant tissue plasminogen activator or alteplase,* ***UK:*** *Urokinase,* ***FVD:*** *Extraventricular drainage or drain,* ***CSF:*** *Cerebrospinal fluid*

significant reduction in mortality. However, it did not present significant differences in the functional outcome of patients. Accordingly, future investigation of primary (or secondary) IVH through imaging examination may help understand why IVH patients show inconsistency, especially in terms of their cognitive abilities, throughout their recovery (17,21).

Although initial studies with rtPA demonstrated some safety and efficacy for ICH, a report from the MISTIE-III trial showed that image-guided minimally invasive surgical techniques associated with rtPA did not produce significant clinical improvements. In the same trial, secondary data analysis was performed and confirmed that only 58% of patients in the intervention (alteplase) group achieved the surgical goal of residual hematoma volume < 15 mL. Moreover, these patients obtained better results than those who did not reach the stipulated surgical goal and those who received standard treatment. Hence, it can be highlighted that the information from the secondary analysis can be beneficial to the clinical course of ICH, bringing safety and an increase in the success rate. The failures found in surgical evacuation bring new methods that need to be improved or created for hematoma evacuation, and a potential therapeutic target may be in the resolution or absorption of this hematoma (30).

UK

At the University Hospital of Caen (France), a pre-clinical trial was conducted in rodents to evaluate the differences between the choice of one fibrinolytic over another in the treatment of IVH. The comparative study between the two substances did not show significant differences; it only proved that both UK and rtPA can be used equally for IVF (Table II). However, UK has the advantage of not causing deleterious effects, such as an increase in inflammation - as assessed by anti-VCAM-1 immunoreactivity - and quantitative analysis of microglial cell infiltration in the perihematomal period, effects presented with the use of rtPA (9).

UK, used to verify the efficacy of fibrinolytic therapy by comparing simple and bilateral EVD in patients with severe SIH, resulted in a decrease in IVH volume over time in both groups, with a more accentuated decrease in the group submitted to bilateral EVD. Theoretically, additional EVD may have some disadvantages, such as causing additional brain damage, but rapid IVH drainage and reduced mortality outweigh the potential disadvantages (6).

Intraventricular thrombolysis is a potentially safer and more effective alternative to EVD alone for reducing intraventricular clot. Furthermore, the use of UK is recommended for prompt clot reduction when faster relief from obstructive hydrocephalus is necessary. The UK dose (25,000 IU every 12 h for 3 days in a row) was also found to be safe and did not result in an increased risk of bleeding complications. The use of UK in EVD combined with the Ommaya reservoir increased clot clearance, shortened the duration of EVD (compared with conventional catheter-based EVD), increased total drainage time, reduced the mortality rate, and the incidence of hydrocephalus (13,29).

A meta-analysis of 10 studies analyzed a sample of 810 patients who underwent EVD associated with rtPA, EVD associated with UK, or EVD alone, the latter intervention corresponding to the control group. The results showed that the combination of EVD and UK or EVD and rtPA improved the survival of patients with IVH compared with those with EVD alone. Furthermore, the association of EVD with fibrinolytics did not increase the risk of cranial bleeding or infection. However, EVD associated with rtPA increased the proportion of surviving patients with severe disability. Thus, EVD associated with UK can be considered the best combination of treatment for IVH (19).

Study Limitations

This study has some limitations: (1) Trials on the efficacy of UK-associated EVD thus far are of insufficient size and quantity to allow any determination of safety or efficacy. (2) In the current literature, the number of studies evaluating the long-term effects of IVF use is insufficient.

CONCLUSION

EVD alone is a common method used to manage hydrocephalus, but its efficacy can be hampered by its shape and anatomical position, making it prone to blockages and infections. However, when used in combination with UK or rtPA, patients have shown better prognoses than with EVD alone, highlighting the effectiveness of this alternative treatment. rtPA is a reliable therapy option that has demonstrated high efficacy. Conversely, there is limited data demonstrating the use of UK alone, and it does not provide sufficient information, particularly in terms of reducing the mortality rate of patients with severe IVH.

AUTHORSHIP CONTRIBUTION

Study conception and design: FSB, NNR

Data collection: FSB

Analysis and interpretation of results: FSB, EMFP, LZP

Draft manuscript preparation: FSB, EMFP, ISR, LMRA, AEAS, LZP, JSB

Critical revision of the article: NNR, EGF, JSB

Other (study supervision, fundings, materials, etc...): FSB, EMFP, AEAS, LZP, NNR, JSB, EGF

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