Role of CT Perfusion in Identifying the Core and the Potentially Salvageable Penumbra in Patients with Acute Non-Haemorrhagic Stroke - Experience at Tertiary Care Center

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Abstract

Objectives: To evaluate the role of CT Perfusion in identifying the core and the potentially salvageable penumbra in brain infarcts by observing perfusion maps (CBV, CBF and MTT). Also to identify patients who would benefit from reperfusion therapy and to evaluate the feasibility of identifying the penumbra on non-contrast CT vide comparison with perfusion maps.

Materials and Methods: A prospective study of 50 patients who presented with acute onset neurological deficit within 6 hours of symptom onset and in whom initial NCCT revealed no evidence of cerebral hemorrhage; evaluated with CT Perfusion was done at tertiary care center in 1 calender year 2014.

Observations: In our study, about 68 percent of patients presented within 6 hours of stroke had salvageable penumbra, were eligible for revascularization therapy. HU less than 25 on NECT significantly correlated with infract core but not with presence of Penumbra. Presence of penumbra cannot be predicted from NECT ASPECT and CBV ASPECT Score.

Results and Conclusion: CT Perfusions study being easily available, faster and cost effective modality to identify patients of acute ischemic strokes having salvageable penumbra for which further can be subjected to revascularization therapy. It is strongly recommended that CT Perfusion should be made an integral part of acute non-haemorrhagic stroke management protocol, wherever the facility is available.

Introduction

Acute ischemic stroke being one of the major non communicable disease in India leading to death and disability. If patients within golden period are identified with salvagable brain tissue, can be treated with revascularization by means if IV thrombolysis or mechanical thrombectomy. CT Perfusions study being easily available, faster and cost effective modality to identify patients of acute ischemic strokes having salvageable penumbra.

Review of literature

Stroke is an acute onset neurological deficit characterized by motor and/or sensory loss caused due to acute vessel occlusion or haemorrhage in the brain parenchyma. Stroke is broadly classified into two categories Haemorrhagic and non-haemorrhagic (Ischaemic).

According to the World Health Organization, 15 million people suffer stroke worldwide each year. Of these, 5 million die and another 5 million are permanently disabled. Developing countries like India are facing a double burden of communicable and non-communicable diseases. Stroke is one of the leading causes of death and disability in India. The poor are increasingly affected by stroke, because of both the changing population exposures to risk factors and, most tragically, not being able to afford the high cost for stroke care. According to the India stroke factsheet updated in 2012, the estimated age-adjusted prevalence rate for stroke ranges between 84/100,000 and 262/100,000 in rural and between 334/100,000 and 424/100,000 in urban areas.

The central goal of therapy in acute ischemic stroke is to preserve tissue in the ischemic penumbra. An infarct typically has a dense ischaemic core, which is irreversibly damaged and non-salvageable. In early stages, the core infarct is surrounded by a less ischaemic potentially salvageable penumbra if the blood supply is restored. Tissue in this penumbra can be preserved by restoring blood flow to the compromised area and optimizing collateral flow. Recanalization strategies, including the administration of intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) and intra-arterial approaches, attempt to establish revascularization so that cells in the penumbra can be rescued before irreversible injury occurs. Restoring blood flow can mitigate the effects of ischemia only if performed quickly.

In addition to limiting the duration of ischemia, an alternative strategy is to limit the severity of ischemic injury. Neuroprotective strategies are intended to preserve the penumbral tissues and to extend the time window for revascularization techniques. At the present time, however, no neuroprotective agents have been shown to impact clinical outcomes in ischemic stroke.

While stroke is essentially a clinical diagnosis, earlier the main role of neuroimaging in the setting of acute stroke was the differentiation of non-haemorrhagic stroke from haemorrhagic stroke, the management of which were drastically different in context of

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thrombolytic therapy. With advances in CT and MRI technologies, role of neuroimaging has been expanded in the clinical management of acute stroke to identifying stroke etiology and potentially salvageable penumbra earliest. Potentially salvageable penumbra is being more accurately identified on CT perfusion and MR perfusion studies.

**Modalities of penumbra imaging of brain**

Emergent brain imaging is essential for evaluation of acute ischemic stroke. Noncontrast computed tomography (CT) scanning is the most commonly used form of neuroimaging in the acute evaluation of patients with apparent acute stroke. The following neuroimaging techniques may also be used for penumbra assessment:

- CT perfusion scanning
- MRI perfusion scanning
- Diffusion weighted imaging; FLAIR-DWI mismatch; DWI-perfusion mismatch.

Unenhanced CT is widely available, can be performed quickly, and does not involve the administration of intravenous contrast material. Early-stage acute ischemia can show features such as the hyperdense vessel sign, the insular ribbon sign, and obscuration of the lentiform nucleus.

CT perfusion having certain advantages over MRI perfusion in the form of being faster, with widespread availability, cost effective, being less sensitive to patient motion and no risk to the patient with implantable medical devices, such as cardiac pacemakers, ferromagnetic vascular clips, cochlear implants and nerve stimulators. During CT perfusion, a rapid intravenous infusion of contrast is administered and sections of the brain are repeatedly imaged. Based on the total amount and speed that blood flows to different vascular territories of the brain this technique can assist in identifying a stroke and potential areas of reversible and salvageable brain tissue in the ischemic penumbra.³

The cerebral blood flow (CBF) is equal to the cerebral blood volume (CBV) divided by the mean transit time (MTT). The MTT is the time difference between the arterial inflow and venous outflow.³⁵ **MTT is the most sensitive measure used to evaluate for flow abnormalities.** It is prolonged in conditions such as hypotension along with occluded and stenotic blood vessels. The area of the brain undergoing infarction has both decreased CBF and CBV. Decreased total CBV is the most specific indicator for an area actually undergoing irreversible ischemia or infarct and is non-salvageable. Areas of the brain that are at risk for injury known as the ischemic penumbra show decreased CBF with normal to increased CBV; CBF-CBV mismatch. This potentially salvageable area of the brain must have an intact cerebral auto-regulation system to maintain homeostasis. Cerebral auto-regulation causes the dilation of the collateral blood vessels and increases the CBV to the areas of the brain that are compromised by decreased CBF.

CT perfusion imaging can identify the penumbra, and it has been used in case reports and studies to guide the treatment of patients in which there is an unknown time of stroke onset, awakening stroke or when the patient cannot communicate the time of onset due to aphasia. These patients may still benefit by intravenous, intra-arterial or mechanical reperfusion. The software package that is used for CT perfusion analyses the images obtained and colour coded maps representing many levels of the brain are produced to help differentiate the potential cause of the flow abnormalities.

**Alberta stroke program early CT score (ASPECTS):** In a patient with acute onset ischemic stroke who presents within the golden period for thrombolysis (3 hours from symptom onset in case of intravenous thrombolysis and 6 hours from symptom onset in case of intra-arterial thrombolysis), **the main issue in deciding management from the clinician’s perspective is whether attempted thrombolysis will have significant impact.** The decision to thrombolysis depends on whether more or less than one third of the territory of the middle cerebral artery (MCA) was involved. If more than third of the territory is involved, the prognosis is poor. There is also a significant risk of haemorrhage in the infarct.⁶⁻¹⁰

The Alberta stroke program early CT score (ASPECTS) was developed to offer the reliability and utility of a standard CT examination with a reproducible grading system to assess early ischemic changes (<3 hours from symptom onset) on pre-treatment CT studies in patients with acute ischemic stroke of the anterior circulation.¹¹ This CT score is simple and reliable and identifies stroke patients unlikely to make an independent recovery despite thrombolytic treatment.

ASPECTS is determined from evaluation of two standardized regions of the MCA territory: the ganglionic and supra-ganglionic levels. Ganglionic level where the caudate, lentiform, internal capsule and insular ribbon each carrying one point. Also cerebral cortices (anterior, lateral and posterior) at ganglionic and supraganglionic levels each carrying one point. All cuts with basal ganglionic or supraganglionic structures visible are required to determine if an area is involved. To compute the ASPECTS, 1 point is subtracted from 10 for any evidence of early ischemic change for each of the defined regions. ASPECTS is ranson from 10 where normal CT scan to 0 indicating diffuse involvement throughout MCA territory.

Large numbers of studies have been done in imaging of penumbra by imaging. In various studies shown that while absolute numerical parameters of CT perfusion maps vary according to individual variability, and reconstruction algorithm employed, qualitative perfusion maps are still a valuable tool to detect early ischemia and identify salvageable brain tissue by comparing with the contralateral hemisphere.

A prospective study of 50 patients who presented with acute onset neurological deficit within 6 hours of symptom onset and in whom initial NCCT revealed no evidence of cerebral hemorrhage; evaluated with CT Perfusion was done in our department in 1 calender year 2014. Institutional ethics committee clearance and approval was obtained and patients were selected via convenient consecutive sampling (non-probability sampling). Written informed consent was obtained from the subjects for inclusion of their images in the study, with the standard disclosures.

**Aims and Objectives**

- To evaluate the role of CT Perfusion in Identifying the core and the potentially salvageable penumbral
placement of a wide bore i.v. cannula, patient was taken for CT scan. Initially, a non-contrast scan was taken covering the entire brain. The non-contrast scan served to rule out any evidence of parenchymal haemorrhage. Signs of an acute infarct like parenchymal hypodensity, hyperdense vessel sign, sulcal effacement, obscuration of lentiform nucleus and insular ribbon sign were also searched for. In patients having findings suggestive of acute infarct, the perfusion scan was planned covering the area of interest. In patients in whom the non-contrast scan was normal, perfusion scan was planned covering the ganglio-capsular region and corona radiata corresponding to the side of neurodeficit.

PHILIPS CT scanners have two protocols for performing CT Perfusion.

- **Non-Jog scans**: In which the table remains stationary. These are performed using infusion of 40–50 mL iv contrast, followed by 20–40 mL saline.

- **Jog scans**: In which the table moves back and forth between two positions. These are performed using infusion of 70 mL contrast, followed by 45 mL saline.

Exclusion Criteria

- **Initial non-contrast CT Brain revealing intracranial haemorrhage**;
- **Patients not consenting for the study**;
- **Patients with deranged renal function (Serum creatinine >1.4 mg/dl)**;
- **Pregnancy**;
- **Known h/o allergy to intravenous contrast material**;
- **Haemodynamically unstable patients**;
- **Paediatric patients**.

Study Protocol

No specific pre-procedure preparations were employed. After placement of a wide bore i.v. cannula, patient was taken for CT scan. Initially, a non-contrast scan was taken covering the entire brain. The non-contrast scan served to rule out any evidence of parenchymal haemorrhage. Signs of an acute infarct like parenchymal hypodensity, hyperdense vessel sign, sulcal effacement, obscuration of lentiform nucleus and insular ribbon sign were also searched for. In patients having findings suggestive of acute infarct, the perfusion scan was planned covering the area of interest. In patients in whom the non-contrast scan was normal, perfusion scan was planned covering the ganglio-capsular region and corona radiata corresponding to the side of neurodeficit.

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In our study, the cerebral perfusion scans were performed using the Non-Jog Protocol using infusion of 50 ml of iv contrast @ 4 ml/sec followed by 40 ml saline @ 2.5ml/sec by using an automated dual power injector. The iv contrast medium used was non-ionic iso-osmolar iodinated contrast material (Iohexol, Omnipaque 300 mg I/ml; GE healthcare). As per the protocol in our institution, a 2 minutes delayed scan was performed covering the entire brain.

**Observations and Results**

Out of the study population of 50 patients presenting with clinical features of acute onset ischaemic stroke, 28 patients (56.0% of the cases) were male and 22 patients (44.0% of the cases) were female. The mean age of our study group was 66.02 years.

In the study population, the most common presenting symptom was combined weakness of upper limb and lower limb, present in 39 patients (78.0% of cases), followed by slurring of speech, which was present in 36 patients (72.0% of cases). The least common symptom was dizziness and imbalance, present in only 3 patients (6.0% of cases).

Majority of the patients (68.0% of the cases) presented within 2 – 4 hours of symptom onset, followed by 30.0% of the cases who presented within 5 – 6 hours of symptom onset while only 2% cases presented within 2 hours.

History of any previous episode of focal neurodeficit indicates increased risk of a second episode. In the study population, 64.0% of the patients had no history of previous similar episode while 32.0% had multiple (>1) episodes of focal neurodeficit.

A patient suffering an episode of acute neurodeficit may either recover completely within 24 hours of symptom onset (as seen in patients with TIA) or recover gradually over a prolonged period of time. This recovery is often partial. In the study population, 33.3% of the cases who suffered similar episode in the past had complete recovery with 24 hours, while 66.7% had gradual partial recovery.

Diabetes Mellitus and Hypertension are both considered independent risk factors for cerebrovascular ischemic episodes. In the study population, majority of the patients (46%) had neither of these two diseases followed by 12 patients (24%) who suffered from hypertension but not diabetes. 9 patients (18%) of the study population suffered from both diabetes and hypertension.

1. **History of any previous similar episode:** In the study population, 32 patients (64.0% of the patients) had no history of previous similar episode while 8 patients (16.0%) had multiple (>1) episodes of focal neurodeficit.

2. **Clinical profile of symptoms:** In our study, the most common presenting symptom was combined weakness of upper limb and lower limb, present in 39 patients (78.0% of cases), followed by slurring of speech, which was present in 36 patients (72.0% of cases). The least common symptom was dizziness and imbalance, present in only 3 patients (6.0% of cases).

3. **Neurological presentation:** In the study population, the most common presenting symptom was combined weakness of upper limb and lower limb, present in 39 patients (78.0% of cases), followed by slurring of speech, which was present in 36 patients (72.0% of cases). The least common symptom was dizziness and imbalance, present in only 3 patients (6.0% of cases).

4. **Risk factors:** Diabetes Mellitus and Hypertension are both considered independent risk factors for cerebrovascular ischemic episodes. In the study population, majority of the patients (46%) had neither of these two diseases followed by 12 patients (24%) who suffered from hypertension but not diabetes. 9 patients (18%) of the study population suffered from both diabetes and hypertension.

5. **Statistical Associations and Correlations between various parameters:**
   - As per the above data, using Chi square test, there is a significant statistical association between HU on NECT and presence of Core Infarct (Tables 4, 6).
   - As per the above data, using Chi square test, there is no significant statistical association between HU on NECT and presence of Penumbra (Tables 3, 7).
   - As per the above data, using Chi square test, there is no significant statistical association between CBV ASPECT Score and presence of Penumbra (Table 8).
   - As per the above data, using Chi square test, there is no significant statistical association between CBV ASPECT Score and Penumbra (Table 9).
   - As per the above data, using Student t test, there is no significant statistical association between NECT ASPECT Score and CBV ASPECT Score (Table 10).
   - As per the above analysis, 38.3% of the cases were suitable for Thrombolysis on the basis of NECT ASPECTS which was significantly more as compared to 30.0% of the cases on the basis of CBV aspects.

6. **Suitability for Thrombolysis on the Basis of NECT and CBV Maps**

   This analysis states that 66.0% of the cases were suitable for Thrombolysis on the basis of NECT ASPECTS which was significantly more as compared to 38.3% of the cases on the basis of CBV aspects.

7. **Prognostic factors:** In the study population, the most common presenting symptom was combined weakness of upper limb and lower limb, present in 39 patients (78.0% of cases), followed by slurring of speech, which was present in 36 patients (72.0% of cases). The least common symptom was dizziness and imbalance, present in only 3 patients (6.0% of cases).

8. **Outcome:** In the study population, the most common presenting symptom was combined weakness of upper limb and lower limb, present in 39 patients (78.0% of cases), followed by slurring of speech, which was present in 36 patients (72.0% of cases). The least common symptom was dizziness and imbalance, present in only 3 patients (6.0% of cases).

9. **Statistical Analysis:** As per the above data, using Chi square test, there is no significant statistical association between HU on NECT and presence of Core Infarct (Tables 4, 6).

   - As per the above data, using Chi square test, there is no significant statistical association between HU on NECT and presence of Penumbra (Tables 3, 7).
   - As per the above data, using Chi square test, there is no significant statistical association between CBV ASPECT Score and presence of Penumbra (Table 8).
   - As per the above data, using Chi square test, there is no significant statistical association between CBV ASPECT Score and Penumbra (Table 9).
   - As per the above data, using Student t test, there is no significant statistical association between NECT ASPECT Score and CBV ASPECT Score (Table 10).

   As per the above analysis, 38.3% of the cases were suitable for Thrombolysis on the basis of NECT ASPECTS which was significantly more as compared to 30.0% of the cases on the basis of CBV ASPECTS (Tables 5, 11).

**Discussion**

The results were correlated with various studies done on role of CT Perfusion in evaluation of patients with acute non-haemorrhagic stroke.

1. **Age Distribution:** Age is the single most important risk factor for stroke. For each successive 10 years after age 55, the stroke rate more than doubles in both men and women. In our study of 50 adult patients presenting with acute onset neurodeficit, the mean age of the study patients was 66.02 years and age group ranging from 40 to 85 years.

   In a study done by A.R.Jain et al with a study group of 83 patients, the median age was 76 years. In a study done by J. Hopyan et al with a study group of 191 patients, the mean age was 67 years with a standard deviation of 16.

2. **Gender Distribution:** In our study of 50 adult patients, 28 patients (56%) were male while 22 patients (44%) were female. In the study done by A.R.Jain et al with a study group of 83 patients, 44.6% patients were female while 55.4% patients were male. In a study done by J. Hopyan et al with a study group of 191 patients, 45.1% were female while 54.9% were male.

3. **Profile of symptoms:** In our study, the most common presenting symptom was combined weakness of upper limb and lower limb, present in 39 patients (78.0% of cases), followed by slurring of speech, which was present in 36 patients (72.0% of cases). These symptoms are consistent with anterior circulation ischemia. Only 3 patients (6.0% of cases) presented with isolated weakness of either upper or lower limb. These symptoms are consistent with anterior circulation ischemia. Only 3 patients (6.0% of cases) presented with isolated weakness of either upper or lower limb. These symptoms are consistent with anterior circulation ischemia. Only 3 patients (6.0% of cases) presented with isolated weakness of either upper or lower limb.

4. **History of any previous similar episode:** In the study population, 32 patients (64.0% of the patients) had no history of previous similar episode while 8 patients (16.0%) had multiple (>1) episodes of focal neurodeficit. 9 patients (18%) of the study population suffered from both diabetes and hypertension.

   In the study done by Hana T. et al with a study group of 87 patients, 73 patients (83.9%) had anterior circulation infarcts while 14 patients (16.1%) had posterior circulation infarcts.

   In the study done by A.R.Jain et al with a study group of 83 patients, 29
patients (34.9% of cases) had previous history of stroke / TIA.

5. **Pre-existing Systemic Diseases:**
Diabetes mellitus and hypertension are both considered independent risk factors for ischaemic stroke. Hypertension is the single most important modifiable risk factor for ischemic stroke. A summary of seven studies assigning a relative risk of 1 for borderline or mild hypertension determined the relative risk to be about 0.5 at a blood pressure of 136/84 mm Hg and about 0.35 at a blood pressure of 123/76 mm Hg.\textsuperscript{17} Case-control studies of stroke patients and prospective epidemiological studies have confirmed an independent effect of diabetes with a relative risk of ischemic stroke in persons with diabetes from 1.8 to 3.0.\textsuperscript{18}

6. **NECT findings in study population:** In our study population, a total of 39 patients (78%) had findings related to acute ischemia while 11 patients (22%) had no CT detectable evidence of acute cerebral ischemia (Table 1).

The sensitivity of standard noncontract CT for brain ischemia increases after 24 hours. However,
in a systematic review performed by Wardlaw et al in 2005 involving 15 studies where CT scans were performed within six hours of stroke onset, the prevalence of early CT signs of brain infarction was 61% (standard deviation ± 21%).

7. Distribution of HU of the Penumbra and core infarct: To the best of our knowledge, there is no significant literature available pertaining to distribution of HU values of the penumbral and HU values of the Core Infarct (Tables 3, 4).

8. Suitability for Thrombolysis on the Basis of NECT and CBV Maps: According to standard ASPECTS criteria, a patient is considered suitable for thrombolysis if NECT ASPECT Score is ≥ 7 or CBV ASPECT Score is ≥ 8. Even in presence of identifiable penumbral, NECT ASPECT Score of <7 or CBV ASPECT Score of <8 is predictive of poor outcome after thrombolysis.

In our study, 47 patients presented with clinical or imaging features of anterior circulation ischemia, for which ASPECTS was applicable. In NECT, 31 patients (66%) had ASPECT Score of ≥ 7 while on CT Perfusion, 18 patients (38.3%) had ASPECT Score of ≥ 8 (Table 5).

Cerebral blood volume ASPECTS sensitivity, specificity, positive predictive value, and negative predictive value for clinical outcome were 60%, 100%, 100%, and 45%, respectively. Hence, only this 18 patients were considered suitable for thrombolysis.

3 patients presented with clinical or imaging features of posterior circulation ischemia, out of whom 2 had presence of identifiable penumbral. These 2 patients were considered suitable for thrombolysis. To the best of our knowledge, there is no significant literature available pertaining to predicting the outcome of thrombolysis in posterior circulation stroke according to extent of involvement.

Conclusion
CT Perfusion plays a pivotal role in the management of acute non-haemorrhagic stroke by identifying patients who still have a salvageable penumbra and are likely to benefit significantly from thrombolysis.

The salvageable penumbra cannot be detected on NECT. Only Perfusion CT or Perfusion MRI is suitable for identifying the penumbra. Considering the time consuming nature of MRI, CT Perfusion has the potential to revolutionize the management of acute stroke patients.

About 68 percent of patients presented within 6 hours of stroke had salvageable penumbra, were eligible for revascularization therapy.

Thus, CT Perfusion has tremendous potential to improve the management of acute non-haemorrhagic stroke by early and accurate detection of the penumbra and extent of involvement. Hence, it is strongly recommended that CT Perfusion should be made an integral part of acute non-haemorrhagic stroke management protocol, wherever the facility is available.

References
4. By Student t test; P = 0.181, Not Significant