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Systemic Review: Role of Tissue Plasminogen Activator for Acute Ischemic Stroke

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ABSTRACT

Background: Using recombinant tissue plasminogen activator (rt-PA) during the first 3 h up to 6 h of stroke was allowed to reduce the poor functional consequences of stroke.

Objectives: assess the effects of intravenous dosage of rt-PA during the first 6 h after on early and late outcomes of acute ischemic stroke (AIS).

Methods: all studies regarding the intravenous rt-PA given within 6 h of onset of acute ischemic stroke up to 2016 were searched the outcomes, and the mortality rates were evaluated at the final follow up.

Results: There was a significant increase in functional outcome by using IV-tPA significantly ($p < 0.01$). A significant decrease was found in intracranial hemorrhage in the patients treated with IV-tPA. The mortality rates were significantly decreased at the end of the follow up period in patients treated with IV-tPA.

Conclusion: The study indicated that using intravenous rt-PA could increase the number of living patients favorable outcome, less disabilities and intracranial hemorrhage among acute ischemic stroke patients during the first 6 hours.

Keywords: Systemic review, tissue plasminogen activator, acute ischaemic stroke, mortality.

INTRODUCTION

Acute ischemic stroke (AIS) is a worldwide cause of disability and death accounting about 87% of the stroke cases. The occlusion of the arteries causes blood deprivation and cell death associated with neural dysfunction[1, 2].

The most effective treatment for AIS is intravenous thrombolysis which could reverse the arterial occlusion and decrease the number of damaged cells as well as improving the recovery and decreasing the rates of death. Another advantage of using intravenous thrombolysis during the early period of stroke would result in significant improving in the neurological functions[3, 4].

Using recombinant tissue plasminogen activator (rt-PA) during the first 3 h up to 6 h of stroke was allowed in patients younger than 80 years[5, 6]. Also, other studies showed that after 6 h the treatment with rt-PA could result in reducing the poor functional consequences of stroke [7, 8].

There is increasing evidence regarding treating the AIS with rt-PA after 6 hours, however, other factors would affect the outcomes including previous chronic diseases including hypertension, heart diseases and diabetes, stroke severity, subtypes and previous usage of antiplatelet drugs[9, 10]. This is a systemic review conducted to assess the effects of intravenous dosage of rt-PA during the first 6 h after on early and late outcomes of AIS.

METHODS

Information sources and search strategy

The electronic database search included 1995 to 2016, Data extraction and quality assessment. Using predetermined forms, data were extracted independently by two authors. Data were collected on study design and conduct, country of study, sample size, and outcome.

From each study, outcome data were extracted in 2x2 tables or using the mean and SD. Study quality assessment was performed using QUADAS-2 (Quality Assessment for Diagnostic Accuracy Studies-2: A Revised Tool) for evaluating the diagnostic accuracy of studies [11]. The tool consists of four key domains covering patient selection, index test(s), reference standard, the flow and timing. Each domain was assessed in terms of risk of bias, and the first three domains were also assessed for concerns regarding applicability. Signaling questions were included in the tool to help judge the risk of bias. The index test(s) for the included studies were the biomarkers and the reference standard.

Inclusion Criteria

The inclusion criteria for the systematic review were all prospective studies with use of Tissue Plasminogen Activator for Acute Ischemic Stroke. Exclusion criteria were retrospective studies, case reports, case series, letters, and reviews; studies that did not include tissue plasminogen activator as a treatment. Studies in

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languages other than English were also excluded where no translated version of the manuscript was available. The studies included in the research met the following criteria including: (1) English studies during the last 20 years, (2) patients with ischemic stroke older than 18 years old, (3) patients who were treated with rt-PA during the first 6 h after stroke, (4) evaluating the outcomes after administration.

Outcomes

The outcomes and efficiency of intravenous rt-PA were assessed from the included studies including the early outcome during the first week, degree of disability, safety outcomes and mortality rates.

Statistical analysis

Statistical analysis was performed using the Cochrane systematic reviews(Review Manager 5.3) and the meta-analysis of the eligible studies performed using the diagnostic test accuracy review stream [12]. Data from each primary study were summarized in a 2x2 table of test results and forest plots constructed showing within-study estimates and confidence interval.

The study was done after approval of ethical board of Northern Border university.

RESULTS

The primary search strategy included 127 papers from which 61 papers met the criteria after removing the duplicates than 20 papers were excluded after reviewing the abstract. Only 41 full texts were eligible from which 20 were excluded for different types of studies then 21 studies were included into qualitative study while 6 were excluded for their specificity and finally 15 studies were included (Fig. 1). The main characteristics of the studies were shown at Table (1).

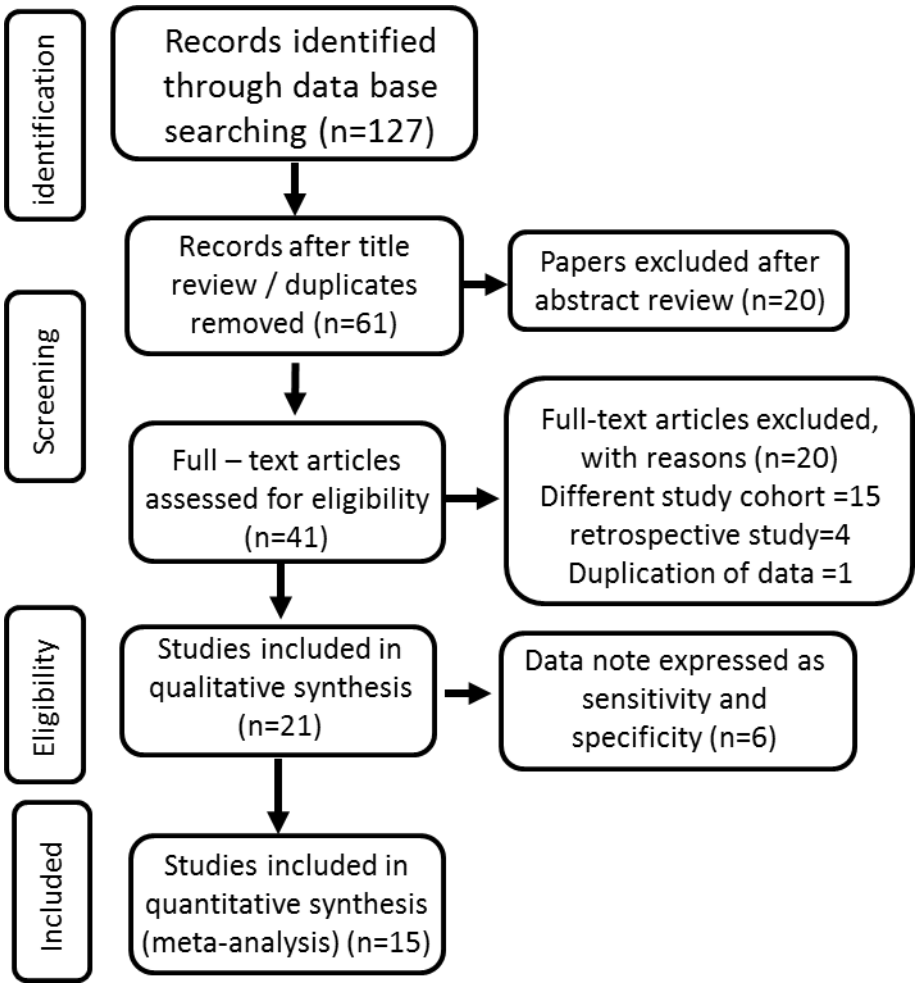

Fig. (1): Flow chart for identification and selection of studies in the systematic review and meta-analysis

Table (1): Main characteristics of studies included in the meta-analysis

No	Year	Title	Author	No. of cases	% weight
1	2015	Use of intravenous tissue plasminogen activator and hospital costs for patients with acute ischaemic stroke aged 18–64 years in the USA	**HeesooJoo,**[13]	39149	16.2
2	1998	Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke	**David Chiu**[14]	30	6.2
3	2006	Safety of Mechanical Thrombectomy and Intravenous Tissue Plasminogen Activator in Acute Ischemic Stroke. Results of the Multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Trial, Part I	**W.S. Smith**[15]	897	8.3
4	2012	Systematic Review of Outcome After Ischemic Stroke Due to Anterior Circulation Occlusion Treated With Intravenous, Intra-Arterial, or Combined Intravenous_Intra-Arterial Thrombolysis	**Michael T.**[16]	5019	4.75
5	2015	Low-Dose Versus Standard-Dose Tissue Plasminogen Activator in Acute Ischemic Stroke in Asian Populations	**Meng-Dong Liu**[17]	1211	8.2
6	2014	Bolus-Infusion Delays of Alteplase during Thrombolysis in Acute Ischaemic Stroke and Functional Outcome at 3 Months	**Paul Acheampong**[18]	276	12.6
7	2014	Intravenous Thrombolysis with Recombinant Tissue Plasminogen Activator for Ischemic Stroke Patients over 80 Years Old: The Fukuoka Stroke Registry	**Ryu Matsuo**[19]	13,521	14.4
8	2000	Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke A Canadian Hospital's Experience	**Kristine**[20]	46	2.1
9	1999	Effects of tissue plasminogen activator for acute ischemic Stroke at one year	**THOMAS G**[21]	624	2.6
10	2015	Thrombolysis for patients with acute ischaemic stroke	**Catangui EJ**[22]	60	3.2
11	2012	Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis	**Joanna M Wardlaw**[1]	7012	4.6
12	2011	Role of Tissue Plasminogen Activator in Acute Ischemic Stroke	**Molly A Hatcher**[23]	821	5.02
13	1995	Tissue plasminogen activator for acute ischemic stroke	**John R. Marler**[24]	333	4.21
14	2000	Use of tissue- Type plasminogen activator for acute ischemic stoke	**Lrene L. Katzan**[25]	3948	3.52
15	2012	The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial	**The IST-3 collaborative group**[26]	3035	4.1

Quantitative data summary and synthesis

RESULTS

Data were summarized for three outcomes, symptomatic intracranial hemorrhage, favorable functional outcome and mortality. Table (2), shows the relationship between IV-tPA and favorable functional outcome at first 10 hours, it was found that there was a significant increase in functional outcome by using IV-tPA significantly ($p < 0.01$) (Figure. 3). Table (3), shows the relationship between IV-tPA symptomatic intracranial hemorrhage, it was found that there was a significant decrease in intracranial hemorrhage in the patients treated with IV-tPA (Figure. 5). Table (4), shows the relationship between IV-tPA dose and mortality at end of follow up, it was found that there was a significant decrease in the mortality rate in patients treated with IV-tPA (Figure. 7).

Publication Bias

Visual inspection of the funnel plot did not identify substantial asymmetry (Fig. 2, 4 and 6). The funnel plot indicated evidence of publication bias among studies concerning favorable functional outcome.

Table (2): Relationship between IV-tPA and favorable functional outcome at first 10 hours

Study	Intervention	Controls	Risk Difference	95% CI	z	P	Weight (%)	
							Fixed	Random
HeesooJoo,	402/20100	952/19049	-0.0300	-0.0336 to -0.0263			54.87	19.27
David Chiu	0/16	1/14	-0.0514	-0.203 to 0.0999			0.032	0.18
W.S. Smith	13/449	27/449	-0.0302	-0.0572 to -0.00311			1.00	4.49
Michael T.	1/90	3/86	-0.0149	-0.0633 to 0.0335			0.31	1.65
Meng-Dong Liu	21/700	36/511	-0.0405	-0.0660 to -0.0149			1.12	4.91
Paul Acheampong	2/140	4/136	-0.00941	-0.0461 to 0.0273			0.54	2.72
Ryu Matsuo	140/7000	326/6521	-0.0300	-0.0362 to -0.0238			18.87	17.26
Kristine	0/20	1/20	-0.0200	-0.141 to 0.101			0.050	0.28
THOMAS G	6/150	4/141	0.0116	-0.0300 to 0.0533			0.42	2.17
Catangui EJ	0/30	2/30	-0.0367	-0.145 to 0.0715			0.063	0.35
Joanna M Wardlaw	70/3500	176/3512	-0.0301	-0.0387 to -0.0215			9.93	15.10
Molly A Hatcher	9/450	11/371	-0.00965	-0.0312 to 0.0119			1.57	6.28
John R. Marler	4/160	8/120	-0.0367	-0.0885 to 0.0152			0.27	1.45
Lrene L. Katzan	42/2100	55/1848	-0.00976	0.0196 to 0.0000300			7.62	13.98
The IST-3 collaborative group	32/1600	100/1435	-0.0497	-0.0645 to -0.0348			3.31	9.89
Total (fixed effects)	742/36505	1706/34243	-0.0294	-0.0321 to -0.0267	-21.164	<0.001	100.00	100.00
Total (random effects)	742/36505	1706/34243	-0.0268	-0.0333 to -0.0203	-8.092	<0.001	100.00	100.00

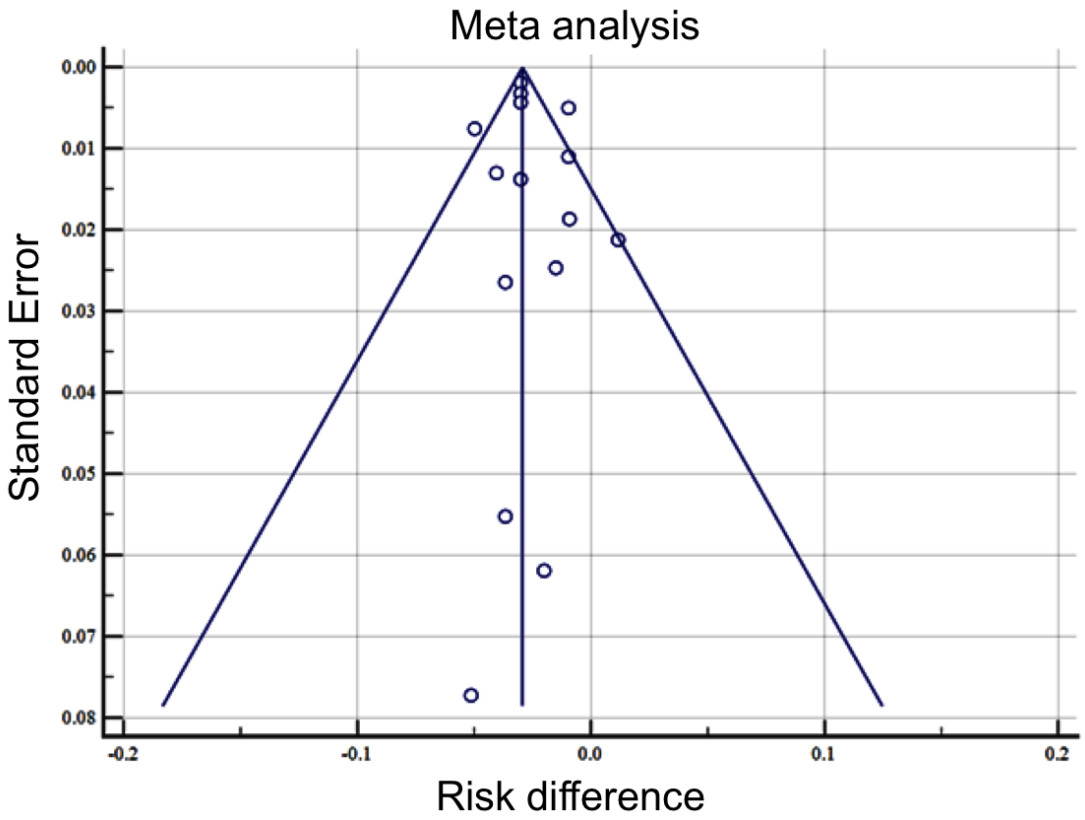

Fig. (2): Funnel plot assessing publication bias.

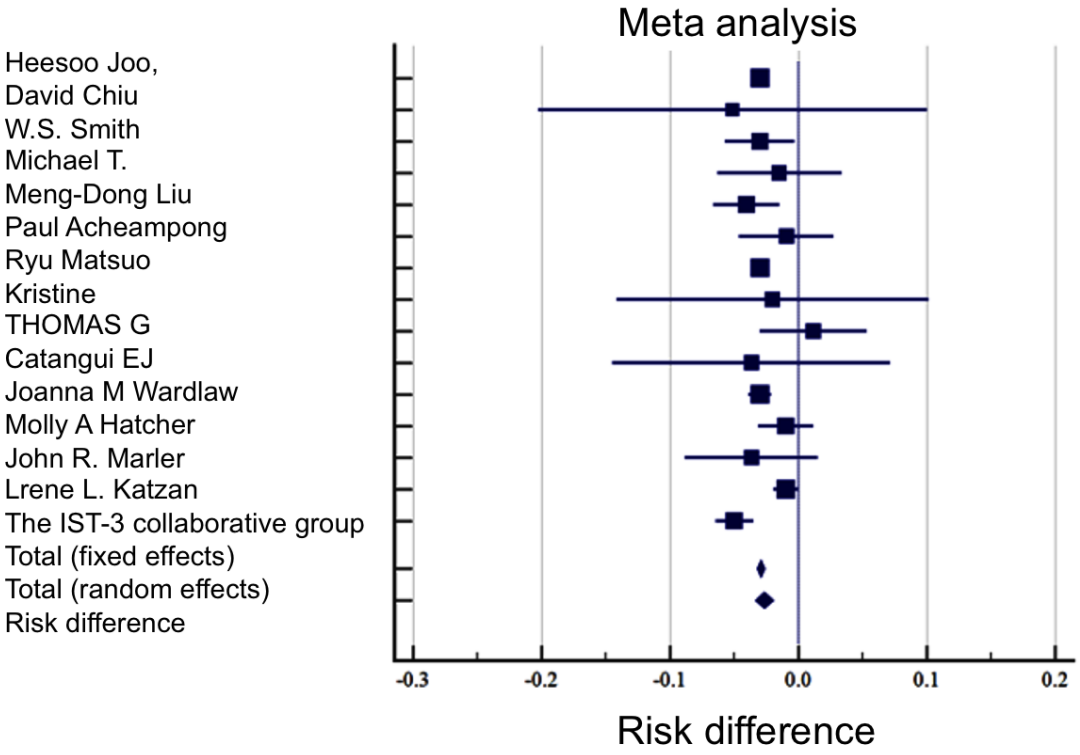

Fig. (3): Relationship between IV-tPA and favorable functional outcome at first 10 hours

Table (3): Relationship between IV-tPA symptomatic intracranial hemorrhage

Study	Intervention	Controls	Risk Difference	95% CI	z	P	Weight (%)	
							Fixed	Random
HeesooJoo,	603/20100	762/19049	-0.0100	-0.0136 to -0.00635			54.48	10.30
David Chiu	0/16	1/14	-0.0514	-0.203 to 0.0999			0.032	0.86
W.S. Smith	8/449	9/449	-0.0000668	-0.0184 to 0.0183			2.16	8.92
Michael T.	1/90	5/86	-0.0381	-0.0954 to 0.0192			0.22	4.00
Meng-Dong Liu	21/700	20/511	-0.00914	-0.0302 to 0.0119			1.64	8.54
Paul Acheampong	1/140	5/136	-0.0268	-0.0624 to 0.00890			0.57	6.42
Ryu Matsuo	70/7000	391/6521	-0.0500	-0.0562 to -0.0437			18.76	10.18
Kristine	0/20	1/20	-0.0400	-0.145 to 0.0650			0.066	1.64
THOMAS G	3/150	6/141	-0.0226	-0.0627 to 0.0176			0.45	5.82
Catangui EJ	0/30	1/30	-0.0233	-0.0968 to 0.0501			0.13	2.87
Joanna M Wardlaw	70/3500	176/3512	-0.0301	-0.0387 to -0.0215			9.85	10.01
Molly A Hatcher	13/450	30/371	-0.0509	-0.0828 to -0.0190			0.71	6.95
John R. Marler	3/160	10/120	-0.0633	-0.117 to -0.00933			0.25	4.30
Lrene L. Katzan	63/2100	37/1848	0.00998	0.000282 to 0.0197			7.71	9.92
The IST-3 collaborative group	32/1600	115/1435	-0.0601	-0.0758 to -0.0445			2.97	9.27
Total (fixed effects)	888/36505	1569/34243	-0.0214	-0.0242 to -0.0187	-15.456	<0.001	100.00	100.00
Total (random effects)	888/36505	1569/34243	-0.0271	-0.0417 to -0.0125	-3.628	<0.001	100.00	100.00

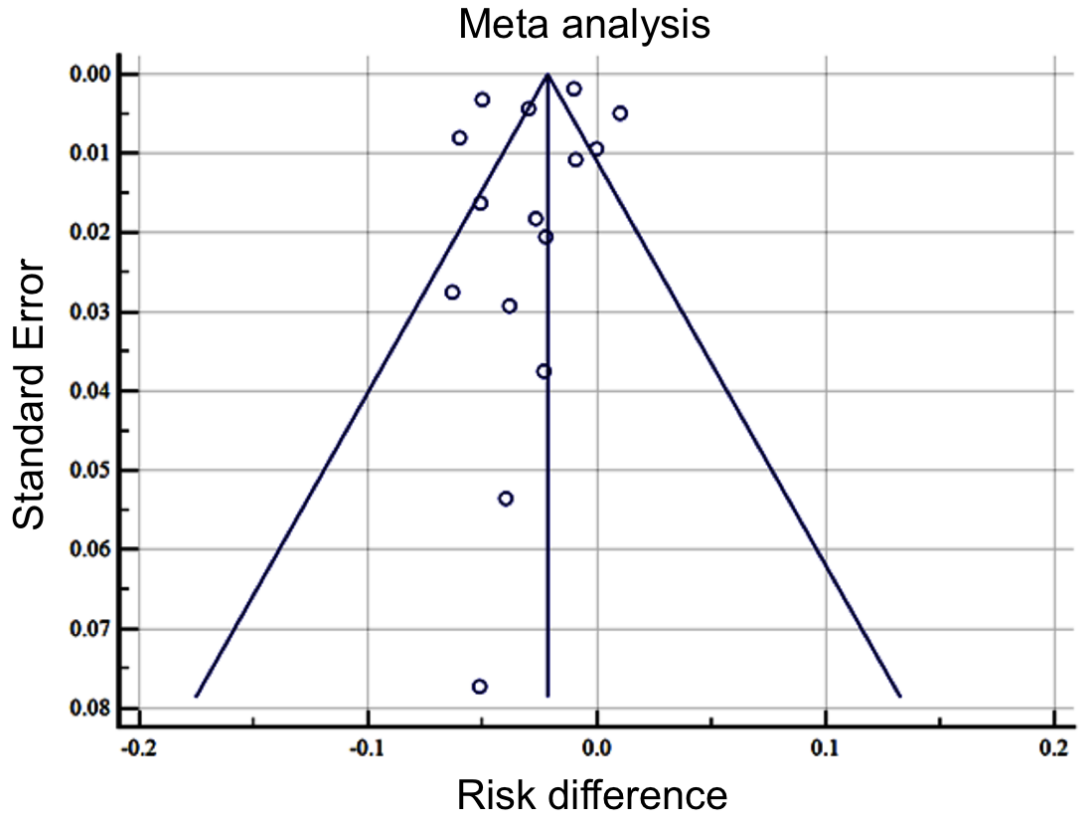

Fig. (4): Funnel plot assessing publication bias.

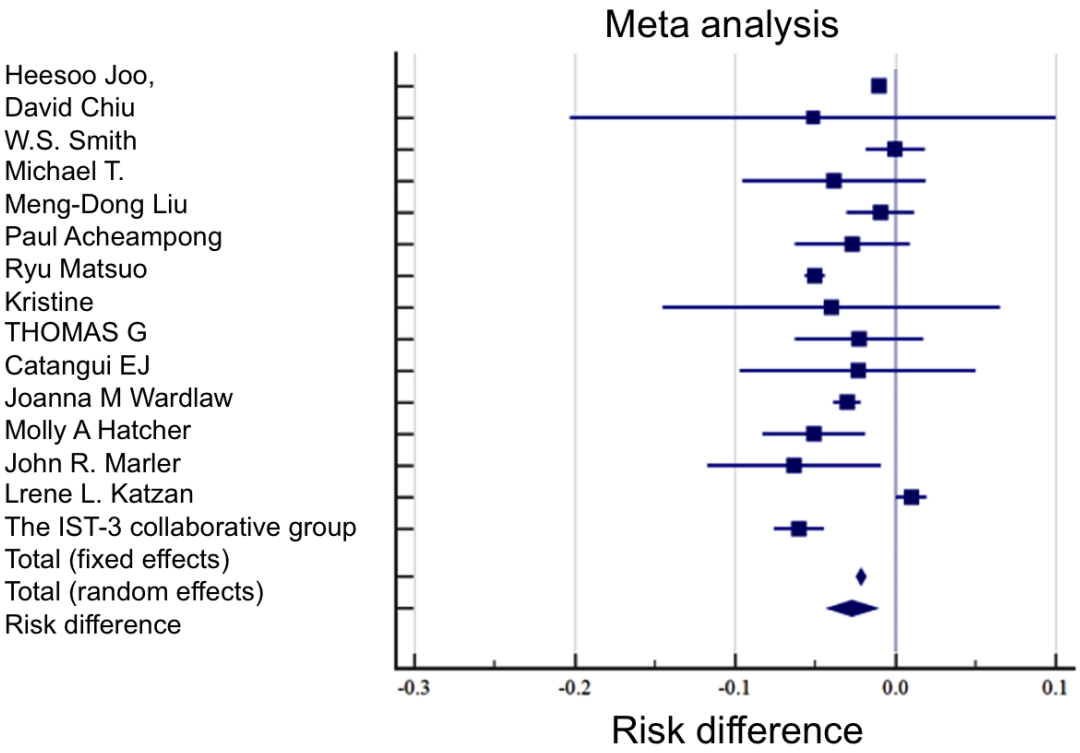

Fig. (5): Relationship between IV-tPA symptomatic intracranial hemorrhage

Table (4): Relationship between IV-tPA dose and mortality at end of follow up

Study	Intervention	Controls	Risk Difference	95% CI	z	P	Weight (%)	
							Fixed	Random
HeesooJoo,	1206/20100	952/19049	0.0100	0.00551 to 0.0145			56.22	9.83
David Chiu	1/16	1/14	-0.00143	-0.185 to 0.183			0.034	1.11
W.S. Smith	8/449	27/449	-0.0402	-0.0657 to -0.0146			1.76	8.57
Michael T.	7/90	6/86	0.0102	-0.0675 to 0.0880			0.19	4.10
Meng-Dong Liu	21/700	15/511	0.000646	-0.0187 to 0.0200			3.06	9.08
Paul Acheampong	2/140	8/136	-0.0388	-0.0847 to 0.00702			0.54	6.63
Ryu Matsuo	280/7000	587/6521	-0.0500	-0.0583 to -0.0417			16.51	9.72
Kristine	1/20	1/20	0.000	-0.135 to 0.135			0.063	1.88
THOMAS G	9/150	13/141	-0.0322	-0.0932 to 0.0288			0.31	5.28
Catangui EJ	2/30	1/30	0.0467	-0.0697 to 0.163			0.084	2.37
Joanna M Wardlaw	210/3500	105/3512	0.0301	0.0204 to 0.0398			12.22	9.66
Molly A Hatcher	36/450	19/371	0.0288	-0.00485 to 0.0624			1.01	7.81
John R. Marler	11/160	7/120	0.0117	-0.0460 to 0.0693			0.34	5.56
Lrene L. Katzan	84/2100	166/1848	-0.0498	-0.0653 to -0.0343			4.76	9.35
The IST-3 collaborative group	128/1600	129/1435	-0.00990	-0.0298 to 0.01000			2.89	9.04
Total (fixed effects)	2006/36505	2037/34243	-0.00456	-0.00799 to -0.00114	-2.610	0.009	100.00	100.00
Total (random effects)	2006/36505	2037/34243	-0.00977	-0.0303 to 0.0108	-0.931	0.352	100.00	100.00

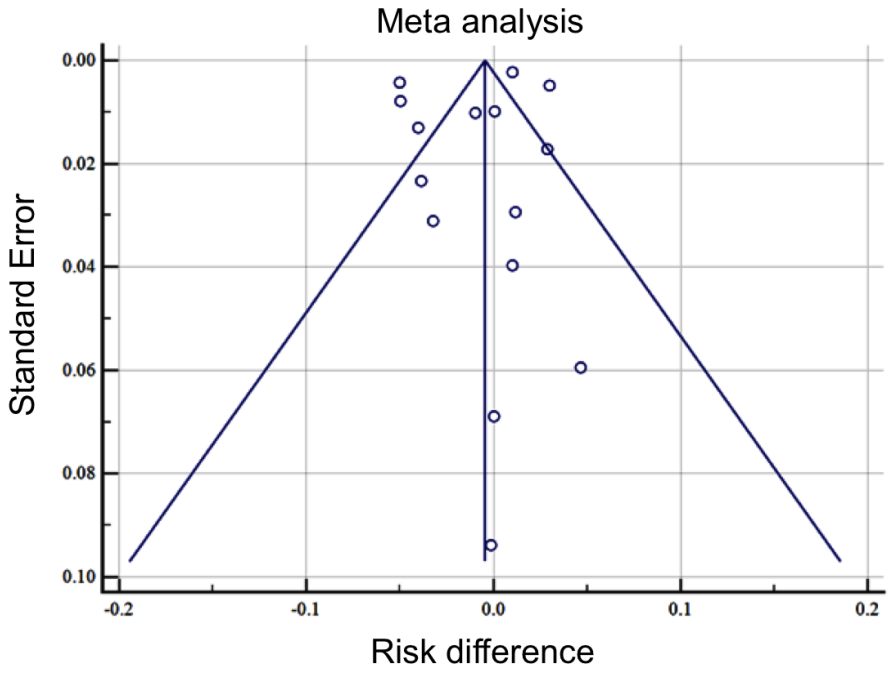

Fig. (6): Funnel plot assessing publication bias.

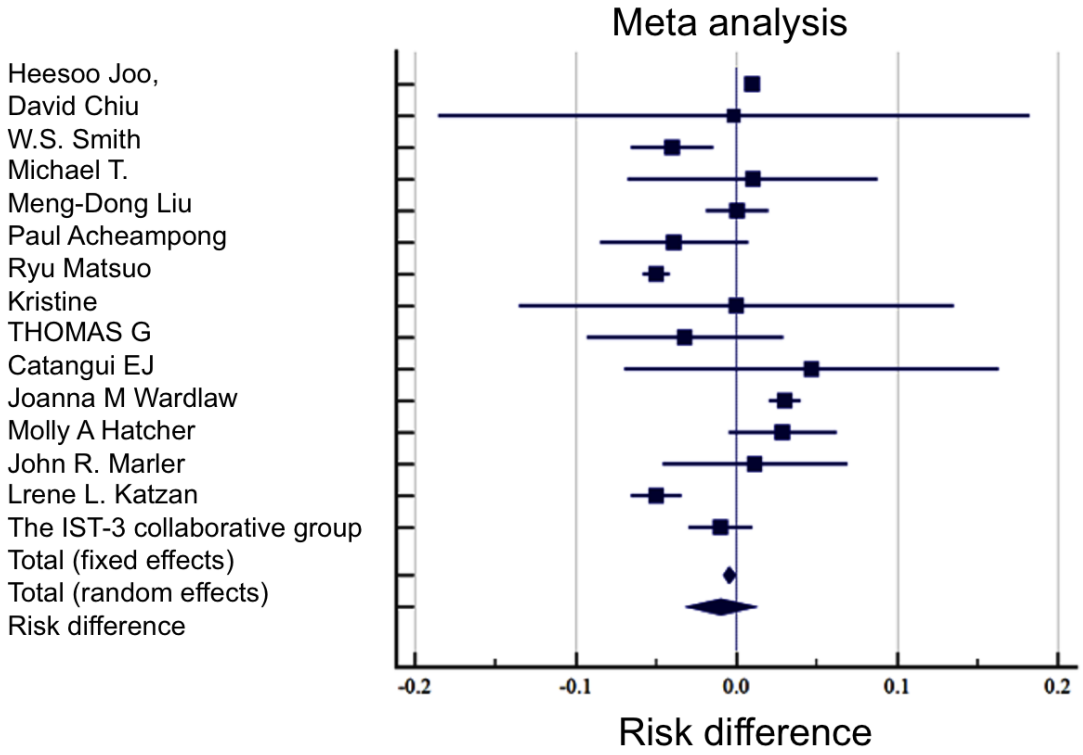

Fig. (7): Relationship between IV-tPA dose and mortality at end of follow up

DISCUSSION

This systemic review and meta-analysis showed that the favorable functional outcome at first 10 hours were significantly increased among patients who administrated IV-tPA significantly ($p < 0.01$) showing that most of subjects had minimal or no disability after IV-tPA[21].

Also, rt-PA use was related significantly with improvement of the neurological pain and good functional outcome[14, 19].Over that low dose versus standard dose showed favorable outcomes, lower mortality rates and low level of intracranial hemorrhage [17].

Most of the studies showed that the risks of intracranial hemorrhage are decreased after

using rt-PA and this was also presented in other studies [14, 18, 20]. Also, there was no association between the use of rt-PA and risk of hemorrhagic complications in many cohorts [19].

As for the mortality rate, the use of rt-PA was negatively associated with in-hospital mortality after adjusting the multiple confounding factors[19]. Other studies showed the same respect of results [18, 21].

This review also highlights the benefits of using rt-PA during the first 6 hours after symptoms which showed that lower levels of death occurred during the follow up period in which patients who survive without hemorrhage will benefit from the effects of rt-PA. Also, rt-PA has many favorable outcomes which may balance the outcomes of using the treatment and reduce the death for long term periods. The longer follow-up in some studies showed that the benefits of using rt-PA may balance its hazards especially in severe strokes thus delaying the treatment would result in unfavorable outcomes particularly among older people.

CONCLUSION

The study indicated that using intravenous rt-PA could increase the number of living patients with favorable outcome, less disabilities and intracranial hemorrhage among acute ischaemic stroke patients during the first 6 hours.

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