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Elevated urea level is associated with poor clinical outcome and increased mortality post intravenous tissue plasminogen activator in stroke patients

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ABSTRACT

Background: Renal dysfunction is associated with poor outcomes in ischaemic stroke but remains unproven post intravenous thrombolysis. We studied the renal function in stroke patients treated with intravenous tissue plasminogen activator (IV tPA).

Methods: We retrospectively analysed consecutive ischaemic stroke patients treated with IV tPA (0.9 mg/kg) from January 2003 to December 2011. Collected data included demographics, medical histories, stroke severity measured by National Institutes of Health Stroke Scale (NIHSS), serum urea, creatinine, estimated glomerular filtration rate (eGFR), platelet, white cell count and international normalised ratio (INR) at baseline. Poor clinical outcome was defined as modified Rankin Scale (mRS) of 2 to 6 at 3 months. Logistic regression analysis was performed to test the association between renal function and clinical outcomes adjusted for confounders.

Results: In the 378 patients included, the median age was 72 (IQR = 62–81) years, 54.2% were male. Median baseline NIHSS was 12 (IQR = 8–18). There was a statistically significant association between all three renal function markers. After adjustments for confounding factors, baseline urea was significantly associated with poor outcome (OR = 1.100; 95% CI 1.010–1.198 per mmol/L; p = 0.028) and mortality (OR = 1.117; 95% CI 1.027–1.213 per mmol/L; p = 0.009), eGFR was associated with mortality (OR = 0.984; 95% CI 0.970–0.998 per mL/min/1.73 m^2; p = 0.026) but not poor outcome (OR = 0.994; 95% CI 0.983–1.004 per mL/min/1.73 m^2; p = 0.230), and serum creatinine was not significant for poor outcome (OR = 1.037; 95% CI 0.967–1.113 per 10 μmol/L; p = 0.306) or mortality (OR = 1.032; 95% CI 0.979–1.088 per 10 μmol/L; p = 0.238). No association was observed between ICH and any renal function test.

Conclusions: Elevated serum urea was independently associated with poor clinical outcome and mortality in acute ischaemic stroke patients treated with IV tPA.

1. Introduction

Intravenous tissue plasminogen activator (IV tPA) is the only intervention shown to be effective in selected acute ischaemic stroke patients [1], but remains grossly underused [2], partially because of uncertainty around patient selection.

Previous studies have confirmed the association between impaired renal function and mortality in stroke patients [3–10]. Patients with end-stage renal disease experience markedly advanced atherosclerotic disease of the cerebral vasculature and an extraordinary high risk of stroke when compared to the general population [11]. In addition, the degree of renal dysfunction present in stroke patients may be a marker of end-organ damage from undetected preexisting untreated diseases or indicate a higher comorbidity burden [5]. These might be the causes that renal dysfunction impedes recovery post stroke.

However, the effects of renal dysfunction on thrombolysis have been only described in small studies of creatinine or estimated glomerular filtration rate (eGFR) with conflicting results [12–14]. Urea is a third biochemical marker of renal function. Previous studies showed that elevated urea predicted poor outcome and increased mortality in patients with myocardial infarction [15–17], acute coronary syndrome [18,19], hypertension [20–22], ischaemic stroke [5,7], and intracerebral haemorrhage [23]. However, serum urea has not been previously investigated in acute ischaemic stroke treated with IV tPA. We hypothesised that impaired renal function, including high serum urea, on admission

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Table 1
Main characteristics of the study population.

Characteristics	All patients (n = 378)	Poor outcomes			Mortality			ICH		
		No (n = 128)	Yes (n = 250)	p value	No (n = 305)	Yes (n = 73)	p value	No (n = 290)	Yes (n = 88)	p value
Renal function										
Serum urea (mmol/L), median (IQR)	7.2 (5.5–9.3)	6.6 (5.0–8.3)	7.7 (5.8–10.0)	0.001	7.0 (5.4–8.9)	8.4 (6.1–11.0)	0.001	7.2 (5.6–9.1)	7.4 (5.4–10.5)	0.402
Creatinine (μmol/l), median (IQR)	90 (78–110)	90 (75–100)	90 (79–110)	0.153	90 (76–105)	100 (80–122)	0.005	90 (79–110)	90 (78–117)	0.300
eGFR (mL/min/1.73 m^2), median (IQR)	64 (51–78)	69 (58–82)	60 (47–75)	0.002	67 (55–80)	53 (40–64)	<0.001	64 (52–78)	65 (48–79)	0.845
eGFR <60 mL/min/1.73 m^2, n (%)	157 (41.5)	37 (28.9)	120 (48.0)	<0.001	108 (35.4)	49 (67.1)	<0.001	121 (41.7)	36 (40.9)	0.902
Demographics										
Age, median (IQR)	72 (62–81)	66 (58–75)	75 (65–83)	<0.001	71 (59–79)	79 (70–85)	<0.001	72 (62–81)	71 (59–82)	0.628
Male sex, n (%)	205 (54.2)	85 (66.4)	121 (48.0)	0.001	181 (59.3)	24 (32.9)	<0.001	152 (52.4)	53 (60.2)	0.223
Past medical history										
Hypertension, n (%)	239 (63.2)	78 (60.9)	161 (64.9)	0.498	189 (62.0)	50 (70.4)	0.218	177 (61.2)	62 (71.3)	0.099
Diabetes mellitus, n (%)	94 (24.9)	27 (21.1)	67 (27.0)	0.258	71 (23.3)	23 (32.4)	0.128	74 (25.3)	21 (24.1)	0.888
Ischaemic heart disease, n (%)	89 (23.5)	29 (22.7)	60 (24.2)	0.799	73 (23.9)	16 (22.5)	0.878	68 (23.5)	21 (24.1)	0.887
Atrial fibrillation, n (%)	96 (25.4)	24 (18.8)	72 (29.0)	0.034	74 (24.3)	22 (31.0)	0.290	67 (23.2)	29 (33.3)	0.068
Hyperlipidaemia, n (%)	195 (51.6)	72 (56.3)	123 (49.6)	0.233	162 (53.1)	33 (46.5)	0.357	151 (52.2)	44 (50.6)	0.808
Previous TIA, n (%)	25 (6.6)	10 (7.8)	15 (6.1)	0.520	21 (6.9)	4 (5.6)	1.000	19 (6.6)	6 (7.0)	1.000
Previous stroke, n (%)	43 (11.4)	11 (8.6)	32 (12.9)	0.236	33 (10.8)	10 (14.1)	0.414	33 (11.4)	10 (11.5)	1.000
NIHSS baseline, median (IQR)	12 (8–18)	9 (6–14)	15 (10–20)	<0.001	11 (7–17)	20 (15–23)	<0.001	12 (7–18)	17 (11–20)	<0.001
Baseline laboratory findings										
International normalised ratio, median (IQR)	1.1 (1.0–1.1)	1.1 (1.0–1.1)	1.1 (1.0–1.1)	0.574	1.1 (1.0–1.1)	1.1 (1.0–1.1)	0.364	1.0 (1.0–1.1)	1.1 (1.0–1.1)	0.096
Platelets ($\times 10^9$/L), median (IQR)	235 (193–287)	229 (194–276)	237 (192–298)	0.520	236 (192–286)	232 (203–295)	0.810	235 (193–290)	234 (185–270)	0.620
White blood cell ($\times 10^9$/L), median (IQR)	7.9 (6.6–9.6)	7.9 (6.5–9.4)	7.9 (6.7–9.7)	0.617	7.9 (6.6–9.5)	8.0 (6.7–9.7)	0.725	7.9 (6.6–9.7)	8.4 (6.6–9.5)	0.546
TOAST classification										
Large-artery atherosclerosis, n (%)	46 (12.2)	16 (12.5)	30 (12.0)	0.457	42 (13.8)	4 (5.5)	0.072	31 (10.7)	15 (17.0)	0.182
Cardioembolism, n (%)	162 (42.9)	49 (38.3)	113 (45.2)		134 (43.9)	28 (38.4)		120 (41.4)	42 (47.7)	
Small-artery occlusion, n (%)	3 (0.8)	0 (0)	3 (1.2)		3 (1.0)	0 (0)		3 (1.0)	0 (0)	
Other determined cause, n (%)	3 (0.8)	1 (0.8)	2 (0.8)		3 (1.0)	0 (0)		2 (0.7)	1 (1.1)	
Undetermined cause, n (%)	164 (43.4)	67 (48.4)	102 (40.8)		123 (40.3)	41 (56.2)		134 (46.2)	30 (34.1)	

Poor outcome was defined as mRS of 2–6. ICH = intracerebral haemorrhage; IQR = interquartile range; GFR = glomerular filtration rate; TIA = transient ischaemic attack; NIHSS = National Institutes of Health Stroke Scale.

was associated with poor clinical outcome and increased mortality in acute stroke patients treated with IV tPA.

2. Methods

2.1. Patient selection

All consecutive ischaemic stroke patients (n = 400) treated with IV tPA (0.9 mg/kg) at Royal Melbourne Hospital from January 2003 to December 2011 were included. Of these patients, 21 were excluded due to missing modified Rankin Scale (mRS) [24] and one was excluded due to missing renal function tests. Therefore, 378 patients formed the study population. The comparison between included patients and excluded patients was conducted. There was no difference of clinical characters between included patients and excluded patients. The Melbourne Health Human Research & Ethics Committee approved the study protocol.

2.2. Clinical assessment and data collection

This was a retrospective analysis of a prospectively collected patient series. The following parameters were recorded in a specific data bank: (1) Demographics (age, gender). (2) Medical histories. (3) Stroke presentation such as baseline National Institutes of Health Stroke Scale (NIHSS) [25] and stroke types according to TOAST classification system [26]. (4) Admission laboratory data including serum urea, creatinine, eGFR, platelet, white cell count and international normalised ratio (INR). Renal dysfunction was defined as <60 mL/min/1.73 m^2. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation as following:

$$\mathrm{eGFR}\left(\mathrm{in\,mL/min/1.73\ m^2}\right) = 32788 \times \mathrm{Serum\ Creatinine}(\exp[-1.154]) \times \mathrm{Age}(\exp[-0.203]) \times (0.742\,\mathrm{if\,female}) \times (1.21\,\mathrm{if\,black}).$$

2.3. Assessment of outcomes

Main outcomes assessed in this study were 3-month poor outcome, defined as mRS of 2 to 6, and death within 3 months. We also recorded intracerebral haemorrhage (ICH), which was analysed according to brain CT within 7 days of tPA.