BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

DOI: 10.1111/1471-0528.16495
www.bjog.org

Review Article

Extending the window for thrombolysis for treatment of acute ischaemic stroke during pregnancy: a review

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Accepted 26 August 2020. Published Online 29 September 2020.

Historically, safety of intravenous recombinant tissue plasminogen activator (IV rt-PA) for the treatment of acute ischaemic stroke (AIS) is limited to use within 4.5 hours from symptom onset. Recent studies suggest the treatment window may be extended when patients have salvageable brain tissue on advanced neuroimaging. This paper describes a novel use of IV rt-PA for treatment of AIS in a pregnant patient within an extended-time window (>4.5 hours, and <9 hours) based on advanced neuroimaging with a favourable outcome.

Keywords Acute ischaemic stroke, extended window, pregnancy, rt-PA, thrombolysis.

Tweetable abstract Novel use of IV rt-PA for treatment of AIS in pregnancy within an extended-time window based on advanced imaging with a favourable outcome.

Please cite this paper as: Dinehart E, Leon Guerrero C, Pham A, Chandra S, Petersen SM, Bathgate S, Ahmadzia H. Extending the window for thrombolysis for treatment of acute ischemic stroke during pregnancy: a review. BJOG 2021;128:516–520.

Introduction

The overall incidence of stroke in pregnancy and the postpartum period is 30 per 100 000 pregnancies.[1] Acute ischaemic stroke (AIS), subdivided into arterial and cerebral venous sinus thrombosis, accounts for 19.9 cases per 100 000 pregnancies. Compared with roughly age-matched nonpregnant women where the incidence of stroke is only 10 per 100 000 patients, pregnancy conveys a substantially higher risk of stroke.[1]

Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) is a known effective treatment for AIS.[2–4] Until recently, the American Heart Association (AHA) guidelines included pregnancy as a relative exclusion criterion for IV rt-PA.[5] As a result, all clinical randomised controlled trials (RCTs) to date evaluating the use of IV rt-PA for the treatment of AIS have excluded pregnancy.

A recent study showed favourable short-term outcomes among pregnant and postpartum (<6 weeks) patients with AIS treated with reperfusion therapy (using IV rt-PA, catheter-based thrombolysis, thrombectomy or a combination), similar to nonpregnant women of reproductive age (18–44 years old).[4] However, the study showed that fewer pregnant women received IV rt-PA compared with nonpregnant women, with the primary reason listed as due to pregnancy or recent surgery.[4] Overall, outcomes and complications were similar between the two populations that received IV rt-PA monotherapy despite a trend toward more severe stroke in the pregnant and postpartum women.[4]

Historically, IV rt-PA was only administered within 4.5 hours from symptom onset.[3,6–8] Recent clinical trials suggest IV rt-PA may be given within an extended-time window beyond 4.5 hours or when timing of symptom onset is unknown up to 9 hours.[6–8] Herein, we describe a novel use of IV rt-PA for treatment of AIS in a pregnant patient within an extended-time window (>4.5 hours, and <9 hours) based on advanced neuroimaging resulting in

complete resolution of symptoms with no adverse side effects.

Case

A 35-year-old Gravida 3 Para 1011 at 28 weeks' gestation was brought to the emergency department 90 minutes after sudden onset of a bi-frontal headache followed by numbness and weakness in the left arm and leg. Her past medical history was significant for migraines with aura. Her maternal grandmother had a stroke at age 80. Medications included prenatal vitamins. Review of symptoms was otherwise negative.

On admission, vital signs were stable, blood pressure of 120/78. She was alert and oriented to person, place, time and situation. Neurological examination was notable for left lower extremity weakness and left hemi-sensory deficit with extinction. Her initial National Institute of Health Stroke Scale (NIHSS) score was 4 (2 for sensory, 1 for extinction and 1 for left lower extremity drift). Glucose was 79 mg/dl. A stroke code was activated. Given that the patient was pregnant with a history of migraines and had a borderline/low NIHSS score, the neurology team had a low suspicion for AIS and favoured the differential diagnosis of a complex migraine. Therefore, an urgent magnetic resonance imaging (MRI) of the brain with magnetic resonance angio- and venography (MRA/MRV) was ordered, as opposed to a non-contrast computed tomography (CT) imaging.

The MRI was completed outside of the traditional 4.5-hour window for IV rt-PA. Magnetic resonance diffusion-weighted imaging (MR DWI) showed a right parietal acute infarction without associated T2/Fluid Attenuated Inversion Recovery (FLAIR) hyperintensity (Figure 1). Magnetic resonance angiography (MRA) of the head and neck confirmed occlusion of a distal M2 branch of the right middle cerebral artery (MCA). Mechanical thrombectomy was initially considered and CT angiogram (CTA) of the head and neck and CT perfusion (CTP) scans were performed. Results re-demonstrated a distal right M2 occlusion and a small

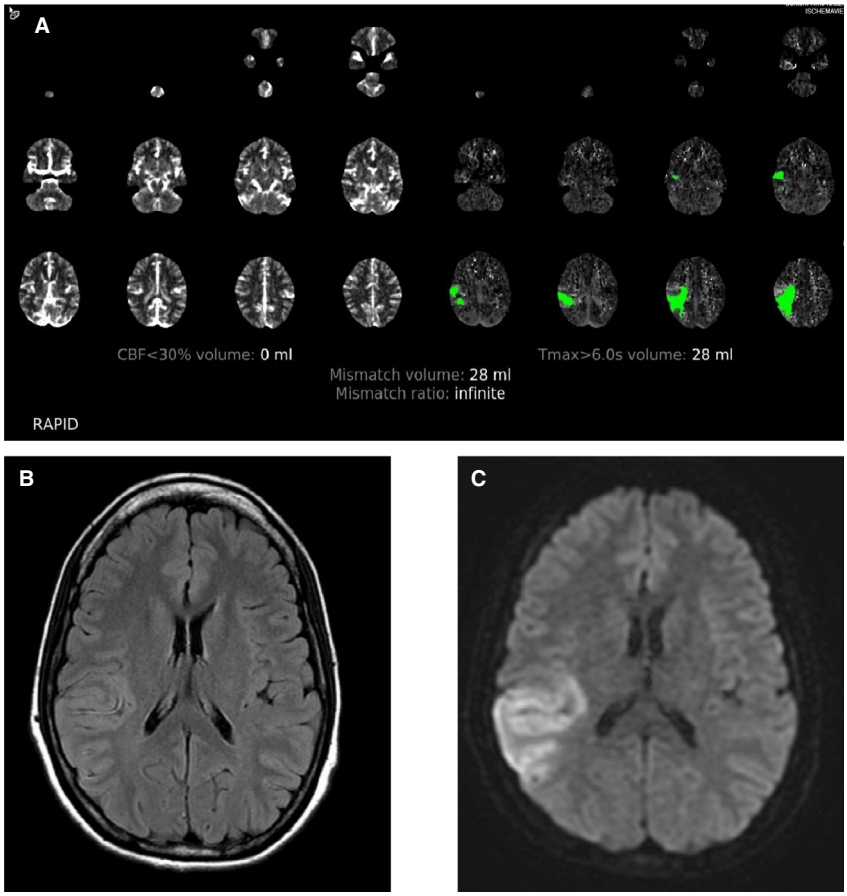

Figure 1. Patient imaging demonstrating criteria for extended window IV rt-PA. (A) Initial CTP (using RAPID software) showing perfusion deficit of 28 ml in green on the right; no core 0 ml usually represented in magenta. (B) Initial MRI showing no T2 changes on FLAIR. (C) Initial MRI showing restricted diffusion on DWI.

perfusion deficit of 28 ml and no core (Figure 1). Given the distal location of the occlusion, the patient was not deemed eligible for mechanical thrombectomy.

After a multi-disciplinary discussion between neurology, neuro-endovascular surgery and obstetrics and gynaecology, and an understanding that the imaging showed only hypoperfusion and not yet infarction of the brain tissue, the patient was deemed a candidate for extended window IV rt-PA. The patient was counselled on the risks of extended window IV rt-PA including increased risk of haemorrhagic conversion within the stroke bed and was informed that this treatment is not yet standard care. The patient agreed to proceed with thrombolysis and received IV rt-PA 0.9 mg/kg IV (10% pushed as a bolus with the remainder given over 60 minutes) 8.5 hours from onset of symptoms and was admitted to the neurology unit for monitoring. Fetal nonstress test (NST) following thrombolysis and daily until discharge was reactive.

On hospital day 1, patient noted resolution of her sensory symptoms and weakness. Repeat MRA of the head and neck showed complete recanalisation of the right M2 occlusion. Patient was started on daily low-dose aspirin 81 mg and prophylactic dosing of enoxaparin 24 hours after the loading dose of IV rt-PA. Work up for AIS subsequently found evidence of a patent foramen ovale (PFO) on trans-thoracic echocardiogram and an otherwise negative work up, including bilateral Doppler ultrasound of lower extremities and unremarkable lipid studies, haemoglobin A1c, TSH and hypercoagulable studies. She was discharged with outpatient follow up with neurology, haematology, cardiology and maternal-fetal medicine. She continued low-dose aspirin 81 mg and prophylactic dosing of enoxaparin until 24 hours prior to her induction.

The patient underwent an elective induction of labor at 39 weeks' gestation with an uncomplicated vaginal birth of a female infant weighing 3.43 kg with APGARs 8 and 9 at 1 and 5 minutes, respectively. Although she suffered from a post-dural puncture headache, she had no other neurological deficit at the time of her delivery and was successfully treated with a blood patch on postpartum day 2. She was discharged postpartum day 3 and was breastfeeding successfully. She continued prophylactic enoxaparin for 6 weeks and postpartum follow up with hematology, cardiology and maternal-fetal medicine (MFM). Patient is planning for closure of her PFO with cardiology.

Discussion

This is the first reported case of AIS with a distal large-vessel occlusion in pregnancy successfully treated with IV rt-PA monotherapy administered within an extended window of time (<9 hours) from onset of symptoms with a favourable outcome. A literature search of PubMed was performed using with the following search terms: 'IV thrombolysis', 'alteplase', 'extended window', 'pregnancy', which revealed no prior reported cases. In this case, the aetiology of the AIS was an undiagnosed PFO with an otherwise negative workup. Early suspicion and diagnosis of stroke is imperative given the limited window of therapeutic management. AIS is time-sensitive, with earlier treatment yielding better outcomes.[9]

The landmark National Institute of Neurological Disorder and Stroke (NINDS) rt-PA Stroke trial published in 1995 was the first clinical trial to demonstrate efficacy for intravenous thrombolytic therapy with rt-Pa for AIS.[10] The treatment window for IV rt-Pa was initially restricted to within 3 hours from symptom onset based on the NINDS trial protocol and later expanded to up to 4.5 hours based on the ECASS III trial published in 2008.[11] Indeed, a pooled analysis of clinical trials testing IV rt-PA along with a US registry study affirmed the time-dependence of IV rt-PA, with earlier treatment yielding better clinical outcomes.[9,12] Beyond the 4.5-hour threshold, the chances of good clinical outcome diminishes and risk of haemorrhagic transformation increases.

Despite being a guideline-recommended therapy for AIS for two decades, fewer than 10% of all AIS patients receive IV rt-PA and a quarter to a third of eligible patients with AIS fail to receive treatment.[13,14] Furthermore, gender disparities in treatment have been suggested, with women less likely to receive thrombolytic therapy despite eligibility.[15] Moreover, clinical trials with IV rt-PA have generally excluded pregnant patients.

The current literature indicates that the short-term outcomes of pregnant patients with AIS treated with reperfusion therapy may be similar to those of nonpregnant women.[4] In many cases, IV rt-PA is the treatment of choice and the recommended dose is 0.9 mg/kg intravenously based on pre-pregnancy weight or early pregnancy weight.[3] At the molecular level, all thrombolytic agents are too large to cross the placenta into fetal circulation, indicating biological evidence of safety in regard to the fetus.[3,4] While no formal study exists evaluating the teratogenic effects of these agents, no obvious teratogenic effects have been reported in the current literature.[3,4] Close monitoring after administration is required due to a small risk of obstetric bleeding and placental abruption.[3]

One reason for physician reticence to use IV rt-PA is the strict time restriction of 4.5 hours from symptoms onset. Most recently, several trials have studied intravenous thrombolysis for treatment of AIS in patients with unknown time of symptom onset based on advanced neuroimaging.[6–8] The trials were designed based on the hypothesis that advanced neuroimaging (MR DWI and/or CTP) could be used safely to select patients with limited tissue injury despite unknown time of symptom onset or

'time from last known well'.[6–8] The 2018 MR WITNESS trial was a prospective study designed to assess safety of IV rt-PA in a population of patients with unknown symptom onset or 'time of last known well'.[8] The primary outcome of interest was symptomatic intracerebral haemorrhage, of which no increased risk was found.[8] Following this trial, two RCTs were published, EXTEND and WAKE-UP. The 2019 EXTEND trial assessed intravenous thrombolysis up to 9 hours after onset of stroke symptoms.[7] The trial excluded pregnant patients. Patients were included in the trial if they were at least 18 years of age, had an initial NIHSS of 4–26 and had hypoperfused but not yet infarcted brain tissue on automated perfusion imaging, the latter indicating salvageable brain tissue. The authors showed that among patients who were treated with IV rt-PA within the extended window of 4.5–9 hours after onset of stroke symptoms, treatment resulted in a higher percentage of patients with no or minor neurological deficits compared with placebo. However, the trial showed a higher percentage of patients in the IV rt-PA group versus placebo who developed symptomatic intracerebral haemorrhage.[7] This finding was similarly reported in the 2018 WAKE-UP trial.[6] Therefore, it is important to counsel patients on the increased rate of symptomatic intracerebral hemorrhage with IV rt-PA when administered in the extended window.

In 2019, the AHA included a level IIa recommendation for administering IV rt-PA to patients who awake with stroke symptoms or have unclear time of onset >4.5 hours from last 'known well' or at baseline state, based on the recent aforementioned trials. Advanced imaging at tertiary care centres is required to assess adequately the eligibility for IV rt-PA in the extended window to determine whether patients have hypoperfused, but not yet infarcted, brain tissue on imaging indicating salvageable brain tissue.[6,7] Importantly, in the extended window, mechanical thrombectomy should be prioritised over IV rt-PA for eligible patients with proximal large-vessel occlusions.[5]

In our reported case, the initial imaging of choice was an MRI, rather than a CT scan. The medical decision making behind this decision was two-fold: (1) minimise radiation exposure risks in pregnancy and (2) our neurology consultants initially favouring the diagnosis of a complex migraine over AIS at presentation. AIS is associated with significant morbidity and mortality and standard practice requires a strict time window for treatment, with CT imaging usually being the first-line modality of choice, given a head CT is considered a 'very low-dose examination" (<0.1 mGy fetal dose) in pregnancy per American College of Obstetricians and Gynecologists (ACOG) guidelines.[16] This is a multi-disciplinary team decision that should be made jointly between neurology and obstetrics and gynecology. MRI results were delayed extending past the traditional 4.5-hour treatment window with IV rt-PA, which led to our need to use IV rt-PA within an extended window from onset of symptoms.

Conclusion

Our case describes the evaluation and management of a patient presenting with AIS who was successfully treated with IV rt-PA within the extended window resulting in complete resolution of symptoms with no adverse side effects. The decision for the appropriate type of reperfusion therapy is one that should be individualised based on a risk (bleeding and stroke severity) and benefit evaluation as well as specialist availability (neurology and neurosurgery). There is still insufficient evidence regarding the safety of IV rt-PA within the extended window in pregnancy. Therefore, further research and patient registries are needed to continue to assess outcomes in pregnant women.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

ED, SC, CLG, AP, SP, SB and HA cared for the patient and took part in the medical decision making during her initial inpatient course. HA was her primary Maternal-Fetal Medicine provider for the continuation of her pregnancy. The manuscript was conceived and designed by ED, AP, SC and HA. ED, AP and CLG performed the literature review and the writing of the report. The manuscript was drafted and revised critically by all authors. All authors gave final approval of the version to be published and contributed to the manuscript.

Details of ethics approval

We have obtained written consent from the patient.

Funding

The authors have no funding to disclose.

Acknowledgements

None. ■

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