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Chronic kidney disease and intravenous thrombolysis in acute stroke: A systematic review and meta-analysis

Jin-Man Jung [a,1], Hyun Jung Kim [b,1], Hyeongsik Ahn [b], Il Min Ahn [b,c], Youngrok Do [d], Jeong-Yoon Choi [a], Woo-Keun Seo [e], Kyungmi Oh [e], Kyung-Hee Cho [f], Sungwook Yu [f,*]

[a] Department of Neurology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea
[b] Department of Preventive Medicine, College of Medicine, Korea University, Seoul, Republic of Korea
[c] Department of Literary Arts, Brown University, RI, USA
[d] Department of Neurology, Daegu Catholic Hospital, Dae-Gu Catholic University College of Medicine, Dae-Gu, Republic of Korea
[e] Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea
[f] Department of Neurology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background: The association between chronic kidney disease (CKD) and hemorrhagic complications or clinical outcomes in patients treated with intravenous (IV) thrombolytic agents is controversial.
Methods: We searched multiple databases for studies on the association between CKD and symptomatic intracerebral hemorrhage (ICH) and/or clinical outcomes in acute stroke patients treated with IV tissue plasminogen activator (tPA). Observational studies that evaluated the association between CKD and outcomes after adjusting for other confounding factors were eligible. We assessed study quality and performed a meta-analysis. The main outcome was symptomatic ICH. The secondary outcomes were poor functional status at 3 months using the modified Rankin Scale, mortality at 3 months, and any ICH.
Results: Seven studies were selected based on our eligibility criteria. Of 7168 patients treated with IV tPA, 2001 (27.9%) had CKD. Patients with CKD had a higher risk of symptomatic ICH and mortality [pooled odds ratio (OR) 1.56, 95% confidence interval (CI) 1.05–2.33 and pooled OR 1.70, 95% CI 1.03–2.81, respectively]. Patients with CKD were likely to have an increased risk of poor outcome at 3 months. There was no significant association between CKD and any ICH.
Conclusions: Chronic kidney disease may significantly affect symptomatic hemorrhagic complications and poor clinical outcomes following administration of IV tPA.

1. Introduction

Chronic kidney disease (CKD) is characterized by a reduced glomerular filtration rate (GFR) and is a risk factor for cardiovascular diseases (CVDs) including ischemic heart disease, stroke, and vascular death [1]. Chronic kidney disease has been associated with CVD risk factors [1–3]. It has also been found to be a strong independent predictor of poor outcome and mortality in acute stroke patients [4–5].

The only drug that has been approved as a first-line therapy for acute ischemic stroke is intravenous (IV) tissue plasminogen activator (tPA), which should be administered within 4.5 h of symptom onset [6]. However, hemorrhagic complications that can lead to functional disability or death are a major concern for patients treated with IV tPA [7]. Approximately half of tPA-treated patients remain functionally dependent or die, suggesting that the efficacy of IV tPA therapy is unsatisfactory [8–10]. Therefore, in order to improve the outcomes of IV tPA-treated patients, it is important to identify specific conditions that are associated with a higher risk of complications with IV tPA treatment.

While CKD can provoke prothrombotic conditions, it has also been associated with hemorrhage because it can induce endothelial and platelet dysfunction [11]. Chronic kidney disease has not received attention as a prognostic factor in randomized controlled clinical trials for IV thrombolytic agents [8–9,12]. Several previous observational studies have yielded conflicting results regarding the association between CKD and hemorrhagic complications or clinical outcomes among patients treated with IV thrombolytic agents [13–24]. This is partly due to small sample sizes, variable baseline characteristics, and differing methods and cut-off values for defining CKD. One meta-analysis of 3 observational studies attempted to address these issues [25], but it is possible that there was bias due to the use of an unadjusted odds ratio (OR) to determine pooled estimates and the failure to consider the risk of bias. More recently, several studies have reported on the

* Corresponding author at: Department of Neurology, Korea University College of Medicine, Korea University Anam Hospital, 73 Inchon-ro, Seongbuk-gu, Seoul 136-705, Republic of Korea.
E-mail address: song4yu@korea.ac.kr (S. Yu).
[1] contributed equally as a first author

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impact of renal function on patients treated with IV tPA. Therefore, the association between CKD and hemorrhagic complications or clinical outcomes in patients treated with IV thrombolytic agents is still inconclusive and furthermore, an up-to-date comprehensive assessment of the safety and efficacy of IV tPA in the context of CKD is needed.

We evaluated the effect of CKD on IV thrombolysis by conducting a systematic review and meta-analysis based on observational studies.

2. Materials and methods

We searched comprehensive databases for studies investigating the association between CKD and symptomatic intracerebral hemorrhage (ICH) and/or clinical outcomes in acute stroke patients treated with IV tPA. This study was based on the Cochrane Review Methods [26].

2.1. Sources of data and literature

A systematic literature search was performed using MEDLINE (January 1, 1976 to April 30, 2014), EMBASE (January 1, 1985 to April 30, 2014), the Cochrane Central Register of Controlled Trials (January 1, 1987 to April 30, 2014) and KoreaMed (June 1, 1958 to April 30, 2014). We applied no restrictions based on language or year of publication in our search. The MEDLINE database was searched using the following keywords and MeSH: stroke, thrombolytic therapy, tissue plasminogen activator, thrombolysis, chronic kidney failure, and glomerular filtration rate. Specific search strategies were developed for each database. The reference sections of included articles and pertinent reviews were further screened to search for additional relevant publications.

2.2. Study selection

Studies were selected by two independent investigators according to explicit inclusion and exclusion criteria (J.J.-M. and D.Y.). Study selection was performed using a 2-step screening process: First, we screened the titles and abstracts of the studies that were selected. Second, we reviewed the entire article. Unpublished conference abstracts were also subject to screening. Studies regarding the safety or efficacy of IV tPA in acute stroke patients were eligible if they (1) reported CKD as defined by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 as a baseline variable [27] and (2) reported the association between outcomes and CKD after adjustment for other confounding factors in a prospectively collected cohort. Retrospective studies that met the first criterion and reported the results of multivariable analyses were also included. A consensus between two investigators was used to resolve any disagreements about the inclusion of specific studies.

2.3. Data extraction

Data extraction was performed independently using a predefined data extraction form, and discrepancies were adjudicated by a third investigator reviewer (C.J.-Y.). The study design, demographic, clinical, and treatment characteristics [*e.g.*, tPA cut-off time from symptom onset (3 h *vs.* 4.5 h), dose of IV tPA (0.6 mg/kg *vs.* 0.9 mg/kg)], cut-off value for poor functional outcome based on the modified Rankin Scale (mRS), definition of (symptomatic) ICH, and statistical methodology were recorded. The odds ratios (ORs) and 95% confidence intervals (CIs) between CKD and symptomatic or any ICH, mortality, or poor functional outcome were extracted.

We aimed to control or reduce the impact of several confounding factors inherent to observational studies. To minimize the effects of the potential confounding factors, we only used adjusted ORs to calculate the pooled estimate. We excluded studies that rendered only unadjusted ORs. When studies included both unadjusted and adjusted ORs, we extracted only the adjusted ORs. We introduced a cut-off value for CKD to be dichotomized based on an eGFR value <60 mL/min/1.73 m^2. We also included studies with a trichotomized CKD cut-off value, particularly when an eGFR <60 mL/min/1.73 m^2 was incorporated into the classification of the trichotomy [18].

2.4. Assessment of methodological quality

Methodological quality was assessed by two independent investigators based on individual study characteristics using the Quality In Prognosis Studies tool [28]. We resolved differences through discussion or, if a resolution was not possible, through adjudication by a third reviewer (C.J.-Y.).

Generally, publication bias tests through funnel plot asymmetry have only been performed when at least 10 studies were included in a meta-analysis [26]. Therefore, because our analysis included only 7 studies, publication bias tests were not performed.

2.5. Definitions of outcomes

The main outcome was symptomatic ICH (defined as "any hemorrhage on follow-up brain images with any neurological deterioration" [9] or "any hemorrhage on follow-up brain images with significant neurological deterioration" [29]). The secondary outcomes were functional status at 3 months assessed with the mRS, mortality (including in-hospital and at 3 months), and any ICH including parenchymal brain hemorrhage and hemorrhagic transformation. A poor outcome at 3 months was defined as mRS combination of 2–6, 3–6, or 4–6.

2.6. Statistical analysis

Meta-analysis could be performed given that outcomes were extracted from more than 2 studies. We performed pooled analyses using the generic inverse variance method with the random effects weighted. Data were expressed as pooled ORs with 95% CIs. To estimate heterogeneity, we used Cochrane Q and I^2 statistics. An I^2 value of ≥50% was considered to denote significant heterogeneity, and random-effects models were used. We explored heterogeneity using predefined subgroup analyses according to the diagnostic criteria of CKD or symptomatic ICH, outcome measurement time, cut-off value for poor functional outcome, tPA cut-off time from symptom onset (3 h *vs.* 4.5 h) and dose of tPA [lower (0.6 mg/kg) *vs.* standard (0.9 mg/kg)]. We used RevMan version 5.3 for all analyses.

3. Results

3.1. Identification of studies

Our searches of the databases and other sources resulted in a total of 558 articles (Fig. 1). Of these, 521 publications were excluded because they did not fulfill the inclusion criteria based on the titles and/or abstracts. For the remaining 37 articles, we reviewed the full text article and identified 7 potentially relevant studies. There were 30 publications that were excluded for reasons, which are described in Fig. 1.

3.2. Study characteristics and patient samples

Seven studies included a total of 7168 patients treated with IV tPA. Among them, 2001 (27.9%) had CKD. Patients with CKD were older, had more co-morbidities and severe strokes, and more frequently used anti-platelet agents (Supplementary Table 1). The features of the included studies are summarized in Table 1. Two studies were based on prospective cohort data and five were based on retrospective data. All studies except two were multicenter-based. Three studies reported follow-up loss at the time that outcome was determined. Information regarding loss to follow-up was available for 1 study because the outcome was measured during hospitalization, but was either not

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