



Published By :  
Surgical Residency Program  
Universitas Syiah Kuala



# Interaction of antifibrinolytic providing intrathecal in intraventricular blood: a systematic review and meta-analysis

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## ABSTRACT

**Introduction:** Intraventricular hemorrhage refers to the presence of blood in the cerebroventricular system. Intraventricular hemorrhage can lead to severe complications such as hydrocephalus. One of the therapeutic modalities for intraventricular hemorrhage is to perform CSF diversion using an external ventricular drain (EVD). To overcome complications related to the use of EVD, there have been several efforts to accelerate its excretion in ventricular blood, one of which is by intraventricular injection of fibrinolytic. The mixed results of studies on intraventricular fibrinolysis prompted investigators to conduct a review and meta-analysis of this treatment modality.

**Method:** We conducted systematic reviews and meta-analyses on several literature databases and included articles in English. We were using the boolean operator AND to search for literature containing all keywords in the databases and analyze the data using SPSS and Revmann.

**Results:** Unfavorable outcomes with the use of intraventricular fibrinolytic therapy in IVH occurred in a median of 51% of cases. The risk of an unfavorable outcome in IVH patients who received intraventricular fibrinolytic was 0.93 times compared to controls. The risk of an unfavorable outcome in IVH patients receiving rtPA and intraventricular urokinase was 0.95 and 0.73 times, respectively, compared to controls. The use of intraventricular fibrinolysis was able to reduce IVH volume by an average of 22.84 cc. The use of intraventricular fibrinolysis was able to improve the modified Graeb Score with an average change of 5.24 points.

**Conclusion:** Intraventricular fibrinolysis administration helps to reduce the risk of unfavorable outcomes in IVH cases.

**Keywords:** fibrinolytic intraventricular, intraventricular hemorrhage (IVH), modified graeb score, unfavorable outcome.

**Cite This Article:** Fitra., Meizikri, R., Alfayat, R., Hidayat, I., Asrizal, C.W. 2023. Interaction of antifibrinolytic providing intrathecal in intraventricular blood: a systematic review and meta-analysis. *Journal of International Surgery and Clinical Medicine* 3(1): 16-21. DOI : 10.51559/jiscm.v3i1.40

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Received: 2022-10-26

Accepted: 2023-01-22

Published: 2023-02-28

## INTRODUCTION

Intraventricular hemorrhage (IVH) is an eruption of blood in the cerebroventricular system since the outbreak of the cerebral or spinal artery. Intraventricular hemorrhage occurs in 40% of patients with intracerebral hemorrhage (ICH). Intraventricular bleeding can lead to serious complications such as hydrocephalus.<sup>1</sup> Apart from causing blockage of CSF flow, IVH causes independent cell damage and BBB damage.<sup>2</sup> Currently, the prevailing theory regarding the pathophysiology of hydrocephalus due to IVH is the obstruction of CSF flow due to blood clots. Blood clot clots often occur in the CSF tract or the mouth of the fourth ventricle, whereas tetra-ventricular hydrocephalus usually results from blockages at the level of the subarachnoid cortical space

and, in some cases, at the outlet of the fourth ventricle.<sup>3</sup> After IVH, obstructive hydrocephalus can occur immediately. In this case, several small blood clots form throughout the ventricular system, and block the passage through the arachnoid villi into venous sinuses and small blood vessels leading to and from ependymal cells.<sup>4</sup>

Because of its effect on the incidence of hydrocephalus, one of the modalities of IVH therapy is to perform CSS diversion using an external ventricular drain (EVD).<sup>5</sup> To overcome complications associated with the use of EVD due to IVH and IVH alone, there are several attempts to accelerate the excretion of ventricular blood. The intraventricular fibrinolytic injection has shown mixed results.<sup>6</sup> American Heart Association / American Stroke Association guidelines conclude

that the efficacy and safety of fibrinolytic in IVH are uncertain.<sup>7</sup> Recently, the CLEAR-III study by Hanley *et al.* (2007) evaluated the effect of IVF for IVH resulting from small ICH and observed a reduced risk of death, which is supported by previous meta-analyses, although there were no good functional outcomes (modified Rankin Score [mRS] less than equal to 3.<sup>8</sup> The mixed results of studies on intraventricular fibrinolysis prompted investigators to conduct a review and meta-analysis of this treatment modality.

## MATERIAL AND METHODS

### Type of studies

This study is an epidemiological study of the bad outcome in IVH cases treated with intraventricular fibrinolysis. This research is a systematic review with a statistical meta-analysis method.

### Type of participants

The study population was all published scientific articles from the literature search regarding intraventricular fibrinolysis in IVH according to predetermined eligibility criteria.

### Type of outcome measures

The overall therapeutic outcome is defined as favorable or unfavorable based on the GOS, mRS, or mortality status of the subject.

### Search Methods and Identifications of Studies

The search is performed using the boolean operator AND to search for literature containing all keywords and OR to search for literature containing alternative keywords including ("Intraventricular hemorrhage" OR "IVH") AND ("Intraventricular fibrinolysis" OR "Intraventricular rtPA" OR "Intraventricular alteplase" OR "Intraventricular urokinase").

### Data Collection and Analysis

The statistical meta-analysis used the SPSS 24 and Revman programs version 5.4 of the Cochrane Review.

### Assessment of study quality and risk of bias in included studies

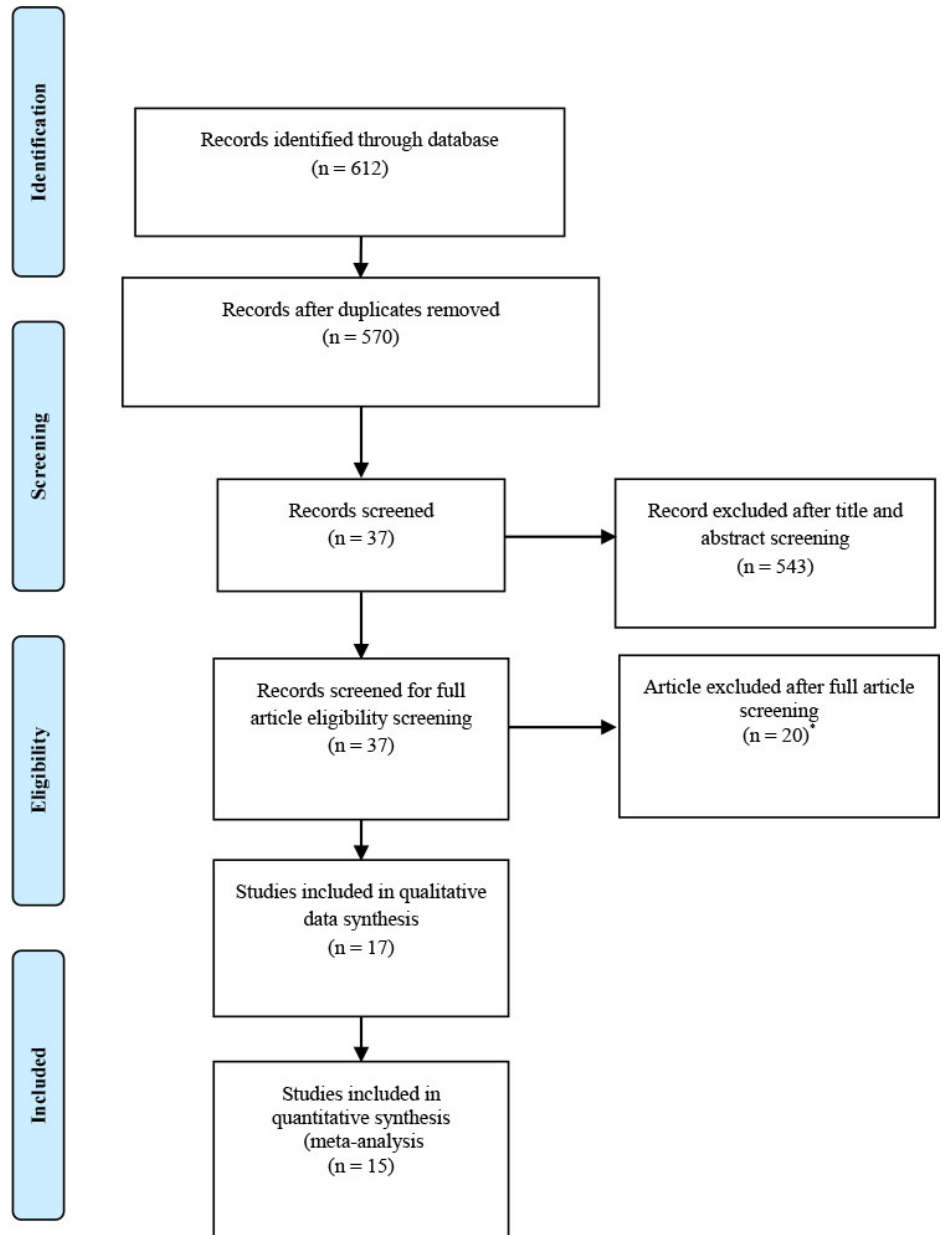
Two investigators will analyze the risk of bias in the study using the Cochrane Collaboration's risk of bias tools for RCT studies and the non-RCT studies using the ROBINS-I.<sup>9,10</sup>

## RESULT

### Literature Search

A total of 570 studies were identified and screened. Of these, 37 studies were assessed for eligibility and 17 studies were included in the meta-analysis. This result is explained well in Figure 1.

There were six RCT studies, one unrandomized clinical trial, eight prospective cohort studies, and two retrospective studies. The total number of patients from all studies included in this systematic review was 941 patients. There are two types of fibrinolytic agents used, rtPA (11 studies) and urokinase (6 studies). Not all studies confirm whether any patient has a double EVD.



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines flowchart.

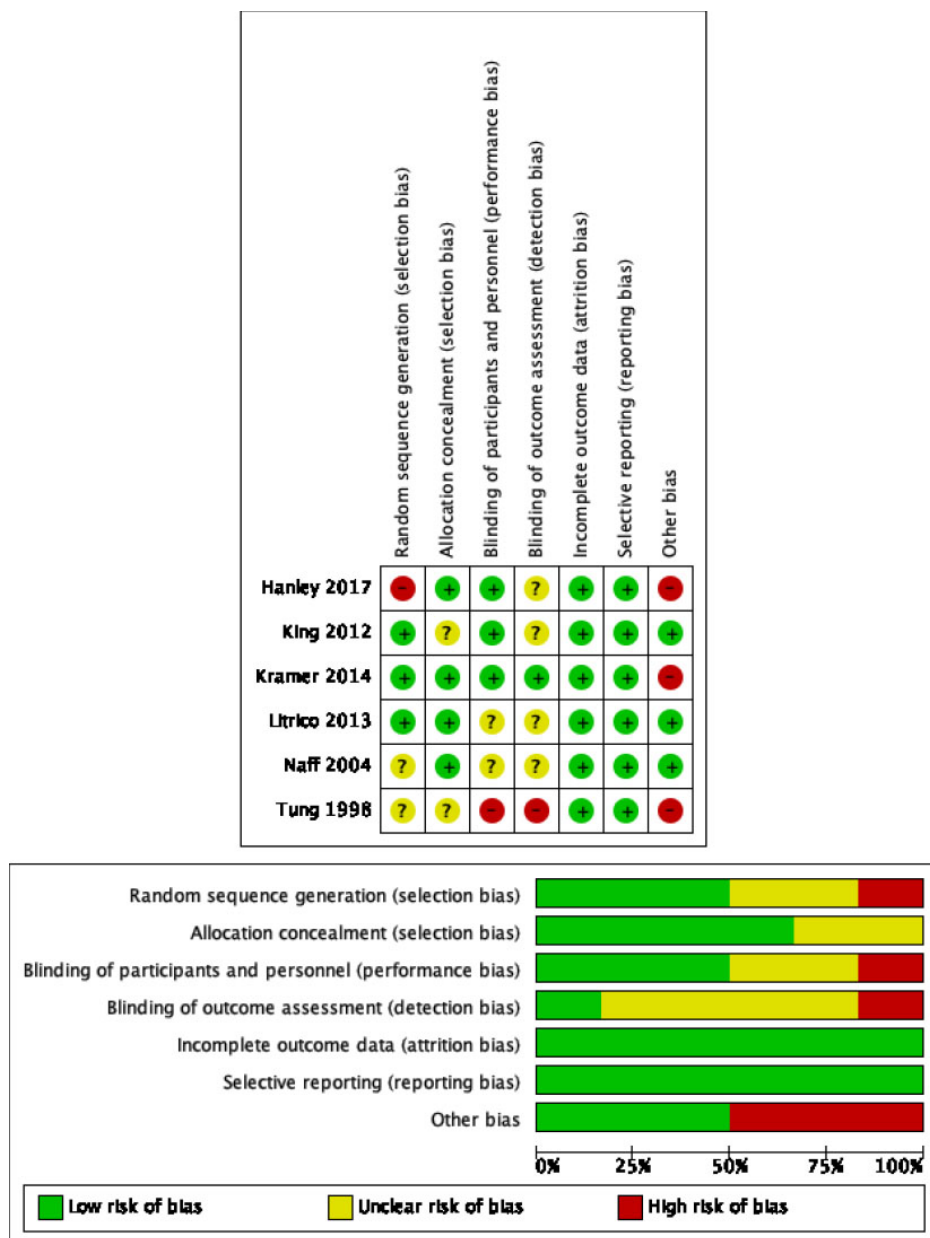
Three studies did not report outcomes in GOS, GOS-E, or mRS so they were not included in the meta-analysis or pooled analysis for unfavorable outcomes.<sup>3,11,12</sup> There were variations between studies in the timing of the outcome assessment. Some studies did not provide information on when the GOS and/or GOS-E and/or mRS were assessed, while several other studies conducted studies at one, three, and six months. Two studies conducted an assessment of the end of hospital admission.<sup>13,14</sup>

### Risk of Bias assessment

The result of the bias risk assessment of the studies involved was measured by ROBINS-I. The result showed in Figure 2 below.

### Comparison of Unfavorable Outcome Risk

A total of ten studies were eligible for inclusion in the meta-analysis regarding the risk of unfavorable outcomes. There is no uniformity of time points for assessments outcome. One study did not explain when the assessment was outcome



**Figure 2.** Result of ROBINS-I assessment. A, Risk assessment of bias using ROBINS-I for non-randomized studies in each study. B, the proportion of bias risk assessment results using ROBINS-I for the non-randomized study.

carried out,<sup>6</sup> three studies assessed the outcome at one month,<sup>8,15,16</sup> two studies at three months,<sup>17,18</sup> one study at six months, one study at 12 months,<sup>19</sup> and two studies on the end of hospitalization.<sup>13,20</sup> three studies did not report outcomes in GOS, GOS-E, or mRS so they were not included in the meta-analysis or pooled analysis for unfavorable outcomes.<sup>3,12,21</sup>

This meta-analysis of the risk of unfavorable outcomes included 392 patients receiving intraventricular fibrinolysis and 393 controls. The risk of

unfavorable outcomes for intraventricular fibrinolysis compared with controls is shown in Figure 1. Overall risk ratio (RR) the unfavorable outcome was 0.93 (95% CI, 0.86 - 1.01), indicating that the fibrinolysis group produced better outcomes, but not statistically significant ( $p = 0.1$ ). Subgroup analysis based on the fibrinolytic agent used also gave similar results, RR 0.95 (95% CI, 0.87 - 1.03) in the rtPA group and RR 0.73 (95% CI, 0.49 - 1.09) in the urokinase group and both are not statistically significant ( $p = 0.22$  and

0.13 both, respectively). The value of  $I^2$  in whole or subgroup meta-analysis showed that between studies are homogenous

Several non-clinical trials also provided data on unfavorable outcomes, consisting of three prospective studies and one retrospective study.<sup>22-25</sup> In the analysis, it was pooled incidence found that unfavorable outcomes in patients receiving intraventricular fibrinolysis occurred in 51% (95% CI, 38% - 64%) cases (figure 4).

### Mean IVH Volume Reduction

Two studies met the criteria for inclusion in the meta-analysis of volume reduction IVH. Research by Hanley *et al.* used rtPA at a dose of 1 mg per 8 hours compared with a placebo. This study reported post-treatment volumes 24 hours after the last dose of rtPA was administered. It was found that the mean volume in patients receiving rtPA was close to 50% of the mean volume in the control group.<sup>8</sup>

Kramer conducted a study with six subjects in each group. In that study, rtPA was used at a dose of 2 mg per 12 hours. It was found that the volume of IVH in the treatment group on the third day after treatment was  $3.0 \pm 4.8$  ml, while in the control group, it was  $4.56 \pm 6.9$  ml.<sup>26</sup>

In the meta-analysis, it was found that there were differences. The mean IVH volume reduction was 4.5 cc (95% CI, 4.27 - 4.74). It is difficult to conclude this meta-analysis because the study by Kramer shows that the mean difference is negative and is assessed as having 0% weight by statistical applications (figure 5).

A pooled analysis was performed to determine the mean IVH volume reduction using intraventricular fibrinolysis. In the pooled analysis, data from the study by Du *et al.* both the groups were single and double EVD included.<sup>21</sup> It was found that the mean IVH volume reduction with intraventricular fibrinolysis was 22.84 ml (95% CI, 21.04 - 24.64). However, these results were heterogeneous ( $I^2 = 98\%$ ) (Figure 6).

### Mean Modified Graeb Score

Three studies meet the criteria to be included in the meta-analysis of the reduction mean modified Graeb Score. Research by Huttner was conducted on

22 patients with a modified Graeb Score of  $8.36 \pm 5.54$  in the treatment group and  $8 \pm 4.75$  in the control group. From the evaluation, it was found that the treatment group had a modified Graeb Score up to  $3.3 \pm 2.7$  while the control group was  $6.3 \pm 3.9$ .<sup>19</sup>

The initial modified Graeb Score in the study by Kramer was  $18.2 \pm 5.2$  in the treatment group and  $17.7 \pm 7.4$  in the control group. In the evaluation, it was

found that the modified Graeb Score was  $7.97 \pm 2.8$  in the treatment and  $6.3 \pm 5.43$  in the controls.<sup>1</sup> Meanwhile, in the study by Varelas, it was found that the modified Graeb Score was  $3.7 \pm 1.2$  and  $4.8 \pm 2.95$  in the treatment and control groups, respectively. In that study, the initial modified Graeb Score was  $8.5 \pm 2.2$  in the treatment group and  $5.3 \pm 2.86$  in the control group.<sup>6</sup>

In the meta-analysis it was found that

the mean reduction modified Graeb Score in patients who received intraventricular fibrinolysis was 3.73 points (95% CI, 3.14 - 4.32) greater than the control. This meta-analysis is homogenous ( $I^2 = 14\%$ ).

Pooled analysis was carried out by including clinical trials to find out how much the reduction was modified Graeb Score given by administering intraventricular fibrinolysis. From six studies, it was found that the reduction modified Graeb Score reached 5.24 points (95% CI, 4.76 - 5.72) with intraventricular fibrinolysis. This study is relatively homogeneous with a value of  $I^2$  of 46%.

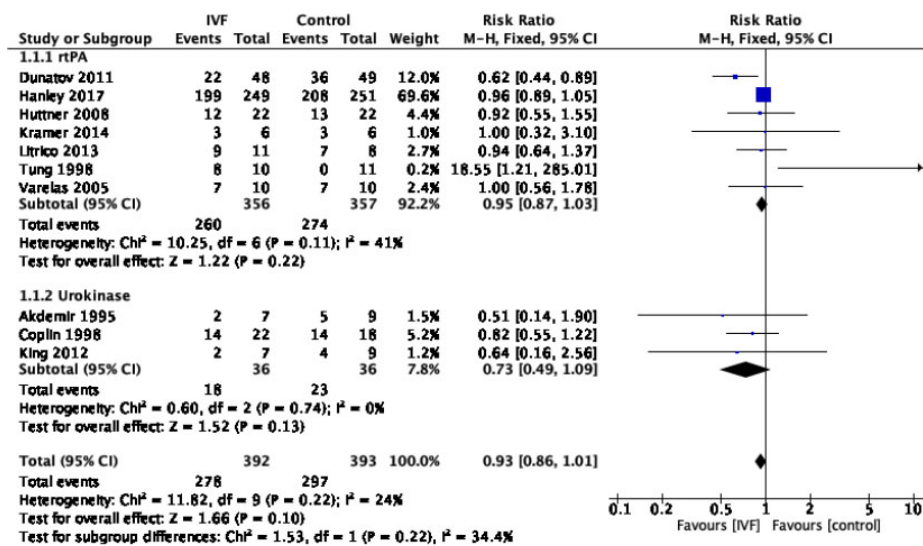
## DISCUSSION

This study involved 17 studies with a total of 941 patients, of which 11 studies used rtPA and 6 studies used urokinase as the fibrinolytic agent. In general, the quality of the research used in this study was quite good, as seen from the risk of bias, which was mostly low.

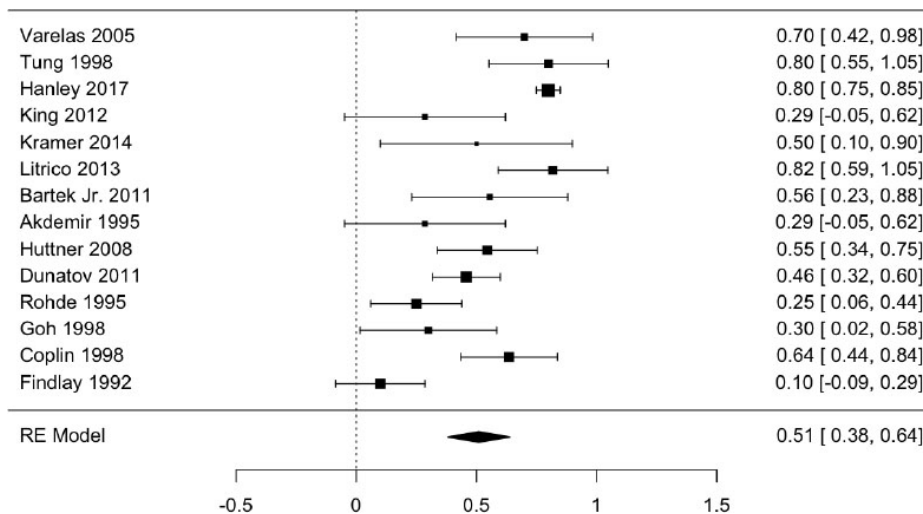
### Risk of Unfavourable Outcome

The risk of unfavorable outcomes in this study was assessed by assessing the risk ratio assessed by a forest plot comparing the control and treatment groups. In general, almost all studies show a lower risk of incidence unfavorable outcomes, except for the studies of Tung et al in 1998 and Varelas et al in 2005.<sup>6,15</sup>

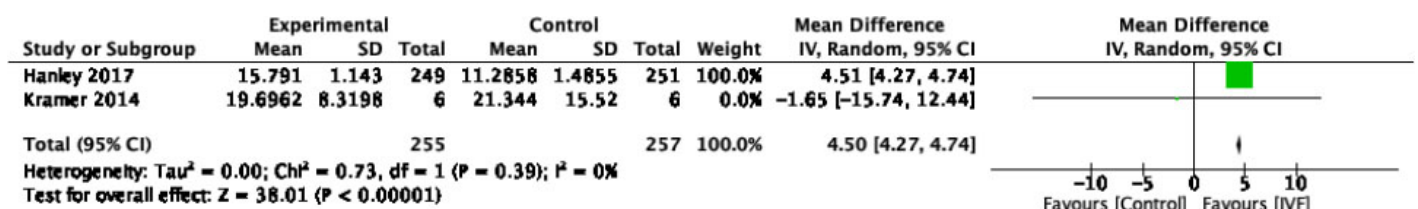
This is reflected in the results of the risk ratio analysis which showed a lower risk of unfavorable outcomes in the treatment group with RR 0.93 (95% CI 0.86-1.01), but this result was not statistically significant ( $p = 0.10$ ). Similar results were found in the risk ratio analysis with the subgroup analysis for the rtPA and urokinase subgroups, both of which showed a lower risk of unfavorable outcomes in the treatment group but were also not statistically significant. The results of this pooled incidence rate analysis also show that the incidence of unfavorable



**Figure 3.** Unfavorable Risk in intraventricular fibrinolysis as a controlled study.

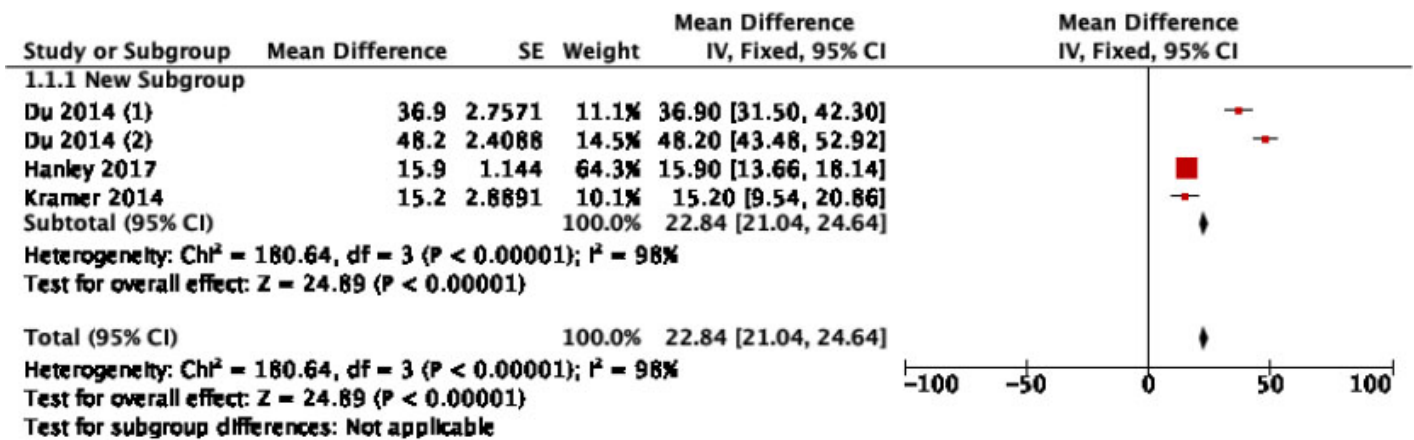


**Figure 4.** Favorable outcome pooled incidence in IVH patients with intraventricular fibrinolysis.

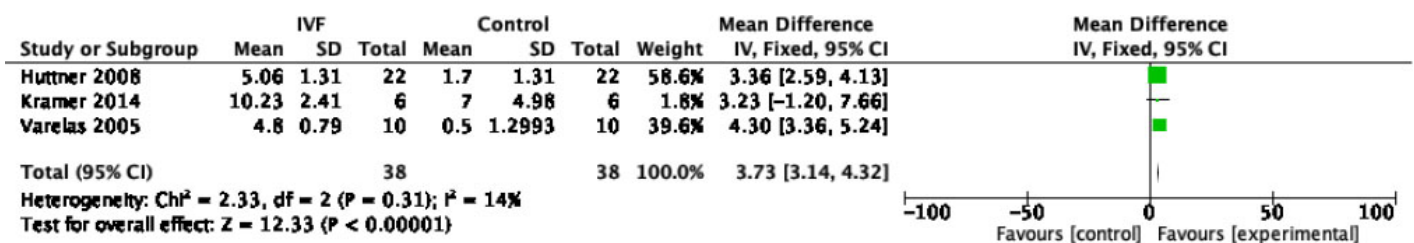


**Figure 5.** The difference between IVH volume reduction in the fibrinolysis group compared to the control group.

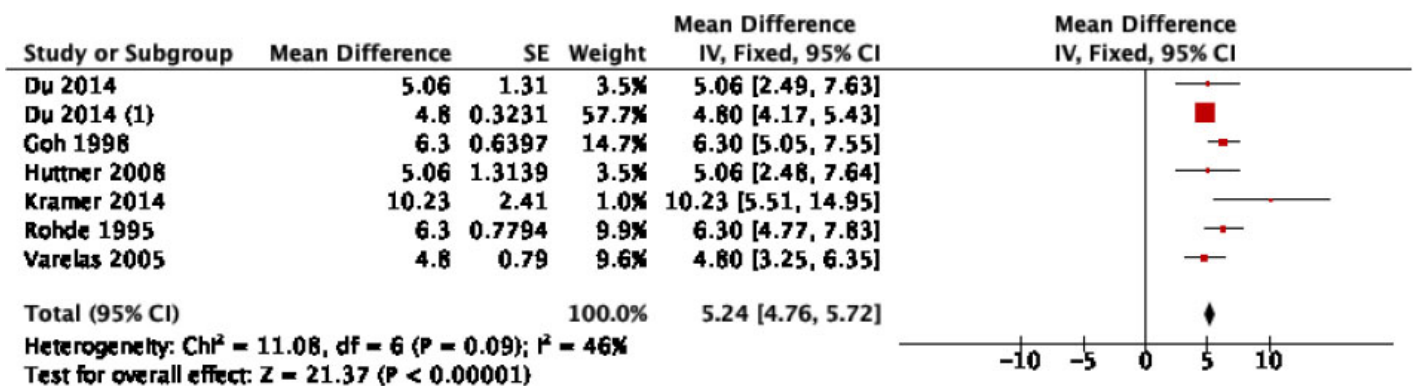




**Figure 6.** Mean of IVH volume reduction in intraventricular fibrinolysis.



**Figure 7.** The difference between mean modified Graeb Score volume reduction in the fibrinolysis group compared to the control group.



**Figure 8.** Pooled risk estimates for IVF outcome to Modified Graeb Score reduction.

outcomes in the included literature is around 51%.

This is following the results of the largest clinical trial using IVF in IVH management, CLEAR-III. The results of CLEAR-III, involving 500 patients, showed that there was no significant difference in outcome in the two groups. However, a significant reduction in the risk of death was found in the treatment group, which could support the intraventricular fibrinolytic administration in IVH cases.<sup>8</sup>

#### Mean IVH Volume Reduction

In this study, there were only 2 studies that could be used to analyze the mean

volume reduction of IVH, Hanley et al and Kramer et al. Unfortunately, the mean difference in Kramer is negative and the weight of the study is 0% so no conclusion can be drawn from the forest plot analysis carried out, even though the overall results show a difference in the mean reduction of 4.5 cc (4.27 - 4.74) and it is significant statistics. The results of the pooled analysis for the mean reduction in IVH values on intraventricular fibrinolysis were also performed and the mean IVH volume reduction was 22.84 ml, several reduction that is quite large, although it cannot be compared with the control group.<sup>8,26</sup>

#### Mean Modified Graeb Score Reduction

The difficulty in analyzing the IVH volume reduction was replaced by the result of the analysis of mean modified Graeb Score reduction. The Modified Graeb Score itself, is a semiquantitative scale for IVH volume measurement, with reliable measure and prognostic validity suitable for rapid use in clinical practice and in research which has been used extensively to assess IVH volume.<sup>27</sup> In this study, 3 pieces of literature can be analyzed by the modified Graeb Score reduction means. The results of the analysis showed that the mean modified Graeb Score reduction was up to 3.73 times in the IVF group compared

to the control group (95% CI 3.14-4.32) and this result was statistically significant ( $p < 0.001$ ). This suggests that fibrinolytic activity is effective in accelerating and increasing ventricular clearance, which supports the recent findings.<sup>6,19,26</sup>

The results of the above analysis are supported by the results of the pooled analysis to assess the modified Graeb Score reduction in intraventricular fibrinolysis administration. The results of the analysis in these 6 studies showed that the modified Graeb Score reduction reached 5.24 points (95% CI 4.76 - 5.72), which is quite high. The results of research by Morgan et al in 2013 showed that each unit increase in the mGS led to a 12% increase in the odds of a poor outcome so a decrease in the modified Graeb Score of 5.24 points can reduce the odds of a poor outcome approximately to 62.88. %.<sup>27</sup>

## CONCLUSION

Intraventricular fibrinolysis administration helps to reduce the risk of unfavorable outcomes in IVH cases. It also accelerates and increases ventricular clearance in IVH cases with a 3.73 times reduction of modified Graeb Score compared to the control group.

## CONFLICT OF INTEREST

None.

## FUNDING

None.

## AUTHOR CONTRIBUTION

All authors contributed equally to this study.

## ETHICAL STATEMENT

N/A.

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