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A prospective study to determine the role of CT perfusion in patients with acute ischemic stroke in the patients of less than 12 hrs of acute stroke symptoms

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Abstract
Aim: To determine the role of CT perfusion in patients with acute ischemic stroke in the patients of less than 12 hrs of acute stroke symptoms.
Materials and Methods: The present study is a prospective study to determine the value of CT in evaluation of cerebral perfusion by use of a bolus of iodinated contrast medium in 30 patients with acute stroke, carried out in Department of Radiodiagnosis, Kamineni Hospitals, L.B. Nagar, Hyderabad. All the patients enrolled in study were evaluating in period of 12 months. After obtaining the informed consent the patient's personal identification information was recorded. The signs and symptoms of acute stroke less than 12 hours duration with any other systemic illness at the time of presentation were noted. Ingenuity 128 slice CT Machine, Phillips. Perfusion CT software - Ingenuity 128 slice CT scanner, Phillips Iohexol Contrast media were used.
Results: Mean age of subjects was 60.8 ± 13.22 yrs. Majority of subjects in the study i.e., 60% were males and 40% were females. 46.7% of lesions were on Right side, 36.7% of them on Left side, 13.3% on Midline and 3.3% on both cerebral hemispheres. Majority of subjects (93.3%) presented with Weakness as symptom. Non contrast CT showed that 40% had Loss of Gray Matter Interface. On CT perfusion 10% had ACA involvement, 33.3% had LCS of MCA involvement. PS value has significant co-relation with hemorrhagic transformation. There was significant association between PS Core infarct and Hemorrhagic transformation. It was observed that there was significant association between Infarct volume and Predicted Modified Rankin Score. There was no significant association between Actual score and Haemorrhagic transformation.
Conclusion: PS elevation more than 5ml/min/100gm appears to be a promising marker for predicting the risk of HT in acute stroke patients. More importantly, a small PCT lesion (<100 mL) identifies patients who will have a small final infarct and good clinical outcome. A large PCT lesion (>100ml) identifies patients who will have a large final infarct and poor clinical outcome. PCT can play an important role in guiding acute stroke treatment.

Keywords: PCT, infarct, PS elevation, stroke

Introduction

According to the World Health Organization (WHO), stroke is the world leading cause of long-term morbidity, and the third leading cause of death in developed countries [1]. Stroke is defined as a rapidly progressive focal or global brain dysfunction of vascular origin lasting more than 24 hours or leading to death within 24 hours [2]. As one of the leading contributors to death and disability worldwide, the burden of stroke is felt physically, socially, economically and emotionally on patients, their families and health care services [1]. Within stroke, several subtypes exist with ischemic stroke representing the majority, accounting for between 67 and 80 % of stroke cases reported in epidemiological studies [1]. Ischemic stroke is more often disabling rather than fatal but remains the most common life-threatening neurological disorder [3]. 10 % of patients with ischemic stroke will die within 30 days of stroke onset, while half of those who survive have persistent disability 6 months later [4]. The remaining 20% of stroke cases are due to intracerebral or subarachnoid haemorrhages which are also potentially devastating conditions with 30-day mortality of primary intracerebral haemorrhage approaching 50 % [5-7].

Ischemic stroke is a vascular disease that is caused by insufficient flow of blood to the brain tissue. In general, stroke results from a thrombotic occlusion of an intracranial artery. Reperfusion following recanalization or bypass of the occlusion, or improved collateral flow is a necessary but not sufficient condition for a favourable clinical outcome with the time from the onset of ischemia to the reperfusion being a pivotal determinant [8]. Thus, therapies that target the prerequisites of reperfusion, such as intravenous thrombolysis (IVT) and intra-arterial interventions are of special interest.

Imaging has a central role in the evaluation of patients with acute stroke. Typically, CT or MRI is performed. Both methods enable the detection of intracranial haemorrhage, allow the approximation of the extent of reversible and irreversible ischemic changes and provide anatomical information on the cerebral and cervical

vasculature [9-10]. These data can be used to predict the clinical outcome and the risk of haemorrhagic complications and to triage the patients to different therapeutic approaches.
MRI perfusion and CT perfusion imaging provide similar information with greater sensitivity and specificity [11]. However, there are certain inherent advantages of CT scan–based imaging. CT scan is more widely available as compared to MRI and thus imaging can be done earlier. It is relatively less expensive. Also, evaluation of the carotids, intracerebral vessels, and cerebral perfusion can be done in a very short time: approximately 5 min. The major disadvantage of CT scan is the exposure to ionizing radiation.
CTP provides absolute and relative information about brain perfusion parameters, namely cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP). MTT is the time between the arterial in flow and the venous out flow. TTP refers to the time taken by the contrast to achieve maximum enhancement (HU value) in the selected region of interest (ROI) before its value starts decreasing. CBV is the volume of blood available per unit of brain tissue and is usually measured as milli litres per 100 gm of blood. Change in CTP parameters in ischemic brain with decrease in CBF due to any cause, cerebral auto regulation ensures adequate CBV by causing capillary dilatation which, in effect, causes increase in MTT and CBV. This continues till the decrease in CBF reaches a critical level (usually 20% of its normal value), at which point auto regulation fails and there is reduction in CBV and CBF. CTP, by measuring these values, tries to identify how much area of the brain is ischemic and/or infarcted. In general, if CTP shows a decrease in CBF with a stable or increased CBV, it signifies reversible ischemia; if both CBF and CBV fall below a critical level, it signifies irreversible infarction [2-13].
The aim of this study was to determine the role of CT perfusion in patients with acute ischemic stroke in the patients of less than 12 hrs of acute stroke symptoms.

Materials and Methods

The present study is a prospective study to determine the value of CT in evaluation of cerebral perfusion by use of a bolus of iodinated contrast medium in 30 patients with acute stroke, carried out in Department of Radiodiagnosis, Kamineni Hospitals, L.B. Nagar, Hyderabad. All the patients enrolled in study were evaluating in period of 12 months, from December 2014 to December 2015.

Inclusion Criteria

All Patients with obvious acute stroke symptoms such as hemiparesis, aphasia, or hemianopia of less than 12 hours duration.

Exclusion Criteria

1. Brain stem symptoms.
2. Haemorrhage in NCCT scan.
3. Contraindications to I.V iodinated contrast like previous allergic reaction or deranged renal function.

Methodology

After obtaining the informed consent the patient's personal identification information was recorded. e.g., name, age, sex, address, contact number. The signs and symptoms of acute stroke such as hemiparesis, aphasia, or hemianopia of less than 12 hours duration with any other systemic illness such as HT, DM at the time of presentation were noted.

Basic Equipment Used to Carry Out the Procedure

Ingenuity 128 slice CT Machine, Phillips
Perfusion CT software - Ingenuity 128 slice CT scanner, Phillips Iohexol Contrast media

Perfusion Imaging

The main principle of our method of perfusion imaging was based on the analysis of plain and contrast-enhanced CT scans obtained at admission. Most important was a sharp bolus of contrast medium resulting from rapid injection (5 mL/s). The software used the maximal slope of the time-density curve (Perfusion CT software; ingenuity 128 slice CT scanner, Phillips) to measure cerebral blood perfusion from dynamically enhanced cerebral CT scans, as described previously. The parameters chosen for evaluating cerebral perfusion are CBF, cerebral blood volume (CBV), time to peak (TTP), mean transit time (MTT), permeability surface area (PS).

Perfusion Imaging Procedure and Follow-up Examinations

Conventional plain CT of 5mm-thick whole brain sections was obtained. Patient was injected with an intravenous bolus of iodinated contrast, typically 50ml (350 mg of iodine per ml) at a rate of 4-5ml/sec. A two-phase CT perfusion/permeability examination was performed.
The first phase involved a 45-second continuous (cine) acquisition of scans reconstructed at 0.5-second intervals to produce a series of 90 sequential images of each of eight sections encompassing a total of 40 mm of selected area of interest depend on the findings of plain scan.
In the second phase of the CT permeability examination, images encompassing the same five to six sections were collected at 30-second intervals for an additional 150- 180 seconds immediately after the first phase.

The scanning parameters for both phases were 80 kVp, 120 mA, 8 × 5-mm collimation, and a gantry speed of 1 second per rotation. The images obtained from the ―cine mode‖ acquisition are used to generate time attenuation curves for an arterial region of interest (ROI), for the whole image on a pixel by pixel basis employing mathematical techniques. A number of perfusion parameters can be obtained from the two-phase perfusion study.

Data Analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Bar diagram and Pie charts were used to represent the data graphically. Chi-square or Fischer Exact* Test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test or Mann Whitney U test was used as test of significance to identify the mean difference between two groups. Paired t test or Wilcoxon Signed Ranks Test was as the test of significance for paired data such as before and after. p value <0.05 was considered as statistically significant.

Results

Table 1: Demographic details

Age	Frequency	Percent
< 50 yrs	5	16.7
51 to 60 yrs	9	30.0
61 to 70 yrs	10	33.3
> 70 yrs	6	20.0
Gender		
Female	12	40.0
Male	18	60.0
Side		
Right	14	46.7
Left	11	36.7
Midline	4	13.3
Both Side	1	3.3
Symptoms		
Weakness	28	93.3
Slurring of speech	7	23.3
Deviation of Angle of Mouth	5	16.7
Giddiness	2	6.7
Duration of Stroke		
<6 hrs	20	66.7
> 6 hrs	10	33.3
Total	30	100.0

Majority of subjects in the study were in the age group 61 to 70 yrs. (33.3%). Mean age of subjects was 60.8 ± 13.22 yrs. Majority of subjects in the study i.e., 60% were males and 40% were females. 46.7% of lesions were on Right side, 36.7% of them on Left side, 13.3% on Midline and 3.3% on both cerebral hemispheres. Majority of subjects (93.3%) presented with Weakness as symptom. 40% of subjects had Right side and Left side (both Upper limb and lower limb weakness respectively). 66.7% of subjects presented with duration of <6 hrs and 33.3% presented with duration >6 hrs. Mean duration was 5.083 ± 3.33 hrs.

Table 2: Distribution of Non-contrast CT & CT perfusion findings

Non-Contrast CT Findings	Present	%	Absent	%
Loss of Gray Matter Interface	12	40.0	18	60.0
Loss of Insular Ribbon	10	33.3	20	66.7
Hyper dense MCA	8	26.7	22	73.3
Hyper dense Basilar	0	0	30	100.0
CT Perfusion findings				
ACA	3	10.0	27	90.0
LCS of MCA	10	33.3	20	66.7
M1 of MCA	11	36.7	19	63.3
M2 of MCA	16	53.3	14	46.7
M3 of MCA	13	43.3	17	56.7
PCA	1	3.3	29	96.7

Non contrast CT showed that 40% had Loss of Gray Matter Interface, 33.3% had Loss of Insular Ribbon, 26.7% had hyper dense MCA and none of them had hyper dense Basilar. On CT perfusion 10% had ACA involvement, 33.3% had LCS of MCA involvement, 36.7% had M1 of MCA involvement, 53.3% had M2 of MCA involvement and 43.3% had M3 of MCA involvement and 3.3% had PCA involvement.

Table 3: Mean difference of CBV, CBF and PS values of Core infarct and Penumbra

		Hemorrhagic transformation (HT)				P value
		Absent		Present		
		Mean	SD	Mean	SD	
Core Infarct	CBV	1.99	0.68	1.49	0.65	0.155
	CBF	10.02	6.14	10.12	4.10	0.974
	PS	3.09	2.40	8.36	6.13	0.006*
Penumbra	CBV	3.49	1.07	2.91	1.38	0.330
	CBF	26.97	11.00	16.85	4.01	0.061
	PS	2.44	2.32	6.86	6.75	0.028*

Evaluation of CBV, CBF and PS values in two patient groups, Patients with hemorrhagic transformation and patients without hemorrhagic transformation shows no significant co relation of CBV and CBF values. However, PS value has significant co-relation with hemorrhagic transformation.

Table 4: Association between PS value and haemorrhagic transformation

		Hemorrhagic transformation				P value
		Present		Absent		
		Count	%	Count	%	
PS Core infarct	<5	2	40.0%	16	88.9%	0.019*
	>5	3	60.0%	2	11.1%	
PS penumbra	<5	3	60.0%	15	88.2%	0.150
	>5	2	40.0%	2	11.8%	

There was significant association between PS Core infarct and Hemorrhagic transformation. Among 5 subjects with HT, 60% had PS value >5. No significant association was observed between PS value of Penumbra and HT.

Table 5: Association between Infarct Volume and Predicted Modified Rankin Score

		Infarct volume						
		<100ml		>100ml		Total		P value
		Count	%	Count	%	Count	%	
Predicted	< 3	22	100.0%	0	0.0%	22	93.3%	<0.001*
	> 3	0	0.0%	4	100.0%	4	6.7%	
	Total	22	100.0%	4	100.0%	26	100.0%	

It was observed that there was significant association between Infarct volume and Predicted Modified Rankin Score. i.e., among 22 Subjects who had infarct volume < 100 ml all the subjects had predicted score of < 3 and similarly among 4 subjects who had infarct volume > 100 ml had predicted score of > 3.

Table 6: Association between haemorrhagic transformation and final patient outcome

		Hemorrhagic transformation				P value
		Present		Absent		
		Count	%	Count	%	
Actual mRS Score	<3	3	60.0%	22	88.0%	0.125
	>3	2	40.0%	3	12.0%	

There was no significant association between Actual score and Haemorrhagic transformation.

Discussion

The results show that time-based perfusion measures are best for defining hypoperfused tissue which is at risk of infarction in the setting of persistent arterial occlusion. Relative MTT, Absolute MTT and TTP all performed similarly in the derivation group implying the best available combinations for detecting tissue at risk (Penumbra). Previous studies show best predictors for penumbra are absolute TTP, relative MTT and absolute MTT in descending order. Our study is well co relating with these studies to define the tissue at risk; Small differences may be attributed to small sample size of our study.

Table 7: Best available time-based parameters for defining "PENUMBRA

Study	Absolute TTP	Relative MTT	Absolute MTT
Mc Verry Ferghal at al. (2014) [14]	>2 SEC	>125%	>7SEC
Wintermark at al. (2006) [15]	>2 SEC	>145%	>7SEC
Our study (2015)	>3 SEC	>192%	>5.5SEC

Table 8: Best available parameters for defining "CORE INFARCT"

Study	Relative CBF	Absolute CBV	Absolute MTT	Relative MTT
Mc Verry Ferghal at al. (2014) [14]	<45%	<2 ml/100gm/min	>8 SEC	>125%
Wintermark at al. (2006) [15]	<45%	<2 ml/100gm/min	>7 SEC	>145%
Our study (2015)	<46%	<2 ml/100gm/min	>8 SEC	>254%

Our study results demonstrate the feasibility of a two-phase protocol for measuring hemodynamic parameters and the PS during one CT perfusion examination. The patients with HT had a significantly higher PS than did those without haemorrhage. A PS threshold of 5 mL/ min/ (100 g) also enabled the differentiation of patients with haemorrhage from those without haemorrhage.

It is important that we identified no significant difference in CBV, CBF between the patients with and those without haemorrhage.

In our study, HT was associated with PS but no statistically significant association with volume of the infarct at presentation at univariate analysis; however, the association with TPA need to be evaluated.

In our study, PS and subsequent HT has no significant association with the final clinical outcome of the patient; However, our sample size was very small it needs to be evaluated on prospective larger number of patients.

Our results, like those in most stroke studies, could have been affected by the specific inclusion and exclusion criteria that we adopted for this study and by whether the studied cohorts had matched clinical data. However, our results show that besides the PS no other factors (e. g, age, sex, diabetes mellitus or hypertension) were associated with HT.

All patients in this series were classified into haemorrhage and non-hemorrhage groups by using follow up CT or MR. MRI Gradient is superior in detection of hemorrhagic transformation of infarct than CT scan. Majority of the patients are followed by CT scan so it could be limitation of our study. However, significant co relation is observed in the group of the patients who were positive for increased PS and hemorrhagic transformation in subsequent scans.

We report that in this highly selected patient group, initial PCT lesion volume is a stronger overall predictor of clinical outcome, especially for those with successful treatment.

In comparison, patients with no recanalization demonstrate enlargement of their initial PCT lesion volume on follow-up imaging, and clinical outcome is more likely to be worse.

Analysis suggests that a cut off volume of >100 mL may identify ―poor outcome patients. Those patients with no recanalization have large infarcts and poor clinical outcomes at follow up, regardless of their initial PCT lesion volumes.

However, for the subset of patients whose initial PCT lesion volumes are much larger than their corresponding NCCT lesion volumes (i.e, large PCT.NCCT mismatch), both final infarct volume and long-term clinical outcome after treatment are more variable.

The NCCT lesion volumes, once visually evident, are strongly associated with irreversible infarction [16]. Although we obtained quantitative PCT lesion volumes using image segmentation; we were forced to estimate the degree of mismatch by direct visual comparison between the abnormal NCCT and PCT regions. Quantitative NCCT lesion volumes could not be reliably measured because of the indistinct margins and limited visual conspicuity typical of acute ischemic NCCT hypodensity. The attenuation differences between normal and oedematous tissue on the initial NCCT images are typically only in the 1– to 3–Hounsfield unit range. Despite our careful use of optimal window width and center level display settings during NCCT image interpretation [17], our preliminary attempts to segment hypo dense NCCT regions were characterized by marked intra observer and inter observer variability. Indeed, many portions of the abnormal, hypodense brain tissue present on the admission NCCT images were detected only retrospectively during careful review of the NCCT scans alongside co registered PCT images.

A potentially important role of PCT imaging in acute stroke may be to improve detection of subtle NCCT findings of ischemia, a frequent problem in stroke clinical trials.

It is noteworthy that in our study a PCT lesion volume of 100 mL identified patients with a ―poor‖ clinical outcome, because 100 mL is approximately equal to one third the brain volume supplied by an MCA [18]. This result is consistent with the European data indicating that intravenous thrombolytic therapy within 6 hours of stroke onset results in poor outcome in patients with initial NCCT lesion volumes greater than one third that of the MCA territory [19, 20].

A limitation of our analysis is that it did not shows co relation of clinical outcome with patients undergone either intra-arterial or venous thrombolysis.

Final infarct location sparing language and motor centers may help to explain the excellent clinical outcome in few patients with initial higher mRS Score and initial PCT lesion volumes of >100 ml.

Despite differences in technique and the tissue characteristics they measure, both diffusion weighted MR and PCT imaging delineate ischemic regions likely to be irreversibly infarcted. Simultaneous review of both the NCCT and PCT images allows a determination of mismatch between unequivocally infarcted tissue (i.e, NCCT) and more conspicuous ischemic tissue with a high probability of infarction (i.e, PCT). More importantly, a small PCT lesion (<100 mL) distal to an arterial occlusion identifies patients who will have a small final infarct and good outcome after successful early treatment.

Conclusions

Our ROI analysis in a series of 30 acute stroke patients shows that the optimal approach to define the infarct core and the penumbra is a combined approach using distinct PCT parameters. The relative CBF of less than 46% of the contralateral normal cerebral hemisphere and the absolute CBV, with a threshold at 2.0 ml/100 gm/min, are the parameters allowing the most accurate delineation of the acute infarct core. The absolute TTP > 3 seconds and the absolute MTT > 5 seconds affords the most accurate delineation of the tissue at risk of infarction. The BBB PS parameter can be measured accurately during the acute stroke CT protocol. PS elevation more than 5ml/min/100gm appears to be a promising marker for predicting the risk of HT in acute stroke patients. Simultaneous review of both the NCCT and PCT images allows a determination of mismatch between unequivocally infarcted tissue (i.e, NCCT) and more conspicuous ischemic tissue with a high probability of infarction (i.e, PCT). More importantly, a small PCT lesion (<100 mL) identifies patients who will have a small final infarct and good clinical outcome. A large PCT lesion (>100ml) identifies patients who will have a large final infarct and poor clinical outcome. PCT can play an important role in guiding acute stroke treatment.

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