Intravenous recombinant tissue-type plasminogen activator thrombolysis for acute central retinal artery occlusion: a meta-analysis

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Abstract

Background: Central retinal artery occlusion (CRAO), an ocular stroke, causes severe and permanent visual impairment. Thrombolytic therapy is currently the main treatment option for CRAO. Intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) has been extensively applied in the treatment of CRAO with the proven advantages of effectiveness and safety. This meta-analysis aimed to assess the efficacy of intravenous rt-PA thrombolysis for the management of CRAO by evaluating the pooled evidence.

Methods: A comprehensive literature search of electronic databases including PubMed, OVID, and Cochrane Library was conducted up to and including March 2019. All studies reporting visual outcomes after CRAO (with thrombolytic therapy) were collected. Patient-level data on visual acuity (VA) and adverse events were recorded and assessed in this analysis. Data were inputted into the statistical software of STATA. The studies were weighted by the inverse of the variance and merged in a random-effects model.

Results: The systematic review process yielded seven eligible studies including 121 patients with CRAO who received the intravenous rt-PA treatment. 62 patients showed improvement in VA (52.0%; 95% CI, 34.0%-70.0%) following rt-PA intravenous thrombolytic therapy. The observed improvement rate in the intravenous rt-PA treatment group was significantly higher than the conservative treatment group (40.4% vs. 13.0%; OR, =5.16; 95% CI, 1.90-14.05). The incidence rate of complications was relatively low (11 out of the 121 patients). Hemorrhage (9/11) was the major reported complication. Mortality was zero.

Conclusion: This meta-analysis indicated that intravenous rt-PA thrombolysis could be an effective and safe strategy for the management of CRAO. However, a more detailed large-scale clinical trial is warranted to strengthen the evidence-based therapeutic guidance.

Background

Central retinal artery occlusion (CRAO), an ocular stroke, is a neurological and ophthalmic emergency that leads to severe and permanent visual impairment and approximately 80% of the cases are presented with visual acuity (VA) of 20/400 or worse [1]. Thrombosis and embolism of the central retinal artery leading to ischemia of the retina are the most prevalent etiology of CRAO [2]. Once the central retinal artery is occluded, irreversible apoptosis of the retina occurs depending on the duration of retinal ischemia. Recently, a meta-analysis suggested that fibrinolysis was favorable within 4.5 hours of symptom onset [1]. Noticeably, CRAO has a poor prognosis with high rate of permanent visual loss (80%) and the low rate of visual recovery (17.7%) in the natural history of CRAO [1,3].

Certainly, there is no consensus about optimal or standard therapeutic treatment for CRAO endorsed by ophthalmological guidelines. Conservative treatments that aimed at promoting downstream movement of the embolus including sublingual isosorbide dinitrate, inhalation of dioxide carbogen, hyperbaric oxygen, ocular massage, intravenous acetazolamide and mannitol, anterior chamber paracentesis,

hemodilution, anticoagulation, antiplatelet drugs and methylprednisolone have been attempted; however with limited therapeutic outcomes [1,2,4]. During the past decades, thrombolytic therapies including intra-arterial and intravenous thrombolysis recanalizing the central retinal artery and restoring retinal blood flow have been investigated for the treatment of CRAO with potential efficacy and safety [1,5]. Although thrombolytic therapies are currently the most effective therapies in CRAO, these therapies are not standard of care and applied on a case-by-case basis. The recovery rate of VA in patients treated with fibrinolytic therapy was significantly higher than those who received conservative treatment [1,4,5]. Intra-arterial thrombolysis is a catheter-directed super-selective interventional procedure to the proximal portion of the ophthalmic artery. Thus, intra-arterial thrombolysis remains a complex and highly expensive therapy. Moreover, preoperative preparation may prolong the therapeutic time window. Consequently, intra-arterial thrombolysis is unlikely to become widely accepted in the management of CRAO in the developing country.

Recently, intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) has been extensively applied in the treatment of CRAO with the proven advantages of feasibility, safety, and effectiveness [6–12]. As a thrombolytic agent, rt-PA acts by inducing fibrinolysis. It converts plasminogen into plasmin, a potent proteolytic enzyme which decomposes insoluble fibrous protein into soluble fragments at the site of fibrin deposition [13]. A pilot study on intravenous thrombolysis with rt-PA in CRAO demonstrated that 10 out of 12 patients with CRAO showed improvement in VA and four exhibited VA improvement of 8 Snellen chart lines [6]. However, a randomized controlled trial (RCT) of rt-PA treatment in acute CRAO on a small sample size showed that only 2 out of 8 patients experienced improved VA at the first week following intravenous rt-PA thrombolysis; however, VA improvement observed in these 2 patients was not sustained at 3 months [8]. The reason for inconsistencies in the findings from different studies may be attributed to the lack of large-scale clinical trial data, publication biases and varied therapeutic time windows.

For the reasons stated above, this meta-analysis aimed at examining the efficacy of intravenous rt-PA thrombolytic therapy for the management of CRAO by evaluating the pooled evidence.

Methods

This study was performed in accordance with a predefined protocol adhering to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Literature Search

We conducted a comprehensive literature search of electronic databases including PubMed, OVID, and Cochrane Library up to and including March 2019. A combination of MeSH-terms and keywords strategy was applied as follows: “central retinal artery occlusion (CRAO)" OR “intravenous thrombolysis” OR “fibrinolysis” OR “recombinant tissue-type plasminogen activator” or “rt-PA”. All studies reporting visual outcomes after CRAO (with thrombolytic therapy) were collected. VA and adverse events were the

important outcomes assessed in this analysis. Articles with non-arteritic CRAO were also included. We excluded studies that were case reports and studies with fewer than five patients, branch retinal artery occlusions, retinal vein occlusions, duplicate publications, letters, and reviews, abstracts from conferences without raw data, and articles with incomplete data or if the full-text cannot be retrieved. Besides, the references of the selected articles were also manually retrieved to obtain all potentially relevant studies. The language of publication was restricted to English.

Data extraction

The data extraction from each included study was performed independently by three reviewers and any disagreement was resolved through a panel discussion. Retrieved articles were screened and reviewed for their eligibility by the same three investigators. Differences in the determination of study's eligibility were resolved through discussion. The following data were extracted from each study: the first author's authors, the year of publication, study design, country, sample size, pretreatment and post-treatment VA, adverse events, and follow-up time.

The quality of the included articles was assessed by some scoring tools. For the randomized controlled trial, the quality of the article was assessed by the the Jadad score [14].Studies with a score ≥ 3 points were considered high quality. For the nonrandomized interventional study, the quality of the article was assessed by the Methodological Index for Nonrandomized Studies (MINORS) [15]. The ideal global score would be 16 for the non-comparative studies and 24 for the comparative studies.

Statistical analysis

Outcomes were reported with a 95% confidence interval (CI). Heterogeneity among studies was assessed with the χ^2-based Q statistic and I^2 tests. $p<0.05$, and $I^2 \geq 50\%$ were considered representative of significant statistical heterogeneity [1416]. At $P>0.10$, the pooled data of each study was calculated via the fixed-effects model (the Mantel–Haenszel method, which weights the studies by the inverse of the variance of estimates). Alternatively, the random-effects model was used if there was heterogeneity among studies. The significance of the pooled OR was determined and data with $p<0.05$ was considered statistically significant. All statistical tests in this meta-analysis were performed using the STATA software, version 14.0 (STATA Corp., College Station, TX, USA).

Results

Overall characteristics of selected studies

After exclusion of duplicate studies, a total of 118 articles were initially identified; however, 111 were rejected based on the exclusion criteria. A total of seven remaining full-text articles that met inclusion criteria were included in this meta-analysis [6–12]. Two of these studies were randomized trial [8,10],

three were prospective study [7,9,12], one was a pilot study [6], and one was a retrospective study [11]. The Jadad scoring for Chen's study and Wu's study was 5 and 2, respectively. Other studies were nonrandomized and non-comparative studies. The scores of MINORS of Kattah's study, Hattenbach's study, Nedelmann's study, Pre´terre's study and Schultheiss's study were 9, 12, 10, 10, and 14, respectively. A total of 121 patients treated with rt-PA intravenous thrombolytic therapy were analyzed. The characteristics of the studies included in the meta-analysis are summarized in Table 1. Patients received the low-dosedose of 50mg rt-PA in only one study [7] and the conventional dose of 0.9mg/kg (maximum, 90 mg) in the other six studies [6,8–12]. There was heterogeneity in the time from the onset of symptoms to treatment in all studies. The improvement of VA was defined in five studies (Table 2). Improvement was defined as an increase in VA increasing by more than three Snellen lines following thrombolytic treatment, equating to a 0.3 change in the log-MAR vision score in three studies [7,8,11].

VA and adverse events

VA outcomes before and after intravenous rt-PA thrombolysis for CRAO are showed in Table 3. 62 patients showed marked improvement in VA (52.0%; 95% CI, 34.0%–70.0%) following intravenous rt-PA therapy (Fig. 1). However, a significant between-study heterogeneity was detected (P = 0.000; I^2 = 78.8%). Therefore, a random-effects model was applied. The observed improvement rate in the intravenous rt-PA treatment group was significantly higher than the conservative treatment group (40.4% vs. 13.0%; OR = 5.16; 95%CI, 1.90–14.05) (Fig.2). Significant between-study heterogeneity was not observed (P = 0.866; I^2 = 0.0%).

Complications of intravenous rt-PA therapy in CRAO were reported in four studies (Table 3). The incidence rate of complications was relatively low (11 out of the 121 patients). Hemorrhage (9/11) was the major reported complication. There were 4 intracranial hemorrhages, 3 gum bleedings, 1 hematuria, and 1 hemorrhage from an abdominal aortic aneurysm. No death was reported from rt-PA intravenous thrombolytic therapy.

Funnel plot showed Kattah's study and Schultheiss's study were significant heterogeneity. We tested the heterogeneity by performing sensitivity analyses excluding the Kattah's study and Schultheiss's study. Excluding the two studies did not significantly alter the results obtained in the previous analysis.

Discussion

This study aimed to perform an updated meta-analysis examining the efficacy of rt-PA intravenous thrombolysis in patients with CRAO. In this meta-analysis, data from 121 patients with CRAO receiving the rt-PA intravenous thrombolysis among seven studies were analyzed. 62 of 121 patients with CRAO showed improved VA. Compared with the conservative treatment (13.0%), the improvement rate was significantly higher in patients treated with rt-PA intravenous thrombolysis (40.4%). Overall, the pooled evidence suggested that rt-PA intravenous thrombolysis was effective in treating CRAO. Furthermore, rt-PA

intravenous thrombolysis in CRAO was a safe therapeutic option. Complications following rt-PA intravenous thrombolysis were detected in only 11 patients. The reported major complication was hemorrhage with no associated mortality.

Alteplase rt-PA is firstly approved for acute ischemic stroke by the U.S. Food and Drug Administration in 1996. A prior Cochrane systematic review concluded that rt-PA treatment for acute ischemic stroke was safe and effective [1517]. CRAO is a stroke of the eye and analogous to ischemic cerebral stroke. As a thrombolytic agent, rt-PA can be administered intravenously or intra-arterially for the treatment of CRAO [10,1618]. Intravenous administration has the advantage of easier access with the nonspecialized physicians in the emergency room and reduced risk of haemorrhagic complications [1719]. However, intra-arterial thrombolysis needs to be performed by an interventional radiologist in the catheter room following sufficient preoperative preparation, thus, delaying the optimal therapeutic time window, which is currently recognized as a limiting factor for the effective treatment of CRAO. Moreover, a RCT study suggested that intra-arterial rtPA could not be recommended for the management of acute CRAO due to similar VA outcomes and the higher rate of adverse events compared with the conservative treatment [1820].

Based on the above mentioned shreds of evidence, intravenous rt-PA treatment was inclined to be used for the treatment of CRAO. Until 2011, the first RCT on intravenous rt-PA treatment in CRAO was performed with negative conclusion [6]. The major reasons for this negative finding of the study included the small sample size (8 patients in the treatment group) and prolonged therapeutic time window from symptom onset to treatment with the average time of 14.4h. Yet another RCT concluded that 16 of 24 patients (66.7%) had exhibited significant visual improvement [10]. In general, the improvement rate of VA following intravenous rt-PA treatment ranged from 0% to 83.3% [6–12]. However, the pooled effect of intravenous rt-PA treatment in CRAO remains unclear. Thus, we performed this meta-analysis.

Unlike an ischemic cerebral stroke, wherein there are guideline-based recommendations for treatment with rt-PA within 4.5 hours of symptom onset [1921], the same robust data are lacking in CRAO. Besides, there is a paucity of data on the optimal time window for effective intervention. The mean time to treatment in the RCT performed by Chen and their colleagues was 14.4 h, longest time window in this meta-analysis [8]. However, the research result of VA improvement was negative. Although the time to treatment was shortest with the average of 3.05h in the prospective study conducted by Schultheiss and the co-workers, the visual improvement was not satisfactory with the improvement rate of 25% [12]. Thus, a considerable association between time to treatment and visual improvement was concluded [7]. This prospective study indicated that time to treatment ≤6.5 hours was significantly associated with a better gain of lines of vision. 53% of patients receiving thrombolytic treatment within 6.5 hours after the onset of symptoms achieved an improvement of three or more Snellen lines, whereas no patient treated after 6.5 hours exhibited a comparable visual outcome. Supposedly, the sooner the intravenous rt-PA therapy was applied for CRAO, the better the visual improvement was achieved. A patients-level meta-analysis showed that intravenous fibrinolysis of rt-PA in CRAO was beneficial at 4.5hours or earlier after symptom onset [1]. This time window of efficacy was in accord with the ischemic cerebral stroke.

This meta-analysis has some inevitable limitations that must be acknowledged. First, a potential source of heterogeneity from the study design and time to treatment exists in the present meta-analysis. Second, there is publication bias because of the relatively small number of patients included in this analysis. Therefore, the results should be interpreted with caution prior the clinical implication of rt-PA intravenous thrombolytic therapy.

Conclusion

To date, this meta-analysis is the most comprehensive review of literature assessing the relative efficacy and safety of intravenous rt-PA therapy in CRAO. This meta-analysis of 7 eligible studies suggested that rt-PA intravenous thrombolytic therapy could be a potentially effective and safe strategy for the management of CRAO. However, a more detailed large-scale RCT is warranted to strengthen evidence-based therapeutic guidance.

Abbreviations

CRAO: Central Retinal Artery Occlusion; CI: Confidence Interval; rt-PA: recombinant tissue-type Plasminogen Activator; RCT: Randomized Controlled Trial; VA: visual acuity

Declarations

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Availability of data and materials

None.

Authors' contributions

Conception and design: YW, HZ; acquisition of data: XTW, YL, YS; statistical analysis and interpretation of data: XTW, YL, DQ, QM; drafting the article: XTW, YL, YS; critically revising the article: YW, YCZ; reviewed submitted version of manuscript: all authors; approved the final version of the manuscript on behalf of all authors: YW. All authors made substantial contribution to this manuscript meeting authorship criteria, agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable for a meta-analysis study.

Consent for publication

Not applicable, same reasoning.

Competing interests

The authors declare that there are no competing interests.

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Tables

Table 1 Summarized characteristics of studies included in the meta-analysis

Author, country, year	Study design	Sample size (M)	Age (mean,range,y)	IVT rt-PA	Other therapy	Time to treatment (mean, range ,h)	Follow-up (m)
Kattah et al [6] USA 2002	Pilot study	12	71.4, 53-89	0.9 mg/kg ≤90mg	IV heparin for 48h Oral warfarin sodium for 1m then Antiplatelet agent	5.80, 2-18	3
Hattenbach et al [7] Germany 2008	Prospective interventional case series Phase II, placebo-controlled randomized trial	28(19) 8(6)	63.3, 30-85 73	50 mg 0.9 mg/kg ≤90mg	IV heparin for 5 days then oral aspirin Antiplatelet agent	6.46, 1.5-12	Mean 2.2 (1 to 4)
Chen et al [8] Australia 2011	Prospective study	11	69.8, 45-88	0.9 mg/kg ≤90mg	No	14.40	6
Nedelmann et al [9] Germany 2015	Randomized trial	24(16)	58.8, 42-76	0.9 mg/kg ≤90mg	Conventional therapy	4.25, 1.75-10.5	≤3
Wu et al [10] China 2016	Retrospective study	30(21)	62.5	0.9 mg/kg ≤90mg	Aspirin therapy	<2 or >72	Mean 3
Pre´terre et al [11] France 2017	Prospective interventional case series	20(10)	72.8, 47-92	0.9 mg/kg ≤90mg	No	4.55	1
Schultheiss et al [12] Germany 2018				0.9 mg/kg ≤90mg		3.05	1

M-man; IVT - intravenous thrombolysis; rt-PA - recombinant tissue-type plasminogen activator; IV - intravenous; m-nonth.

Table 2 Definition of the improvement of VA in the included studies

Author, country, year	Definition of the improvement of VA
Kattah et al [6] USA, 2002	No
Hattenbach et al [7] Germany, 2008	Changes in BCVA were defined as improvement (increase of 3 or more Snellen VA lines), stable (within <3 lines from baseline VA), and worse (loss of 3 or more Snellen VA lines). Improvement was defined in Snellen VA by ≥3 lines between baseline and 6 months, equating to a >0.3 change in the logMAR vision score.
Chen et al [8] Australia, 2011	No Cured indicated that the VA improved by ≥4 lines. Markedly effective indicated that the VA improved by >3 lines. Effective indicated that the VA improves by >2 lines. Ineffective showed no improvement.
Nedelmann et al [9] Germany, 2015	A decrease of ≥0.3 log-MAR was considered as a major improvement Functional recovery was pre-defined as a BCVA of LogMAR ≤0.5 (Snellen equivalent: 6/20)
Wu et al [10] China, 2016	
Pre´terre et al [11] France, 2017	
Schultheiss et al [12] Germany, 2018	

rA - visual acuity; BCVA - best corrected visual acuity; logMAR - logarithm of minimal angle of resolution.

Table 3 The improvement rate of VA and adverse events following intravenous rt-PA therapy in CRAO

Author, country, year	VA (median, range)		Improvement	Adverse event (n, %)
	Pretreatment	Post-treatment	VA (%)	
Kattah et al [6]	HM,	20/200,	83.3%	No
US, 2002	LP-CF1	NLP-20/25		
Hattenbach et al [7]	HM,	HM,	32.0%	No
Germany, 2008	NLP-20/100	NLP-20/25		
Chen et al [8]	HM,	NR	0%	ICH (1, 12.5%)
Australia, 2011	HM-CF			Retinal neovascularization (1, 12.5%)
Nedelmann et al [9]	HM,	0.02 [a],	54.5%	No
Germany, 2015	0-0.1[a]	0-0.9 [a]		
Wu et al [10]	LP-0.02[a], ≥NLP	0.1-0.3 [a], ≥NLP	66.7%	Gum bleeding (3, 12.5%)
China, 2016	HM	NR	55.2%	ICH (3, 10.0%)
Pre´terre et al [11]				Hematuria (1, 3.3%)
France, 2017	LP (mean)	6/240 (mean)	25.0%	Orolingual angioedema (1, 5%)
Schultheiss et al [12]				Hemorrhage from an abdominal aortic aneurysm (1, 5%)
Germany, 2018				

VA - visual acuity; HM - hand motions; LP - light perception; CF - counting fingers; NLP - no light perception; NR - no report; ICH - intracranial hematoma; a - logMAR vision score.

Figures

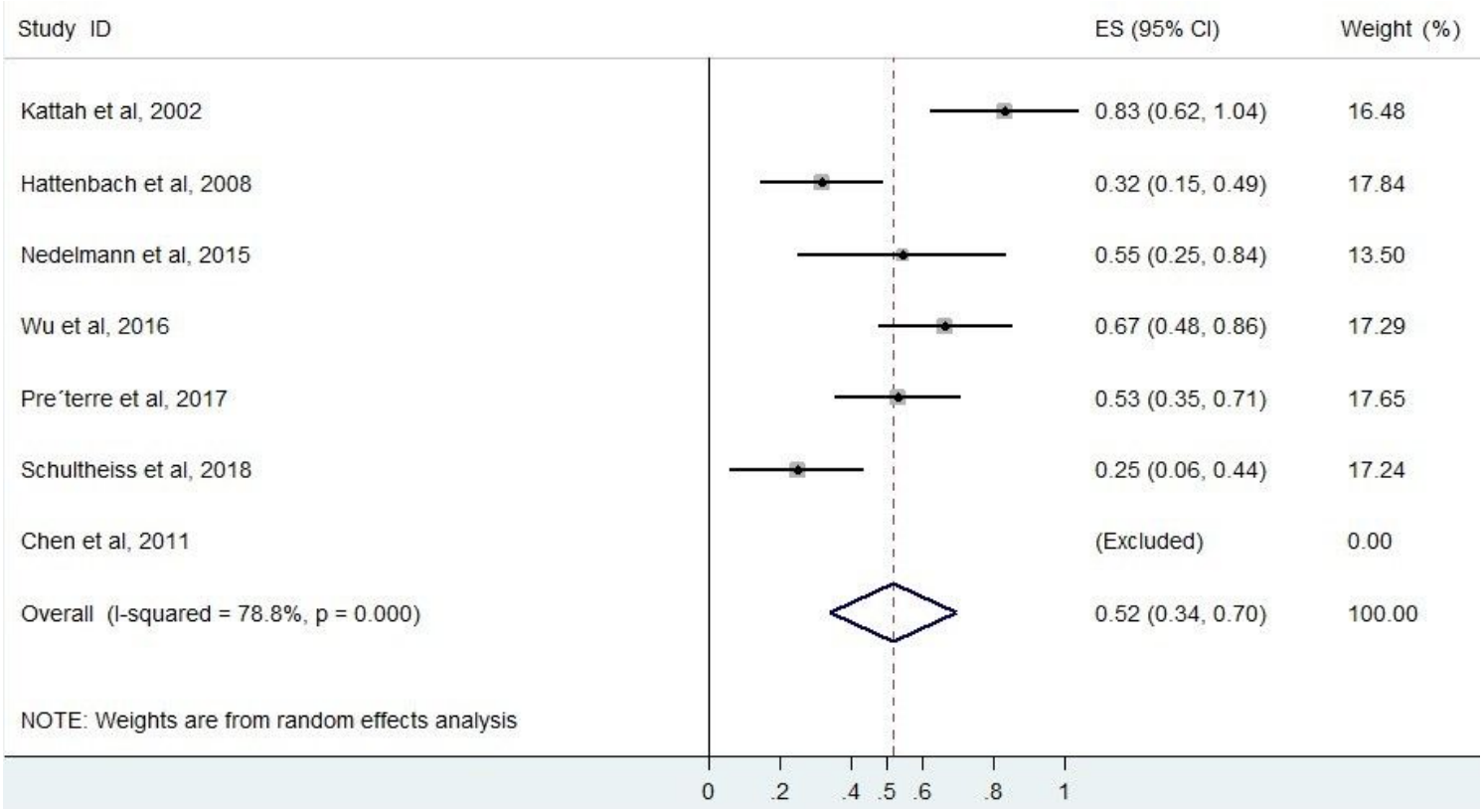

Figure 1

The improvement rate of VA following rt-PA intravenous thrombolysis in CRAO.

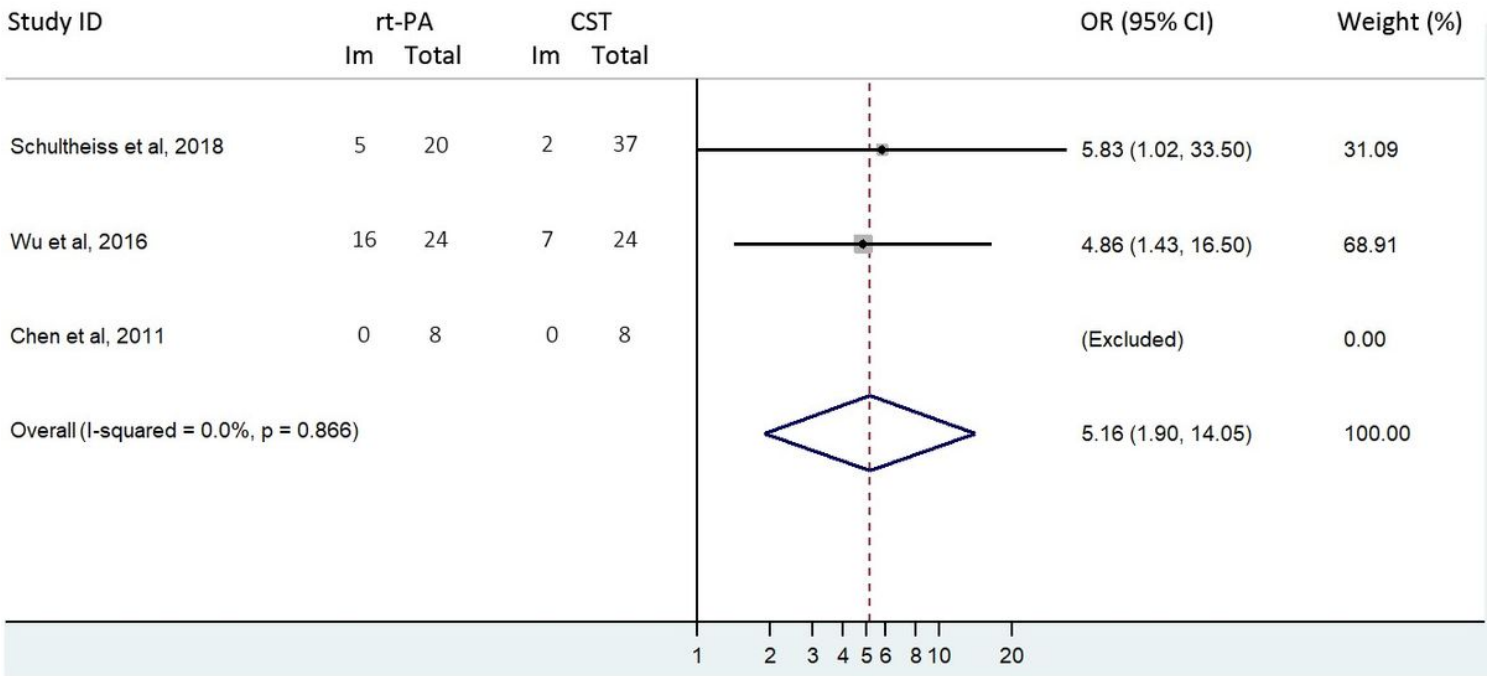

Fig. 2 Comparing the improvement rate of VA following rt-PA intravenous thrombolysis with the conservative treatment. Im -improvement; CST - conservative treatment.

Figure 2

Supplementary Files

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