Local Fibrinolytic Therapy for Intraventricular Hemorrhage

A Meta-Analysis of Randomized controlled trials

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Introduction

- Previous preclinical and clinical studies suggested that intraventricular fibrinolysis (IVF) with rt-PA or urokinase through an EVD into the ventricles accelerates the clearance of IVH and is largely safe and that urokinase might be better than rt-PA.
- However, CLEAR-III, the largest RCT, showed that while IVF reduces mortality, it does not improve functional outcomes in most patients.
- Therefore, we undertook a meta-analysis to re-examine the role of IVF in the treatment for IVH, and to perform subgroup analysis based on the fibrinolytic agents used to examine any potential differences in efficacy and safety of rt-PA vs. urokinase in IVH.

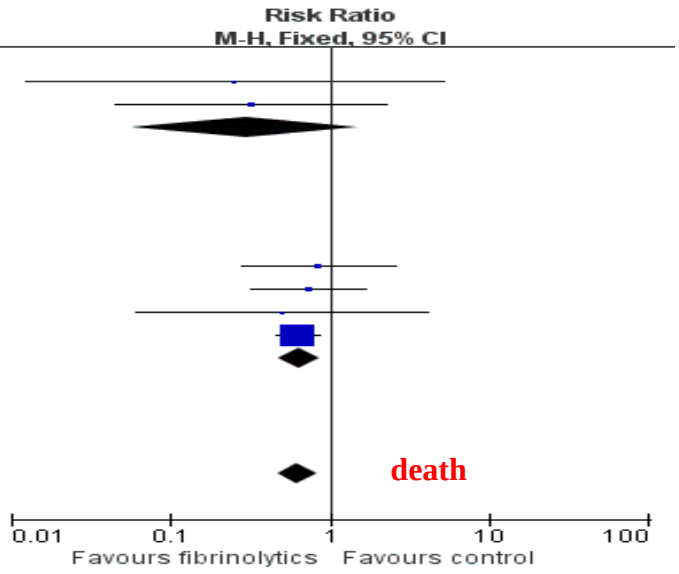
Materials and Methods

- **Data sources**: Ovid Medline and Embase from inception to January 20, 2017.
- **Eligibility criteria for selecting studies**: RCTs in participants with non-traumatic IVH comparing the administration of rt-PA or urokinase through an EVD with normal saline through EVD or EVD placement alone.

Results

- Six RCTs involving a total of 607 IVH patients were included; 2 trials investigated urokinase and 4 rt-PA.
- The overall risk of bias was not less than moderate across studies.
- The administration of fibrinolytic agents reduced death from any cause at the end of follow-up (RR 0.63, 95% CI 0.47 to 0.83; participants = 598; studies = 6; I2 = 0%)
- Subgroup analysis showed that urokinase did not result in reduction of death (RR 0.30, 95% CI 0.06 to 1.53; participants = 28; studies = 2; I2 = 0%). Use of rt-PA, on the other hand, resulted in significant reduction of death (RR 0.65, 95% CI 0.48 to 0.86; participants = 570; studies = 4; I2 = 0%).

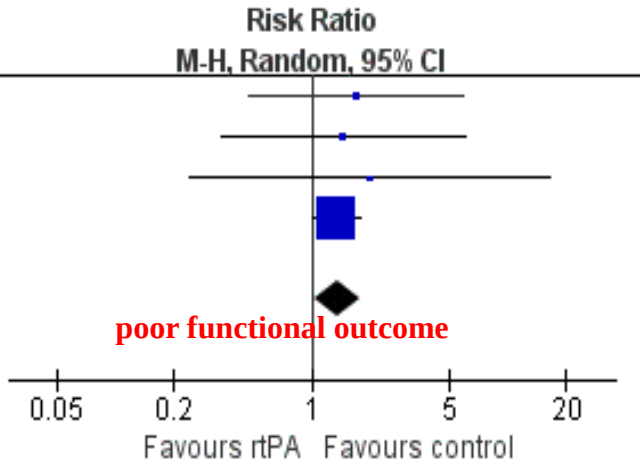
Study or Subgroup	Fibrinolytics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.1 urokinase							
Naff 2004	0	7	1	5	1.9%	0.25 [0.01, 5.13]	2004
King 2012	1	7	4	9	3.8%	0.32 [0.05, 2.27]	2012
Subtotal (95% CI)		**14**		**14**	**5.7%**	**0.30 [0.06, 1.53]**	
Total events	1		5				
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%							
Test for overall effect: Z = 1.45 (P = 0.15)							
1.1.2 rtPA							
Naff 2011	5	26	5	22	5.9%	0.85 [0.28, 2.55]	2011
Litrico 2013	5	11	5	8	6.3%	0.73 [0.31, 1.69]	2013
Kramer 2014	1	6	2	6	2.2%	0.50 [0.06, 4.15]	2014
CLEAR III 2017	46	246	73	245	79.9%	0.63 [0.45, 0.87]	2017
Subtotal (95% CI)		**289**		**281**	**94.3%**	**0.65 [0.48, 0.86]**	
Total events	57		85				
Heterogeneity: Chi² = 0.39, df = 3 (P = 0.94); I² = 0%							
Test for overall effect: Z = 2.95 (P = 0.003)							
Total (95% CI)		**303**		**295**	**100.0%**	**0.63 [0.47, 0.83]**	
Total events	58		90				
Heterogeneity: Chi² = 1.26, df = 5 (P = 0.94); I² = 0%							
Test for overall effect: Z = 3.21 (P = 0.001)							
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%							



- The use of rt-PA did not reduce the proportion of survivors with poor functional outcome (RR 1.36, 95% CI 1.04 to 1.77; participants = 570; studies = 4; I^2 = 0%), or the composite endpoint of death and poor functional outcome (RR 0.96, 95% CI 0.83 to 1.11; participants = 570; studies = 4; I^2 = 0%).

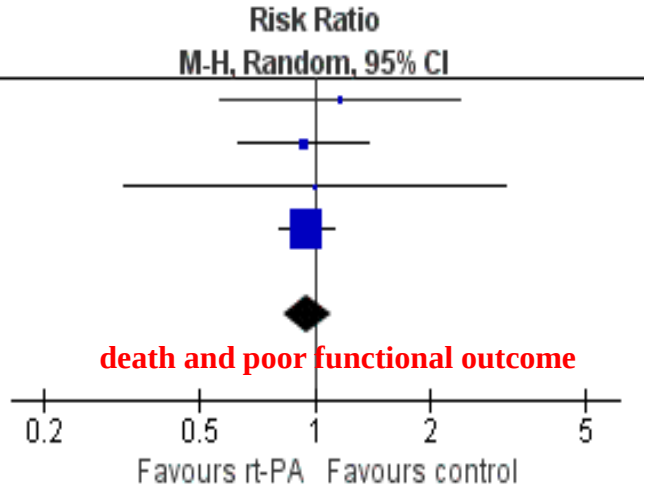
Study or Subgroup	rtPA Events	rtPA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naff 2011	6	26	3	22	4.4%	1.69 [0.48, 5.99]	2011
Litrico 2013	4	11	2	8	3.4%	1.45 [0.35, 6.09]	2013
Kramer 2014	2	6	1	6	1.6%	2.00 [0.24, 16.61]	2014
CLEAR III 2017	83	246	62	245	90.7%	1.33 [1.01, 1.76]	2017
Total (95% CI)		**289**		**281**	**100.0%**	**1.36 [1.04, 1.77]**	
Total events	95		68				

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)

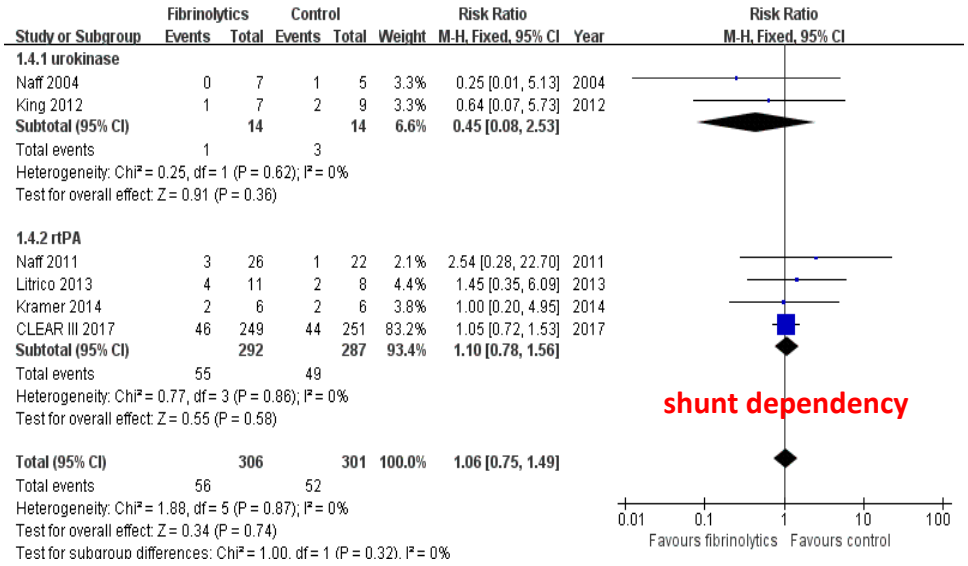


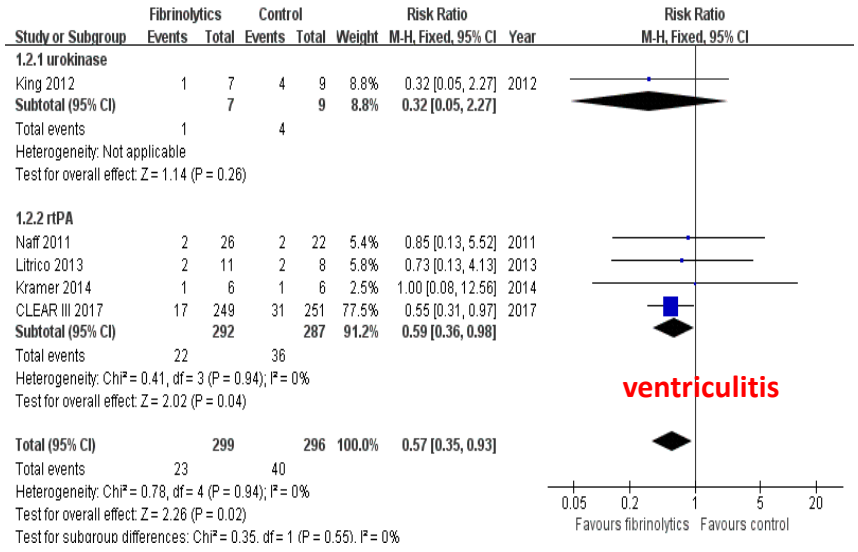
Study or Subgroup	rt-PA Events	rt-PA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naff 2011	11	26	8	22	4.2%	1.16 [0.57, 2.37]	2011
Litrico 2013	9	11	7	8	14.6%	0.94 [0.64, 1.37]	2013
Kramer 2014	3	6	3	6	1.7%	1.00 [0.32, 3.10]	2014
CLEAR III 2017	129	246	135	245	79.5%	0.95 [0.81, 1.12]	2017
Total (95% CI)		**289**		**281**	**100.0%**	**0.96 [0.83, 1.11]**	
Total events	152		153				

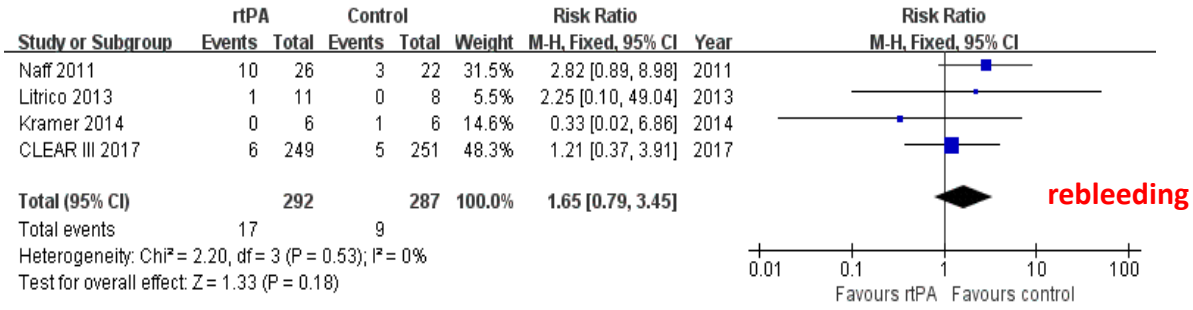
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 3 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)



- The use of IVF did not reduce the need for shunt placement (RR 1.06, 95% CI 0.75 to 1.49; participants = 607; studies = 6; I2 = 0%);
- There was no increase in adverse events with fibrinolytics compared to control, including ventriculitis (RR 0.57, 95% CI 0.35 to 0.93; participants = 595; studies = 5; I2 = 0%), and rebleeding (RR 1.65, 95% CI 0.79 to 3.45; participants = 579; studies = 4; I2 = 0%).







Conclusions

- Although the use of IVF in patients with IVH is largely safe, currently used dosage regimen in most patients with IVH is unlikely to benefit their functional recovery or shunt dependency.

- Its benefit is limited to a reduction in mortality at the expense of increased number of survivors with moderately severe to severe disability.

- Subgroup analysis does not suggest that IVF with urokinase is better than rt-PA.

- The decision to use IVF in IVH patients should take into consideration the patient's/family's attributes towards survival & dependency.

- Our analysis is limited by the small number of urokinase trials, and the overwhelming number of subjects included from one trial (CLEAR-III).