Original Research Paper

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"ASSESSMENT OF SEVERITY AND EXTENT OF CEREBRAL ISCHEMIA BY COMPUTED TOMOGRAPHY (CT) PERFUSION STUDY"

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ABSTRACT **Background:** Acute ischemic stroke(AIS) is a leading cause of morbidity and mortality worldwide. This study aims at assessing the extent and severity of the cerebral ischemia by CT perfusion study in AIS patients in a tertiary care hospital, north east India. **Results:** Among total of 67 patients, majority(67.2%) presented late (> 6 hrs) ,with moderate severity NIHSS score (mean 10.84). Significant negative correlation noted between NECT ASPECTS and core infarct volume (Spearman's Rho- 0.85) and between CTP ASPECTS and infarct core volume as well (Rho -0.84). An NIHSS score of ≥16 is strongly associated with a large core volume (> 70 mL) infarct (Youden index 0.7692,Sensitivity 76.92,specificity 100). Mean volume of penumbra (absolute mismatch volume) was high (51.5±8.1 mL) in early stroke(< 6 hrs) as compared to late (41.2±23.4mL). In early (91.66%) and even late group patients(53.33%) majority had target mismatch. 60% of the patients with Wake Up Stroke(WUS) , had target mismatch pattern, suggesting CTP can predict the salvageable penumbra even in WUS patients. An NECT ASPECTS score of 6 or more is strongly associated with target mismatch group (Youden index 0.5485,Sensitivity 91.89,specificity 62.96) and a score of ≤6 is strongly associated with large core volume infarcts (Youden index 0.7662,Sensitivity 92.31,specificity 84.31). **Conclusions:** CT perfusion is effective modality to detect acute ischemic changes in stroke .It helps to categorize the patients into target mismatch group who are benefited ,and large core volume infarct group who are unlikely to be benefited ,by the reperfusion therapy. A good proportion of stroke patients presenting late or with WUS, had a target mismatch pattern, whose ischemic penumbra could be salvaged by the therapy.

KEYWORDS : CT perfusion, Acute ischemic stroke, ASPECTS, Ischemic penumbra, Target mismatch

BACKGROUND

Stroke is a heterogenous syndrome caused by multiple disease mechanisms, all of which result in abrupt disruption of normal cerebral blood flow, causing derangements of cerebral function. It is the second leading cause of death and the third leading cause of disability in the world(1,2). Stroke can be broadly classified into two classes :ischemic and haemorrhagic. The former accounts for an estimated 80-85% of cases; the rest are haemorrhagic(3).Atherosclerosis of the carotid arteries is the most common predisposing condition for stroke. 87% of the stroke risk could be attributed to modifiable risk factors such as hypertension, obesity, hyperglycemia, hyperlipidemia, and renal dysfunction, and 47% to behavioral risk factors such as smoking, sedentary lifestyle, and unhealthy diet.(4)

Normally, there is continuous perfusion of brain during systole and diastole, with 15-20% of the cardiac output going to the brain. This continuous and high blood flow is important as the brain uses glucose exclusively for energy metabolism and is unable to store energy. Cerebral blood flow has an autoregulatory mechanism, which is multifactorial involving, neurogenic, myogenic, and metabolic controls. This tries to maintain a mean arterial pressure of 60-100 mm Hg and a cerebral blood flow of 50-60 ml/100 gm of brain per minute. When there is a reduction in cerebral blood flow, the autoregulatory mechanism attempts to compensate by increasing the blood pressure and inducing vasodilatation. However, if the blood flow reduction falls below a critical level, infarction or tissue death results.(5).

Non-enhanced computed tomography (NECT) is widely used in acute stroke imaging due to its rapid performance, high tolerance, and high reliability(6). In stroke, NECT is used to exclude acute hemorrhage and for detection of large areas of clearly infarcted tissue (7). However, it is difficult to detect early infarct signs by NECT. The limited overall sensitivity for NECT to detect acute ischaemia in the first hours after stroke onset has led to the use of alternative or complementary imaging modalities to provide additional information (8). CT perfusion (CTP) is performed for physiological evaluation of the cerebral parenchyma, which allows better detection of ischemia. In acute ischemic stroke, CTP imaging of brain may increase diagnostic accuracy, aid treatment target identification, and provide prognostic information about functional or clinical outcome(9). Moreover, perfusion imaging can identify patients who benefit from reperfusion beyond the conventional time window or in whom time of symptom onset is unknown(10). Cerebral artery occlusion results in irreversible death of a component of cerebral tissue, which is referred to as the core infarction. There is an additional component of brain tissue that is ischemic, but viable, which is referred to as the penumbra(11).Although both the ischemic core and penumbra are dysfunctional, the penumbra is viable upon restoration of blood flow(12). In the absence of reperfusion, the penumbra will eventually grow into the ischemic core. CTP technique may be used to determine volume of core infarction and of the penumbra(11).CTP study measures perfusion parameters, namely cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP). Regions of brain with severely reduced CBV or CBF correspond to the region of core infarction. Regions of brain with prolongation of the MTT or TTP, have been shown to accurately measure the penumbra in patients with acute ischemic stroke(13). Studies have shown good agreement of CTP findings with DWI and MR perfusion(14).This study aims to assess extent and severity of ischemia in stroke with differentiation of salvageable ischemic penumbra from unsalvageable infarct core, thus to help the clinician in planning the appropriate management .The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is widely used in clinical practice to assess the extent of early ischemic changes on brain imaging for acute stroke treatment.

ASPECTS is a 10-point scoring system with anatomical regions distributed over the MCA territory. An ASPECTS score ≤ 7 equates to more than one-third of the MCA territory and is associated with increased risk of hemorrhage and poor outcome(15). During CTP, as iodinated contrast passes through the brain, it causes transient hyperattenuation that is directly proportional to the amount of contrast in the vessels and blood in the brain. CBV is defined as the volume of flowing blood in a given volume of brain. CBF is the volume of flowing blood moving through a given volume of brain in a specified amount of time. MTT is the average time it takes blood to transit through a given volume of brain. All three CTP parameters can be depicted either visually—on a color scale—or numerically, using selected regions of interest. In normal brain, there is bilaterally symmetric perfusion in the cerebral hemispheres with higher CBF and CBV in gray matter (cortex, basal ganglia) compared with white matter. Well-perfused gray matter appears red/yellow, white matter appears blue, and ischemic brain is blue/purple. Brain with normal MTT appears blue and slower the transit time, the closer to the red end of the scale(15).

The infarct core shows matched reduction in both CBV and CBF. An ischemic penumbra is seen as a "mismatch" between markedly reduced CBV in the infarcted core and a surrounding area (penumbra) characterized by decreased CBF with normal or even transiently increased CBV. Prolonged MTT over 145% that extends beyond the core infarct area (so-called CBV/MTT mismatch) also characterizes the ischemic penumbra(15). The National Institutes of Health Stroke Scale (NIHSS) is the most widely used deficit rating scale in modern neurology(16).

METHODS

It is a hospital based cross sectional study conducted in a tertiary care centre (Gauhati Medical College, Guwahati, Assam). Purposive sampling was done and included 67 consecutive patients attending emergency department who are suspected to have acute stroke. Patients who are diagnosed to have intracerebral hemorrhage , those who had previous allergic reactions to contrast agents, whose renal function tests are deranged, pregnant patients ,uncooperative and unstable patients were excluded from the study. Demographic details , onset to door time, risk factors assessment, baseline NIHSS score are documented. Based on onset to door time, patients are classified into early (<6 hrs), late(> 6 hrs) and wake up stroke. Patients underwent NCCT scan of brain to identify hemisphere affected, to rule out hemorrhagic stroke, to look for early ischemic changes and to calculate NCCT ASPECTS. In case of posterior circulation stroke pc ASPECTS score is used. All examinations were performed using 256-slice detector CT (Philips Brilliance iCT, Philips Healthcare). Acquisition parameters were used: 80 kV, 120 mAs, collimation 64×1.25). A dual-head power injector (Sino Power -D) was used to inject 40 mL of a non-ionic contrast medium (Iohexol injections USP, Omnipaque 350 mg/mL, GE health care) at a rate of 4-5 mL/s, followed by a 50-mL saline flush at a rate of 7 mL/s. In all cases, 18 G IV access, usually located in the cubital vein, was used for injection. The CT perfusion was started simultaneously with the contrast material injection. Data acquisition involves continuous cine imaging for 45 seconds over the same slab of tissue (1–16 sections). Perfusion data were analysed using commercially available software for perfusion evaluation on an Extended Brilliance Workstation. The data set is evaluated for motion artefacts and automatic motion correction is done. ROIs were placed manually onto (a) the central part of a cerebral artery (commonly ACA) and (b) venous sinus (commonly the superior sagittal sinus) to provide arterial and venous time-attenuation curves. The CBV map was calculated from the area under the time-attenuation curves during the first contrast material bolus passage. The MTT, the average time required for the blood to cross the capillary network, was calculated by using a deconvolution operation. The CBV, CBF,MTT and TTP maps (summary maps) are evaluated for areas of hypoperfusion. Absolute Mismatch volume is calculated by subtracting the infarct core volume from the volume of critically hypoperfused tissue. The mismatch ratio is calculated by dividing volume of critically hypoperfused tissue by infarct core volume. CTP ASPECTS score is calculated by CBV map. According to the mismatch ratio and volume of core, patients are divided into three groups, 1.) target mismatch group (where mismatch ratio is more than 1.8, volume of core is less than 70 mL and perfusion lesion volume is more than 15 mL) , 2.) Non target mismatch group, (where mismatch ratio is less than 1.8 and volume of core is less than 70 mL) 3.) large core volume group (volume of core is more than 70 mL). Statistical analysis was performed using SPSS 20.0 software. Continuous variables were described using mean and SD and categorical values were described using frequency and percentage. Correlation coefficient was calculated with Spearman ρ. Significance level was 0.05.

RESULTS AND DISCUSSION:

In the study mean age of presentation of stroke patients is 61.54 years and slight male predominant incidence(Male: Female ratio 1.3: 1). With a hypertension is the most common risk factor (74.6%) seen in the stroke patients. Majority of the cases (67.2%) presented with onset to door time > 6 hrs) (whereas 17.9 % early and 14.9% WUS) .Mean onset to door time was 7.41(±2.02) hrs. Most patients presented with moderate severity NIHSS score, with mean a score of 10.84.MCA territory is the most commonly infarcted vascular region (82.09 %) followed by PCA (10.45%).Majority of the patients had NCCT ASPECTS score in the range 6 – 10 (76%). Mean NCCT ASPECTS was 6.91. Mean CTP ASPECTS was slightly less (6.18) than CTP ASPECTS.There was a general trend in decrease of volume of infarct core with increase in NCCT ASPECTS (Fairly strong negative relationship, Spearman's Rho -0.853).There was a strong negative correlation between CTP ASPECTS and infarct core volume as well (Spearman's Rh -0.841, p value 0.0001).There was significant correlation between baseline NIHSS score and infarct core volume with a linear increase in the core volume with respect to NIHSS score (p value <0.01, Spearman's rho0.765). In the present study an NIHSS score of 16 is strongly associated with a large core volume (> 70 mL) infarct(Youden index 0.7692, Sensitivity 76.92, specificity 100).Area under the curve (AUC) is 0.945, and p value is <0.01.Therefore a patient presenting with a NIHSS score of 16 or more is highly likely to have a large core volume infarct and is unlikely to be benefited by reperfusion therapy. The baseline NIHSS score at presentation in cases of posterior circulation was lower than MCA territory strokes(Mean NIHSS in MCA was 12.29 and PCA was 3.55).Mean volume of penumbra (absolute mismatch volume) in the early stroke was high (51.5±8.16 mL) in early stroke(< 6 hrs) as compared to late (41.24±23.49 mL). Mean mismatch ratio in our study is 2.65±1.24, it is more in the early group (3.54±1.00) as compared to late group (2.51±1.24).The percentage of ratio absolute mismatch volume to volume of critically hypoperfused tissue is found to be more in the early group (mean 69.64 ±9.65) as compared to late (mean 52.11±17.99). The percentage of ratio absolute mismatch volume to volume of critically hypoperfused tissue has significant correlation with onset to door time(p value 0.04).

In our study population, 41.7% had target mismatch (Penumbral group).Among early group (< 6 hrs) stroke patients majority had target mismatch (91.66%). Even in stroke patients, majority late(> 6 hrs) more than half patients(53.33%) had target mismatch pattern, who would be benefited by a reperfusion therapy. 60% of the patients with WUS, who had unknown onset time of symptoms, had target mismatch pattern, suggesting that even in WUS patients CTP can predict the patients having salvageable ischemic penumbra who could be potential candidates for reperfusion therapy. Mean baseline NIHSS score(15.08± 3.98 vs 10.28 ±2.71), onset to door time (8.92± 2.43 hrs vs 6.52± 1.47 hrs) ,were higher in non penumbral pattern group as compared to target mismatch group. Mean volume of the total hypo perfused tissue is 76.08 mL. The mean core volume is 40.61mL and absolute mismatch volume is 43.99 mL. The mean volume of true at risk penumbra is 33.33 mL and volume of benign oligemia is 10.55 mL. The final infarct volume is found to be 51 ml .Mean NECT ASPECTS (7.72±1.08 vs 6.87±1.1) and CTP ASPECTS (6.87±1.13 vs 4.48 ±2.17) was more in the target mismatch group as compared to nonpenumbral pattern group. An NECT ASPECTS score of 6 is strongly associated with a target mismatch group (Youden index 0.5485,Sensitivity 91.89,specificity 62.96). Therefore, a patient with an NECT ASPECTS of more than 6 is likely to be benefited by reperfusion therapy. NECT ASPECTS score of ≤6 is strongly associated with large core volume infarcts (Youden index 0.7662, Sensitivity 92.31, specificity 84.31).

Table 1. Baseline characteristics

Age (Mean ± S.D)	61.54 ± 10.72	
Male : Female (%)	56.7 : 43.3	
Risk factors (%) 1.Diabetes 2. Hypertension 3. Hyperlipidemia 4. Smoking	 22.4 74.6 34.3 32.8	
Onset to door time Early (<6h) Late (6-24hrs) WUS	% [Mean ± S.D (hrs)] 17.9% (4.96 ±0.92) 67.2% (8.07 ± 1.70) 14.9 %	
NIHSS categories	Minor (1-4)	11.9%
	Moderate (5-15)	70.1%
	Moderate to Severe (16-20)	16.4%
	Severe (21-42)	1.5%
Distribution according to vascular territory	ACA	4.5
	MCA	82.1
	PCA	10.4
	PICA	1.5
	SCA	1.5

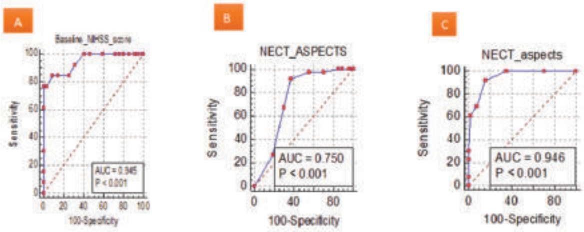

Chart 1. Receiver operating characteristic (ROC)
A) prediction of Large core volume infarct by baseline NIHSS score.
B) prediction of the target mismatch by NECT ASPECTS
C) prediction of large core volume infarcts by NECT ASPECTS

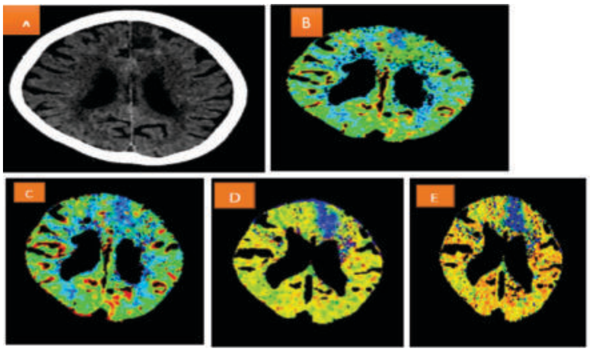

Figure 1.shows acute left ACA territory infarct. (A) axial NCCT brain shows hypodensity with loss of grey white matter differentiation involving the left frontal region in parasagittal location. (B- E) axial CBV map (B) at the same level shows a perfusion defect, a larger TTP defect (E) in keeping with mismatch. (C) is CBF map and (D) is MTT maps showing the same perfusion defects

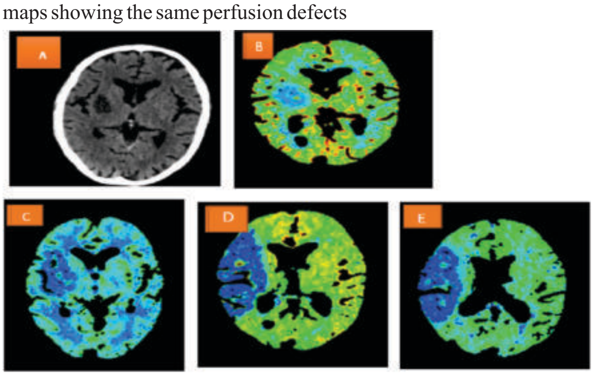

Figure 2.shows acute right MCA territory infarct (A) axial NCCT brain shows hypodensity with loss of grey white matter differentiation involving the right lentiform nucleus, extending to external capsule and part of internal capsule . (B- E) axial CBV map (B) at the same level shows a perfusion defect in the same area (slightly larger as compared to NCCT), CBF (C) MTT(D) and TTP (E) maps show a much larger area of perfusion defect involving fronto temporoparietal lobes suggestive of a mismatch pattern with larger penumbra and a smaller core.

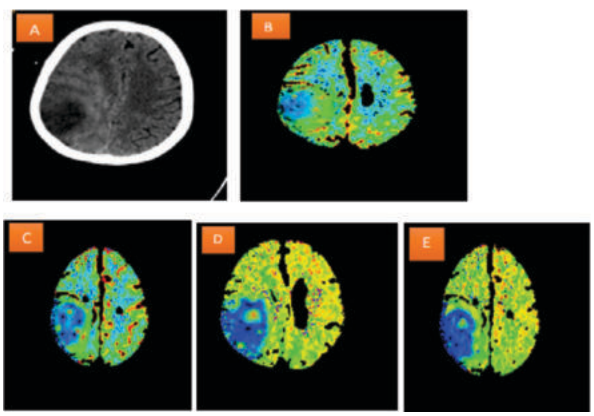

Figure 3. shows acute right MCA territory infarct (A) axial NCCT brain shows hypodensity with loss of grey white matter differentiation involving the right parietal lobe . (B- E) axial CBV map (B) at the same level shows a perfusion defect, CBF (C) MTT(D) and TTP (E) maps show defect almost in the same area without any mismatch suggesting minimal penumbra(non penumbral pattern).

CONCLUSIONS

The present study on the CT Perfusion evaluation of acute ischemic stroke revealed that CT perfusion is a very effective modality to detect acute ischemic changes in cerebrovascular disease which helps in most accurate assessment of the infarct core, salvageable brain tissue (penumbra) and their extent. It helps to identify the proportion of patients with target mismatch who are benefited by the reperfusion therapy. It is also efficient in finding out large core volume infarct patients who are unlikely to be benefited by the therapy. Majority of the patients present in the late phase, in our part of the country, probably which can be rectified via strong patient education campaigns to help recognize stroke early and, respond quickly and appropriately. A high rate of modifiable risk factors including hypertension, diabetes, dyslipidemia and smoking is found in our study population, which can be controlled or modified by optimal secondary prevention strategies. There was a strong negative correlation between NCCT,CTP ASPECTS and infarct core volume signifying the importance of ASPECTS score in predicting the core and hence the final infarct volume. In the present study an NIHSS score of ≥ 16 is strongly associated with a large core volume (> 70 mL) infarct, who are unlikely to be benefited and hence need not be selected for reperfusion therapy.

A good proportion of stroke patients presenting late or who had wake up stroke , had a target mismatch pattern, whose ischemic penumbra could be salvaged by reperfusion therapy. These patients , would not have been detected without the perfusion study evaluation ,by time criteria alone.. An NECT ASPECTS score of more than 6 strongly predicted with a target mismatch group, who can be treated by reperfusion. In clinical practice, a combined NCCT along with CTP evaluation may better delineate acute ischemic stroke patients who may not benefit from thrombectomy/ thrombolysis and avoid excluding patients who may benefit from it, especially where detailed MRI evaluation is not available in the emergency situation.

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