INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Intravenous thrombolysis in acute ischemic stroke patients with prestroke disability：A systematic review and meta-analysis

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Review question / Objective: **P:AIS patients with prestroke disablity PSD I:IVT C:AIS patients without prestroke disablity O: mortality, sICH, favorable functional outcomeFFO S:prospective and retrospective study.**
Eligibility criteria: **We defined disable as broadly outlined by the Rankin Focused Assessment[8] and divided the disability into prestroke disable(modified Rankin Scale(mRS)≥2), severe disability(mRS=5) and death(mRS=6). Studies that spanned the selection criteria: (1) articles that involved patients with AIS treated with IVT, (2) articles that identified the association of presence or absence of PSD with safety and efficacy outcomes,(3) adult patients (>18 years old), and (4) language had to be English. We imposed limits on studys that< 50% of the enrolled patients received IVT, case reports, reviews, letters and meta-analyses.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 August 2022 and was last updated on 25 August 2022 (registration number INPLASY202280098).

INTRODUCTION

Review question / Objective: **P:AIS patients with prestroke disablity PSD I:IVT C:AIS patients without prestroke disablity O: mortality, sICH, favorable functional outcomeFFO S:prospective and retrospective study**

Rationale: **Background Intravenous thrombolysis (IVT) is the first-line therapy demonstrated to be safe and effective in acute ischemic stroke (AIS). However, the benefit for prestroke disability(PSD) is controversial. Objective To determine the association of PSD with the safety and efficacy of IVT among patients with AIS. Methods We searched PubMed, Embase**

and the Cochrane Library for published researchs providing outcomes of AIS patients with PSD receiving IVT from inception to May 23, 2022. We performed random-effects meta-analysis to pool outcomes including death, 24h NIHSS improvement, symptomatic intracerebral haemorrhage(sICH), favorable functional outcome(FFO) , the favourable outcome and mortality prevalence.

Condition being studied: To determine the association of PSD with the safety and efficacy of IVT among patients with AIS.

METHODS

Search strategy: We performed a systematic search to select studies providing outcomes of AIS patients with PSD receiving IVT in PubMed, Embase and the Cochrane Library from study inception to May 23, 2022, without language restrictions.PUBMED

#1. "Cerebrovascular Disorders"[MH]
#2. "Brain Ischemia"[MH] OR "Hypoxia-Ischemia, Brain"[MH] OR "Ischemic Attack, Transient"[MH]
#3. "Stroke"[MH] OR "Stroke, Lacunar"[MH] OR "Infarction, Posterior Cerebral Artery"[MH] OR "Brain Stem Infarctions"[MH] OR "Infarction, Middle Cerebral Artery"[MH] OR "Infarction, Anterior Cerebral Artery"[MH]
#4. Stroke[ti:ab] OR cerebr* vascul* infarct*[ti:ab] OR cerebrovasc* infarct*[ti:ab] OR cerebr* vasc* event*[ti:ab] OR cerebrovasc* event*[ti:ab] OR cva [ti:ab] OR transient ischemic attack*[ti:ab] OR tia[ti:ab]
#5. #1 OR #2 OR #3 OR #4
#6. "Thrombolytic Therapy"[MH] OR thromboly* therap*[ti:ab]
#7. "Fibrinolysis"[MH] OR fibrinoly*[ti:ab]
#8. "tPA" [ti:ab] OR "t-PA"[ti:ab] OR "rtPA" [ti:ab] OR "rt-PA" [ti:ab] OR "IV-tPA" [ti:ab] OR "IV rt-PA" [ti:ab]
#9. "alteplase" [ti:ab] OR "actilyse" [ti:ab] OR "activase" [ti:ab] OR "alteplasi" [ti:ab] OR "alteplasum"[ti:ab] OR "alteplasum" [ti:ab] OR "cathflo activase"[ti:ab] OR "GRTPA"[ti:ab] OR "SRT-PA"[ti:ab] OR "CAS Registry Number 105857-23-6"[ti:ab] OR "RN: 105857-23-6"[ti:ab]
#10. #6 OR #7 OR #8 OR #9
#11. Disabled Persons[MH] or Disabled Person[ti:ab] or Handicapped[ti:ab] or People with Disabilities[ti:ab] or Persons with Disabilities[ti:ab] or Persons with Disability[ti:ab] or Physically Handicapped[ti:ab] or Physically Disabled[ti:ab] or Disabled, Physically[ti:ab] or Physically Challenged[ti:ab] or Disability[ti:ab] or MRS[ti:ab] or Modified Rankin*[ti:ab] or Rankin*[ti:ab].
#12. Humans [MeSH Terms]
#13. #5 and #10 and #12EMBASE
#1. 'brain infarction'/exp OR 'brain ischemia'/exp OR 'cerebrovascular accident'/exp OR 'cerebral artery disease'/exp OR 'occlusive cerebrovascular disease'/exp
#2. 'lacunar stroke'/exp OR 'middle cerebral artery occlusion'/exp OR ('brain artery'/exp AND 'artery occlusion'/exp)
#3.'brain ischemia':ti,ab,kw OR 'cerebral ischemia':ti,ab,kw OR 'ischemic attack':ti,ab,kw OR 'transient ischemic attack':ti,ab,kw OR 'ischemic stroke':ti,ab,kw OR 'cerebral infarction':ti,ab,kw
#4. #1 OR #2 OR #3
#5. 'plasminogen activator'/exp OR 'fibrinolysis'/exp OR 'tissue plasminogen activator'/exp
#6. 'fibrinolytic agents':ti,ab,kw OR 'anti thrombin':ti,ab,kw OR 'tissue plasminogen activator':ti,ab,kw OR 'intravenous tissue plasminogen activator':ti,ab,kw OR 'IV tissue plasminogen activator':ti,ab,kw OR 'IV recombinant tissue plasminogen activator':ti,ab,kw OR 'Recombinant human tissue-type plasminogen activator':ti,ab,kw
#7. 'tPA':ti,ab,kw OR 't-PA':ti,ab,kw OR 'rtPA':ti,ab,kw OR 'rt-PA':ti,ab,kw OR 'IV-tPA':ti,ab,kw OR 'IV rt-PA':ti,ab,kw
#8. 'alteplase':ti,ab,kw OR 'actilyse':ti,ab,kw OR 'activase':ti,ab,kw OR 'alteplasi':ti,ab,kw OR 'alteplasum':ti,ab,kw OR 'alteplasum':ti,ab,kw OR 'cathflo activase':ti,ab,kw OR 'SRT-PA':ti,ab,kw OR 'UNII-1RXS4UE564':ti,ab,kw
#9. #5 OR #6 OR #7 OR #8
#10. 'Disability'/exp OR 'ADL disability':ti,ab,kw OR 'immobility':ti,ab,kw OR 'invalidity':ti,ab,kw OR ' limited mobility':ti,ab,kw OR 'neurodisability':ti,ab,kw OR 'physical

disability':ti,ab,kw OR 'walking difficulty':ti,ab,kw OR 'work disability':ti,ab,kw OR 'Handicapped':ti,ab,kw
#11. 'animals'/exp NOT 'humans'/exp
#12. #4 AND #9 AND #10 NOT #11 1429
COCHRANE
(thrombolysis[All Fields] OR tPA[All Fields] OR tissue plasminogen activator[All Fields]) AND (ischemic stroke[mesh] or ischemic stroke[All Fields]) AND (Handicapped[mesh] or Disabilities:ti,ab,kw or Persons with; Person:ti,ab,kw or Disabled:ti,ab,kw or Persons with Disabilities:ti,ab,kw or Handicapped:ti,ab,kw or Disability, Persons with:ti,ab,kw or People with Disability:ti,ab,kw or Disabled Person:ti,ab,kw or Persons with Disability:ti,ab,kw or Persons, Disabled:ti,ab,kw or People with Disabilities:ti,ab,kw or Disabilities, People with:ti,ab,kw or Physically Disabled:ti,ab,kw or Physically Handicapped:ti,ab,kw or Disabled, Physically:ti,ab,kw or Handicapped, Physically:ti,ab,kw or Physically Challenged:ti,ab,kw or MRS[All Fields] or Modified Rankin*[All Fields] or Rankin*[All Fields]). 1090.

Participant or population: AIS patients with PSD and without PSD.

Intervention: IVT.

Comparator: AIS patients without PSD.

Study designs to be included: prospective and retrospective study.

Eligibility criteria: We defined disable as broadly outlined by the Rankin Focused Assessment[8] and divided the disability into prestroke disable(modified Rankin Scale(mRS)≥2), severe disability(mRS=5) and death(mRS=6). Studies that spanned the selection criteria: (1) articles that involved patients with AIS treated with IVT, (2) articles that identified the association of presence or absence of PSD with safety and efficacy outcomes,(3) adult patients (>18 years old), and (4) language had to be English. We imposed limits on studys that< 50% of the enrolled patients received IVT, case reports, reviews, letters and meta-analyses.

Information sources: PubMed, Embase and the Cochrane Library.

Main outcome(s): We included 10 studies yielded 245773 participants that reported the outcomes in PSD patients with AIS undergoing IVT. In unadjusted analyses, PSD was associated with mortality (10 studies; odds ratio[OR] 1.739, 95% CI, 1.336–2.407), FFO(7 studies; OR 1.057, 95% CI, 1.015–1.100), 24h NIHSS improvement(5 studies; OR 0.840, 95% CI, 0.819–0.917, p=0.000), sICH(9 studies; OR 0.773, 95% CI, 0.481–1.243). In adjusted analyses, PSD was associated with mortality (7studies; ORadj 1.789, 95% CI, 1.413–2.264), FFO(5 studies; ORadj 1.087;95%CI, 1.002-1.179), 24h NIHSS improvement(5 studies; ORadj 0.837, 95% CI, 0.799–0.876), sICH(5 studies; ORadj 0.857, 95% CI,0.725–1.012). The prevalences of FFO and death in patients with prestroke mRS of 2 to 5 were 49% (0.42-0.56), 37% (0.21-0.53), respectively.

Quality assessment / Risk of bias analysis: The Newcastle-Ottawa scale was assessed risk of bias of the cohort studies. The risk of outcome bias was considered as moderate. The detailed confounders that were included in the adjusted analyses of available studies were displayed in supplementary materials 4. The overall score of Newcastle-Ottawa scale was considered to represent an overall high quality. The detailed were displayed in Table2. Funnel plot inspection revealed no evidence of asymmetry in studies reporting the unadjusted outcomes. The Egger test was not applicable because of the small number of studies (<10).

Strategy of data synthesis: The ORs and standardized mean differences and their corresponding 95% confidence intervals (CIs) were calculated to measure the effect size and evaluate the association of PSD (vs no PSD) with safety and efficacy outcomes among AIS patients treated with IVT. For the qualitative interpretation of heterogeneity, I2 > 50% and I2 > 75% were considered substantial and considerable

heterogeneity, respectively[9]. A funnel plot was evaluated publication bias across individual studies, while funnel plot asymmetry was assessed using the Egger linear regression test with a p < 0.10 significance level. We used a random-effects model to calculate the pooled ORs in both the overall and subgroup analyses. An equivalent z test was performed for each pooled OR, and we considered a 2-tailed value of p < 0.05 as statistically significant. All statistical analyses were conducted with the Comprehensive Meta Analysis(CMA2.0) and Cochrane Collaboration's Review Manager Software Package (RevMan5.3).

Subgroup analysis: Unadjusted analyses Among patients with AIS treated with IVT, PSD was associated with higher odds of pooled mortality (10 studies; OR 1.739, 95% CI, 1.336–2.407, p = 0.000, I2 =91.640%; Figure2.1) , FFO(7 studies; OR 1.057, 95% CI, 1.015–1.100, p = 0.007, I2 =94.951%; Figure2.2). No significant association was noted for a history of PSD and odds of 24h NIHSS improvement(5 studies; OR 0.867, 95% CI, 0.819–0.917, p=0.000, I2 =27.991%; Figure2.3), sICH(9 studies; OR 0.773, 95% CI, 0.481–1.243, p = 0.288, I2 =85.687%; Figure2.4). Significant heterogeneity (I2 >50%) was found for all the outcomes in the unadjusted analyses except for 24 h NIHSS improvement. adjusted analyses In adjusted analyses, PSD was associated with an increased odds of mortality (7 studies; ORadj 1.789, 95% CI, 1.413–2.264, p = 0.000, I2 =80.904%; Figure3.1), FFO(5 studies; ORadj 1.087; 95% CI, 1.002-1.179, p =0.044, I2 =0%; Figure3.2). No significant associations were observed for 24h NIHSS improvement(5 studies; ORadj 0.837, 95% CI, 0.799–0.876, p = 0.000, I2 =48.073%; Figure3.3), sICH(5 studies; ORadj 0.857, 95% CI,0.725–1.012, p = 0.069, I2 =35.309%; Figure3.4). Based on the analysis of adjusted data, heterogeneity was significantly reduced. In addition, it is interesting that we might have stumbled across a research that provide an overview of investigating the association of PSD recived IVT vs without. PSD with IVT was related to an increased likelihood of favorable outcome(defined as a return to the pre-stroke mRS 3 months after AIS)(OR 7.26, 95% CI,2.51–21.02, P=0.001), major neurological improvement(defined as an improvement of ≥8 points on the NIHSS from baseline or a NIHSS score of 0 at discharge)(OR 3.7, 95% CI,1.32–10.35, P=0.001). Importantly, the prevalence of three-month mortality, ICH, and sICH did not differ between the two groups.We additionally evaluated those studies based on different definitions of PSD[defined as Prestroke mRS=2-5 or mRS=3-5]. We found that mortality (mRS 2-5: 2 studies; ORadj 1.343, 95% CI, 0.803–2.248, p = 0.261, I2 = 26.309%; mRS 3-5: 5 studies; ORadj 1.930, 95% CI,1.481–2.515, p = 0.000, I2 = 72.665%; Figure3.1) and FFO(mRS 2-5: 2 studies; ORadj 1.121, 95% CI, 1.028–1.222, p = 0.010, I2 = 0%; mRS 3-5: 3 studies; ORadj 0.866, 95% CI, 0.684–1.096, p = 0.232, I2 = 0%; Figure3.2) were differentially expressed in the two groups under different PSD definitions. Unfortunately, no statistical significance was observed for a lower odds of pooled mortality in mRS=2-5.

Sensitivity analysis: We performed additional analyses for the adjusted associations, stratified by study type (prospective vs retrospective studies) and after removal of a retrospective study. No difference in the adjusted associations of PSD with the likelihood of sICH, FFO, 24h NIHSS improvement and mortality. We removed a study from mortality group, heterogeneity (I2 =28%) was observed between the studies, the reslut indicated statistically significant. The heterogeneity of other groups(24h NIHSS improvement, sICH) was reduced, which were 0%, 12%, respectively. The reslut indicated statistically significant. We believe that the results of the removed articles are different due to the different research design schemes, which leads to the differences in results (supplementary materials 5).

Language restriction: English.

Country(ies) involved: China.

Keywords: Intravenous thrombolysis, Ischemic stroke, Disability, Outcome,Meta-analysis.

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