Perfusion CT and Catheter Delivered Thrombolytics in Management of Acute Stroke

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Introduction

Stroke is an abrupt onset injury due to a vascular insult resulting in damage to brain by ischemia or hemorrhage. In recent times, perfusion computed tomography (CT) and catheter based delivery of thrombolytics have redefined the management of acute cerebral ischaemia [1]. Perfusion CT is multislice CT based imaging tool utilised for qualifying and quantifying early ischaemic brain changes by generating cerebral perfusion maps. Advances in endovascular therapy have allowed access to intracranial vasculature and intra arterial thrombolysis.

Case Particulars

A 45 year old male presented on 23 Oct 2003 at 1600 hrs with right sided hemiparesis, grade 1 power and aphasia of less than 3 hours duration. There was no evidence of brain stem symptoms or seizures. CT scan of brain performed on Siemens Sensation 4 at 1630 hrs showed no signs of hematoma or infarction. Perfusion CT was then performed in standardised sections covering anterior, middle and posterior cerebral arterial territories with 50 ml of nonionic contrast agent (Ultravist 300, Schering) administered at a flow rate of 5 ml per second via antecubital vein using a power injector.

Perfusion CT generated quantitative cerebral perfusion maps for cerebral blood flow (CBF), cerebral blood volume (CBV), and time to peak (TTP) perfusion. It revealed a decrease in CBF, a decrease in CBV, and a delay in TTP at the posterior parietal and temporo-occipital territory of left middle cerebral artery (MCA), suggestive of salvageable ischaemic cerebral parenchyma (Fig 1). A cerebral angiogram performed on 23 Oct 2003 at 1900 hrs showed a focal filling defect at left middle cerebral artery bifurcation suggesting an acute thrombus (Fig 2). A fast tracker 325 (Boston Scientific) 3 F microcatheter was passed coaxially, under fluoroscopic guidance upto the supraclinoid internal carotid artery (ICA). Superselective

catheterisation was not attempted due to vasospasm, which restricted the positioning of the catheter tip at left ICA bifurcation. 10 lakh units of urokinase was delivered over 30 minutes. The window period from onset of presentation to commencement of thrombolytic therapy was approximately 5 hours. Thrombolysis was stopped when patient had bleeding from the gums. Bleeding stopped two hours after conclusion of therapy. Patient was post-procedurally placed on 3200 units bd low molecular weight heparin (Fluxum). The sheath was removed the next morning at 0830hrs. Clinically, he had recovered power in the left upper limb (grade 2). After 48 hours, he had recovered his speech and right upper limb (RUL) power had improved to grade 4. A follow up perfusion CT was performed a week later using similar acquisition parameters, contrast amounts and flow rate which showed normal and symmetrical CBF, TTP maps with restoration of reperfusion.

Fig. 1 : Perfusion CT showing a delay in time to peak perfusion at the posterior parietal territory of left MCA, seen as a localised area of altered color. A follow up perfusion CT performed a week later using similar acquisition parameters, contrast volume and flow rate showed reperfusion with restoration of a symmetrical TTP map

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Fig. 2 : A cerebral angiogram performed at time of presentation showed a focal filling defect at left middle cerebral artery bifurcation with features suggesting an acute thrombus.

Discussion

In normal conditions, blood flow in brain is regulated by complex metabolic and cellular processes reacting to activity level of local neurons. However, this is destabilised in acute stroke, leading to a variety of cerebral perfusion disturbances. Perfusion CT is a multidetector CT application that quantitatively analyses cerebral perfusion changes by mapping CBF, CBV and TTP. The possibility of using a CT scanner to measure CBV was first discussed by Axel in 1980 [2]. The analysis is based on the “central volume principle”, which states that CBF is the ratio of the blood volume within all blood vessels in a given volume of tissue (CBV) to mean transit time (MTT) of the contrast from the arterial input to the venous drainage ($CBF/CBV=MTT$) [3].

In most cases of acute stroke, the above parameters discriminate between infarction and potentially salvageable margin of ischaemic “tissue at risk” surrounding the core of infarction. Areas of less severe CBF reduction with preserved CBV values are considered to represent “ischaemic penumbra” or tissue that is at high risk for infarction, but not yet irreversibly infarcted. The larger the ischaemic penumbra relative to the core, more likely the patient benefits from early thrombolytic therapy. The timely initiation of thrombolytics for rescuing ischaemic penumbra is key to management of brain attack [4]. If both CBV and CBF are reduced dramatically, the tissue is considered irreversibly infarcted and successful recanalisation is remote [5].

In an acute stroke setting, perfusion CT offers fast and reliable identification of stroke signature; improved choice of treatment modality, including exclusion of patients from thrombolytic therapy; pinpointing the vascular origin of ischaemic insult; and determination

of neurological consequences of the stroke, including final infarct size, clinical outcome and hemorrhagic risk. Perfusion CT technique has disadvantages of limited amount of brain imaged with restricted volume of coverage, even in the latest multidetector CT systems, high radiation dose (additional radiation dose of approximately 300 mSv), inaccuracy due to assumption on an intact blood brain barrier, which is frequently not the case in some of the ischaemic events and its inadequate role in study at rest that may need “challenge tests” with vasodilating agents like acetazolamide to determine the ability of the vascular bed to respond to a stress.

The National Institute for Neurological Disorders and Stroke (NINDS) in 1995, evaluated the effectiveness of thrombolysis in acute cerebral ischaemia by using intravenous recombinant tissue plasminogen activator (rTPA) [6]. This study which analysed results of a 3 hour and 6 hour treatment window from the time of ictus to administration of rTPA, showed no short-term benefits, but improved functional status at 3 months, with 30% increased likelihood of no or minimal disability at 3 months post ictus as compared to placebo. The contraindications for thrombolysis are mentioned in Table 1.

Thrombolysis in stroke is essentially performed with either intravenous thrombolysis (IVT) or local intraarterial thrombolysis (LIT). LIT requires neurointerventional skills integrated with a digital subtraction angiography Unit. The “Prolyse in acute cerebral thromboembolism trial” (PROACT II) analysed data on 180 patients with stroke of upto 6 hours duration and angiographically proved middle cerebral artery

Table 1

Contraindications to thrombolysis

Check list of important contraindications

- History of intracranial hemorrhage
- Symptoms suggestive of subarachnoid hemorrhage
- Another stroke or serious head trauma within the preceeding 3 months
- Rapidly improving or minor neurological deficit
- Systolic blood pressure above 185 mmHg or diastolic blood pressure above 110 mmHg
- Seizure at the onset of stroke
- Major surgery within 14 days, gastrointestinal hemorrhage or urinary tract hemorrhage within the previous 21 days
- Arterial puncture at a noncompressible site within the previous 7 days
- Anticoagulants or heparin administration within the 48 hours preceding the onset of stroke and elevated partial-thromboplastin time
- Prothrombin times greater than 15 seconds (INR > 1.7)
- Platelet counts below 100,00 per cubic millimeter
- Glucose concentrations below 50 mg per deciliter (2.7 mmol per liter) or above 400 mg per deciliter (22.2 mmol per liter)

(MCA) occlusion randomised to receive either LIT with ProUrokinase (ProUK) or placebo by intrarterial route. Higher recanalisation rates (66% vs 18%), low disability scores in more patients (40% vs 25%), lower mortality (25% vs 27%) and an increased rate of symptomatic cerebral haemorrhage with neurological deterioration (10% vs 2%) were seen in the Pro UK group as compared to control [7,8], clearly demonstrating the efficacy of LIT. No trials have compared LIT with IVT directly, but PROACT II had a lower rate of symptomatic intracranial haemorrhage as compared to NINDS trial at 6 hours (10% vs 12%), LIT tends to be efficacious at lower doses as compared to IVT, as seen in the case reported where only 10 lakh units of urokinase produced a dramatic recovery. Experimental evidence from animal experiments in a canine model show that intra arterial (IA) thrombolysis uses 100 times lower dose of lytic agents as compared to IVT and achieve similar levels of lysis [9]. This suggests that systemic effects of lysis, resulting in haemorrhage, are less likely with the IA route of administration. LIT also offers the possibility of immediate treatment of critical stenotic lesions, mechanical clot disruption and extraction with simple snares or aspirating devices. Angiography allows analysis of the pattern of vascular compromise and collateral supply that has direct impact on the feasibility of thrombolysis even after the usual window period of 6 hours in some cases, particularly in the posterior circulation [10]. Intracerebral haemorrhage (ICH) was shown to be related to dose of anticoagulants and lower doses reduced its incidence. Predictors of ICH included high national institute of health stroke score (NIHSS), cerebral oedema and mass effect on CT scans [6].

Thrombolytic agents currently available for clinical use are Urokinase (UK) and rTPA, and variants thereof, which act by delivering plasmin to the fibrin containing thrombus thereby achieving rapid proteolytic dissolution of a clot. They differ in their pharmacology and fibrin specificity. The relative merits of rTPA and UK for thrombolysis may be debated, however, there is no clinical advantage that has been shown for rTPA as compared to UK.

To conclude, extremely rewarding results can be achieved by a combined use of perfusion CT and intra-

arterial thrombolytic therapy in acute stroke, which requires accurate patient selection for thrombolysis while bringing about timely revascularisation of salvageable brain tissue.

Conflicts of Interest

None identified

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