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Clinical Study

Remote intracerebral haemorrhage post intravenous thrombolysis: Experience from an Australian stroke centre

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ABSTRACT

Remote intracerebral haemorrhage (rICH) is defined as intracerebral haemorrhage (ICH) post thrombolysis in brain regions without visible ischaemic changes. There is uncertainty that clinical outcomes and risk factors for rICH are different to those for local ICH. We investigated the morbidity, mortality and factors associated with rICH. We hypothesised that a previous history of cerebral ischaemic events is associated with increased risk of rICH. We included consecutive acute ischaemic stroke patients from 2003 to 2012 who were treated with intravenous thrombolysis. Clinical data included demographics, stroke classification, vascular risk factors and laboratory results. Clinical outcome was defined by modified Rankin Scale (mRS) score at 3 months. Baseline and follow-up CT scans were analysed for all ICH, and further dichotomised to rICH and local ICH. Clinical outcomes between rICH and local ICH were compared after adjustment for confounding factors. Four hundred and two patients were included in the study. The median age was 71 (interquartile range 60–79) years, and 54% were male. ICH (local ICH and rICH) was detected in 21.6% (87/402) of all patients post thrombolysis. The incidence of rICH was 2.2% (9/402). Most rICH were classified as haemorrhagic infarct category 2 (HI2) ($p = 0.002$). The proportion of patients with previous transient ischaemic attacks was significantly higher in the rICH group (33.33% *versus* 2.56%; odds ratio [OR] 18.75, 95% confidence interval [CI] 3.06–114.38; $p = 0.007$). The proportion of mRS scores 0–2 at 3 months was significantly higher in the rICH group (50% *versus* 28%; adjusted OR 10.469, 95%CI 1.474–74.338; $p = 0.019$). The 3 month mortality rate was 22.2% (2/9) in the rICH group and 36% (27/75) in the local ICH group (OR 0.53, 95%CI 0–2.51, $p = 0.703$). rICH was an infrequent complication after intravenous thrombolysis in our series. The clinical outcome of rICH was significantly better than local ICH. Of note, previous episodes of transient ischaemic attack were significantly higher in the rICH group, suggesting previous ischaemic injury as an underlying mechanism.

1. Introduction

Symptomatic (or severe) intracerebral haemorrhage (sICH) is a major complication after the administration of tissue plasminogen activator (tPA) for acute ischaemic stroke [1]. The incidence of intracerebral haemorrhage (ICH) ranges from 6.2% to 43% according to different studies [2]. sICH is defined as ICH coinciding with neurological deterioration. The incidence of sICH within 24 to 36 hours after the onset of ischaemic stroke among patients given tPA ranges from 1.7% to 6.4% [1,3–5]. The mortality rate of sICH within 3 months in the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) was 11.3%, and 45.2% of sICH patients were functionally dependent at 3 months [5].

The mechanism of post tPA ICH has been attributed to ischaemia-reperfusion injury [6]. At the onset of brain ischaemia, a cascade of events is initiated by the release of cytokines by astrocytes and endothelial cells, leading to leucocyte recruitment and activation [7]. Free radicals and proteolytic enzymes released by leukocytes in turn disrupt the blood–brain barrier, causing blood extravasation towards the brain tissue [8,9]. Further damage to the blood–brain barrier follows during reperfusion, whereby leukocyte–endothelial interaction, complement activation and reactive oxygen species cause damage to cellular proteins, DNA and the plasma membrane [10]. Restored blood flow also causes further cerebral oedema or haemorrhage [10]. tPA itself may impact haemorrhagic transformation rates by amplifying matrix

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metallopeptidase 9, increasing excitotoxicity and impacting vasoactivity [10].

Remote intracerebral haemorrhage (rICH) is defined as ICH in a brain region without visible ischaemic damage [11]. Previous studies suggested that rICH was infrequent but possibly had more severe clinical sequelae [12]. The incidence of rICH is reported to range from 1.3% to 2.8% [11,13]. However, the morbidity and mortality of rICH is unclear. Furthermore, the clinical characteristics of rICH have not been documented in an Australian population to our knowledge.

We conducted a retrospective analysis of all patients who received intravenous tPA at a single Australian stroke centre. We aimed to investigate the incidence, associated factors and clinical outcome of rICH. We hypothesised that a previous history of cerebral ischaemic events would be associated with an increased risk of rICH.

2. Methods

The data of all acute ischaemic stroke patients treated with tPA at the Royal Melbourne Hospital between January 2003 and January 2012 were retrospectively analyzed. All patients from 2003 to 2008 were treated within 3 hours after onset of stroke symptoms, and within 4.5 hours in patients treated from 2008 to 2012. Baseline patient information collected included demographics (age, sex), stroke risk factors (smoking, hypertension, hyperlipidaemia, diabetes, ischaemic heart disease, structural heart disease, atrial fibrillation, peripheral vascular disease, history of previous stroke or transient ischaemic attack [TIA]) and time interval between onset of symptoms and tPA admission. Oxfordshire Community Stroke Project (OCSP) classification was utilised for stroke type allocation [14]. Neurological assessment was performed using National Institutes of Health Stroke Scale (NIHSS) score on admission, modified Rankin Scale (mRS) score at 3 months and mortality.

Follow-up CT scans were analyzed for ICH (Fig. 1, 2). The CT scans were reviewed by one assessor (B.Y.) who received dual training in neuroradiology and neurology. ICH was assigned to one of the European Cooperative Acute Stroke Study (ECASS) groups, either haemorrhagic infarcts (HI1: small petechiae; HI2: confluent petechiae) or parenchymal haematomas (PH1: <30% of the infarcted area with mild space-occupying effect; PH2: >30% of the ischaemic area with significant mass effect), based on CT scan [15]. rICH was defined as any extra-ischaemic cerebral haematomas (multiple or single focus). rICH was subclassified into rHI1, rHI2, rPH1, and rPH2. Presence of sICH was defined according to the SITS-MOST classification, namely the presence of a local or remote PH2 type lesion on CT scan 22–36 hours after treatment combined with a neurological deterioration of 4 or more points on the NIHSS or death. Good functional outcome was defined as achieving mRS score 0–2 at 3 months.

2.1. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA) and Stata version 12IC (StataCorp, College Station, TX, USA). Continuous data were expressed as median and interquartile range (IQR). Baseline patient data and stroke risk factors were compared between rICH and local ICH groups using Pearson's chi-squared test (with Yates' correction for 2×2 tables or, in the case of small expected frequencies, Fisher's exact test) for categorical variables and the Mann–Whitney U test for continuous variables. Comparison was also conducted between rICH and non-rICH (local ICH and non-ICH) groups. Corresponding effect sizes were estimated using odds ratios (OR) and the Hodges–Lehmann median shift

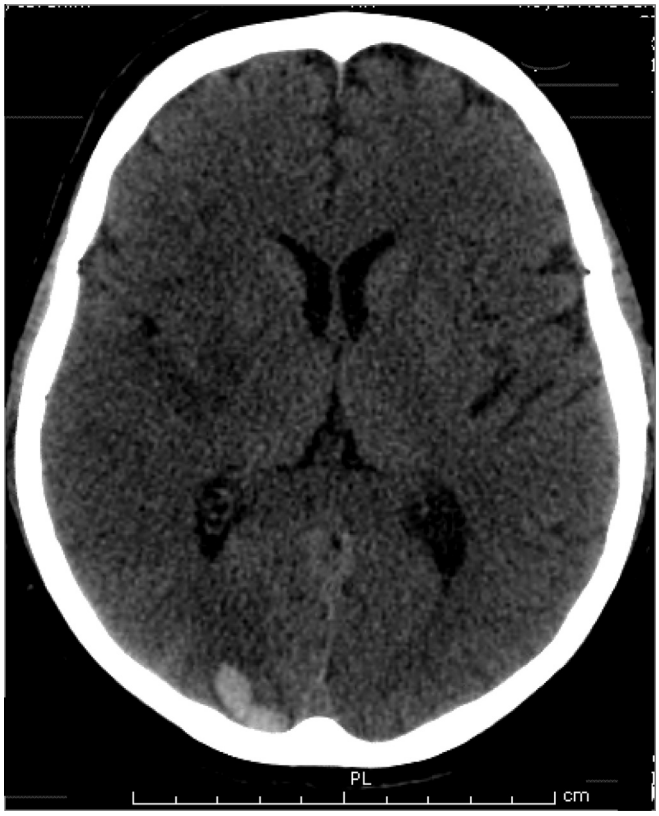

Fig. 1. Patient presented with right middle cerebral artery thrombosis and was treated with tissue plasminogen activator. This follow-up axial CT scan showed right occipital haemorrhage.

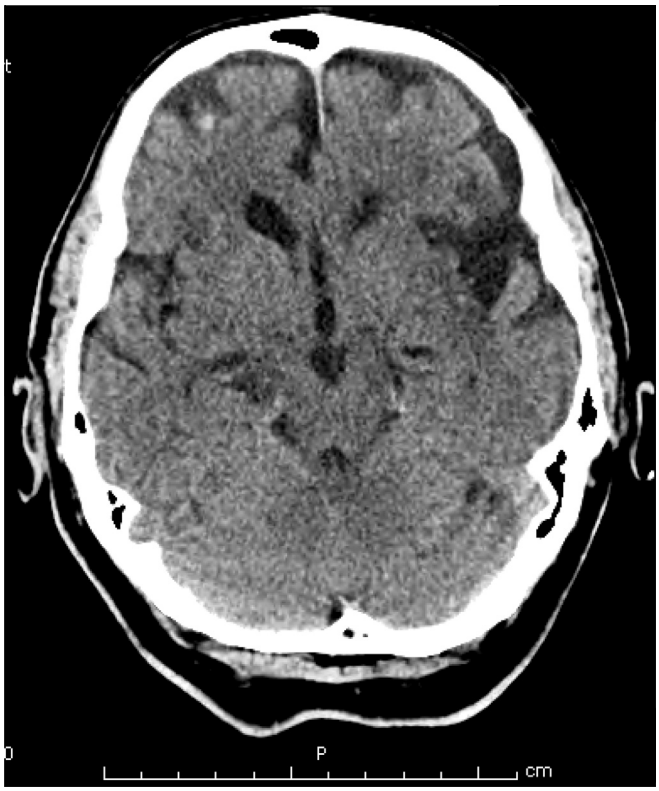

Fig. 2. Patient presented with left middle cerebral artery thrombosis and was treated with tissue plasminogen activator. This follow-up axial CT scan showed bifrontal small haemorrhages.