Diffusion tensor imaging- MR tractography in stroke patients to predict clinical outcome.

Abstract:

Background: The challenge for neuroscience in patients with stroke is to provide accurate prediction of functional impairment post-stroke, to aid therapy and to help early recovery. Sensitivity of Diffusion Tensor Imaging (DTI) metrics to predict clinical outcome by using Modified Rankin Scale and Barthel score in early stroke was the objective of the study.

Materials and methods: A prospective observational study was conducted between October 2019 to October 2021 involving 86 patients with stroke. DTI sequences were taken on day 2 to day 10 after stroke. National Institute of Health Stroke Scale (NIHSS) were obtained at the time of scan. Modified Rankin Score (MRS) and Barthel index scoring were used to to do the clinical assessment and were done on day7, day 30 and day 90.

Results: There was weak positive correlation between NIHSS and fractional anisotropy (FA) and NIHSS and Axial Diffusivity Curve(ADC).There was a strong positive correlation between NIHSS and Voxels (Infarct), and this correlation was statistically significant (rho = 0.75, p = <0.001. There was weak positive correlation between rADC and MRS of day 7, day 30 and day 90 . There was a strong positive correlation between Voxels and NIHSS, and this correlation was statistically significant (rho = 0.75, p = <0.001).

Conclusion: NIHSS is a well known clinical indicator to classify severity of stroke. DTI metric-FA and rFA is a surrogate marker to predict long term motor outcome in stroke patients.

Keywords: Stroke, Diffusion Tensor Imaging, NIHSS, Barthel index.

Introduction:

Stroke is a leading cause of disability worldwide. Motor impairments occur in most patients with stroke in acute phase and contribute substantially to disability. The challenge for clinical neuroscience is to provide accurate prediction of functional impairment post-stroke, to aid therapy and to help early recovery. Traditionally, functional outcomes are determined by initial neurological deficit and age[1,2].

Diffusion tensor is a nine-element mathematical matrix quantity from which magnitude (diffusivity) and directional bias (anisotropy) of water molecule motion can be derived. The most widely used DTI metrics are: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). FA describes the degree of anisotropy (represented as an ellipsoid), a value between 0 (isotropic) and 1 (the most anisotropic)[3-5].

The DTI metric functional anisotropy (FA) is influenced by myelination, diameter, density, and orientation of axons. It can be used to measure white matter microstructure integrity and reorganization during stroke recovery, even in areas distant from injury. The biggest value is supposed to be found in the center of the tracts. For Cortico Spinal Tract (CST) analysis in stroke or other focal brain lesions, FA results can be reported as ratios between FA extracted from the ipsilesional and the contralesional hemispheres (rFA = FA ipsilesional/FA contralesional). Post-stroke, FA values decline from Wallerian degeneration and recover over a period of weeks to months[6,7,8].

In out study we aimed to assess whether anisotropy using Diffusion Tensor Imaging in the corticospinal tract correlates with motor outcome after stroke. Correlation of DTI metrics in early

stroke with NIH stroke scale, at presentation, keeping it as gold standard were assessed. Sensitivity of DTI metrics to predict clinical outcome by using Modified Rankin Scale [9] and Barthel score[10] in early stroke was the objective of the study.

Materials and methods:

A prospective observational study was conducted between October 2019 to October 2021 in the Department of Internal Medicine of a tertiary Institute. 86 patients with stroke, admitted in the Department of Internal Medicine with both radiological imaging and clinical follow-up were included in the study.

Patients with age >50 years, Single anterior circulation stroke and no prior history of stroke or white matter pathology were included in the study. Patients with claustrophobia/ implants/ other contraindications for MRI scanning, patients with intracranial hemorrhage and patients with large infarct involving most of brain parenchyma were excluded from the study.

Informed consent was taken from all the patients included in the study. Institutional ethics committee approval was taken before the initiation of the study. The study was conducted by the principles laid down by the Declaration of Helsinki.

Radiological And Clinical Assessment:

Image acquisition done using Magnetic Resonance Imaging- Philips Achieva 1.5 Tesla (using SENSE- NV- 16 coil) The imaging parameters are as follows: Sequences- flair (axial sections) and DTI (high iso- 32 directions)Parameters for DTI sequence- B factor of 1000s/mm2 and TE of 100.

National Institute of Health Stroke Scale (NIHSS)[11] **(Figure 1)** was measured at the time of obtaining scan. DTI and Flair sequences were taken on day 2 to day 10 after stroke. FA and AD were calculated in section where infarct is largest, at the centre of infarct and white matter. Three such values were taken and average is considered. Receiver operating characteristic (ROC) curves were drawn above the level of infarct, at the level of infarct and below the level of infarct. ROC size depends upon size of infarct and track fibres. Infarct size was defined as small, medium and large if size is <2cm, between 2 to 4cm and >4cm respectively. The Location is described as in internal capsule, supracapsular- cortex, subcortical white matter, centrum semiovale, corona radiata.

Modified Rankin Score (MRS)**(Figure 2)** and Barthel index**(Figure 3)** scoring were used to to do the clinical assessment. MRS and Barthel scores were taken on day 7 of stroke. Post processing of DTI to obtain FA,AD and number of fibres was done and recorded. MRS and Barthel scores were taken on day 30 and 90 for clinical outcome **(Figure 4)**.

Statistical analysis:

Data analysis was done using SPSS software version 23.0(Norman.H.Nie, IBM, New york, America).To determine association of variables with motor deficit severity, chi-square test was used for categorical variables and ANOVA test for quantitative variables.Receiver operating characteristic (ROC) curves were used to determine DTI metric cut-offs for the infarct. Multivariate ordinal logistic regression was used to predict long term motor outcome.

Results:

A total of 86 patients were included in the study. Most of the patients 38/86(44.1%) belonged to the age group of 61-70 years **(Table 1)** Majority of the patients were males(55). Approximately 51%, 33% and 13% of patients had infarct in the left Middle Cerebral Artery, right Middle

Cerebral Artery and right Middle Cerebral Artery and Anterior Cerebral Artery territory respectively. Most of the patients (59%) had supracapsular infarct**(Figure 5)**. Approximately 45% and 44% had small and medium sized infarcts respectively. Approximately 30%, 23% and 22% of patients had infarct of moderate size in the supracapsular region, small size in internal capsule and small size in supracapsular region, respectively **(Table 2)**.

Majority of the patients (53%) had moderate stroke according to NIHSS and 3% of patients had minor stroke**(Figure 6)**. Mean rFA of patients with severe stroke, moderate to severe stroke, moderate stroke and minor stroke was 0.382, 0.596, 0.634, and 0.721 respectively. Mean rADC of patients with severe stroke, moderate to severe stroke, moderate stroke and minor stroke was 0.396, 0.488, 0.621, and 0.712 respectively. Mean rVoxels of patients with severe stroke, moderate to severe stroke, moderate stroke and minor stroke was 0.391, 0.572, 0.638, and 0.692 respectively.

On day 7, 60% of patients has severe disability and 40% had moderate to severe disability. On day 30, 52% had moderate to severe disability and 48% had moderate disability. On day 90, 6% had moderate disability, whereas, 52% and 42% had slight and no disability respectively. On day 7, all patients were totally dependent. On day 30, 65% had severe dependency and 35% had moderate to severe dependency. On day 90, 7% had severe dependency, whereas, 65% and 28% had moderate and slight dependency respectively.

About 23% of patients had small capsular infarct and 9% had large supracapsular infarct.The patients with small capsular infarct had slightly lesser rFA and rVoxels.Though about 50% and 40% of patients of small capsular and large supracapsular infarct resepectively had moderate to severe stroke, 65% and 75% of patients with small infarct had poor motor outcome on day 30

(Table 3). Mean FA, ADC and Voxels of the infarct are 0.36, 0.54 and 989 respectively. Mean rFA, rADC and rVoxels of the infarct are 0.5, 0.66 and 0.48 respectively .

43% of patients had moderate to severe stroke according to NIHSS. Among them, 9% and 12% had poor motor outcome according to MRS and Barthel score at day 90 respectively. Among the 43% of patients with severe stroke according to NIHSS, 30% had moderate supracapsular stroke.Their mean FA, ADC and Voxels was 0.36, 0.54 and 675$\pm$ 412 respectively. Their mean rFA, rADC and rVoxels was 0.5, 0.67 and 0.5 respectively **(Table 4)**.

There was weak positive correlation between NIHSS and FA and NIHSS and ADC.There was a strong positive correlation between NIHSS and Voxels (Infarct), and this correlation was statistically significant (rho = 0.75, p = <0.001**Figure 7**). There was weak positive correlation between rFA and MRS of day 7, Barthel score of day 30 and MRS of day 90 (**Figure 8**). There was weak positive correlation between rADC and MRS of day 7, day 30 and day 90 (**Figure 9**). There was a strong positive correlation between Voxels and NIHSS, and this correlation was statistically significant (rho = 0.75, p = <0.001).There was weak positive correlation between rVoxels and Barthel score at day 7, MRS and Barthel score at day 30 and MRS at day 90. FA cut off value for poor outcome i.e., MRS $\geq$4 and Barthel score of $\leq$60 on day 30 with sensitivity of 90% and specificity of 92% is 0.356**(Figure 10)**. rFA cut off value for poor outcome i.e., MRS $\geq$4 and Barthel score of $\leq$60 on day 30 with sensitivity of 91% and specificity of 92% is 0.465.

Discussion:

The proposed predictors of motor outcome include motor deficit on admission, infarct volume and location and corticospinal tract involvement.NIHSS during presentation has been proved to categorise severity of stroke and hence predict overall clinical outcome. However, it does not predict motor outcome specifically. More than half of the patients with moderate to severe stroke

(according to NIHSS) were having poor motor outcome (according to MRS and Barthel index) at day 30. However, <20% were moderately or severely dependent/ had moderate to severe disability at day 90. Puig et al found that fewer patients had motor deficits in 2 year follow up owing to better treatment and rehabilitation facilities [12].

DTI metrics- FA and rFA has been proved to be a predictor of motor outcome after stroke with cut-off values defined to predict moderate to severe disability and dependency.Lindenberg et al in their study concluded that voxel based analysis of corticospinal tracts might outperform FA.Number of fibres/ voxels and rVoxels had strong positive correlation with NIHSS score which was statistically significant, thus associating to severity of stroke. However, it showed weak positive correlation with disability/ dependency scores at different time periods. Also, no significant cut-off value with good sensitivity and specificity could be derived to predict poor motor outcome.Other DTI metrics like diffusion tensor, eigenvalues might be useful, according to Lindenberg et al [13].

Puig et al Evaluated 70 patients rFA was correlated with degree of motor deficit at 2 years (Motoricity index). Puig et all concluded that lower FA values were associated with greater motor deficit and thus worse motor outcome at 3 months. More than 50% of patients after stroke require specialised rehabilitation and early information from rFA analysis might help tailor rehabilitation **(Table 5)**.Limitations of Puig et all study were-NIHSS not being sensitive for motor impairment and More sensitive score to be administered at day 30 to predict long term motor outcome.

Thomalla et al Negative correlation on comparing rFA and NIHSS and strong positive correlation on comparing rFA and motor indices at time of presentation and day 90. However, the sample size of Thomalla et all study was less hence statictical analysis was limited. Also Thomalla et all

focussed on patients with moderate stroke and hence most patients recovered by day 90 [14] **(Table 6).**

Chunshui et al evaluated 9 patients with motor pathway subcortical infarct NIHSS and Motoricity index. rFA of CST monotonously decreased during first 3 months and then relatively remained unchanged. Changes in rFA between the first two time periods correlated with MI and NIHSS after 1 year of stroke.Therefore Chunshui et al found that changes in rFA within first two weeks correlated with clinical (NIHSS) and motor (MI) outcome after 1 year **(Table 7)**.Thus, this predictive ability may contribute to determination of optimal strategies for stroke treatment and rehabilitation at early post stroke stage[15].

Conclusions:

NIHSS is a well known clinical indicator to classify severity of stroke. However, not a good predictor of long term motor outcome.FA, ADC and voxels and their ratios with normal contralateral side, were reduced in infarct.Number of fibres/ voxels and rVoxels positively correlated with NIHSS score (statistically significant), thus associating to severity of stroke at presentation. However, no specific cut-off value with good sensitivity and specificity could be derived which predicted motor outcome of the patient.Location and size of the infarct along the corticospinal tract also affected the motor outcome of patients i.e., patients with small infarct in the internal capsule had poor motor outcome. DTI metric- FA and rFA is a surrogate marker to predict long term motor outcome in stroke patients.

Conflicts of interest:

There were no conflict of interests for any of the authors.

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TABLE 1 : Age distribution

Age	Frequency	Percentage
51-60 Years	19	22%
61-70 Years	38	44.1%
71-80 Years	20	23.2%
81-90 Years	8	9.3%
>90 Years	1	1.2%

TABLE 2: Distribution of patients with respect to infarct location n=86

Infarct Type	**Number**	**Percentage**
Large - Internal Capsule	1	1.2%
Large - Supracapsular	8	9.3%
Moderate - Internal Capsule	14	16.3%
Moderate - Supracapsular	24	27.9%
Small - Internal Capsule	20	23.3%
Small - Supracapsular	19	22.1%

Table 3: Comparison of large supracapsular infarct and small capsular infarct with various parameters

Parameters	**Large supracapsular (n=8)**	**Small capsular (n=20)**
FA (infarct)	0.36	0.37
ADC (infarct)	0.58	0.54
Voxels (infarct)	1338+792	970+476
rFA	0.49	0.45
rADC	0.66	0.66
rVoxels	0.59	0.46
NIHSS (>16)	4 (50%)	8 (40%)
MRS day 7 (>4)	8 (100%)	20 (100%)
MRS day 30 (>4)	3 (38%)	13 (65%)
Barthel day 7 (<60)	8 (100%)	20 (100%)
Barthel day 30 (<60)	4 (50%)	15 (75%)

Table 4: Various parameters in patients with poor outcome

NIHSS > 16	**(Number of patients)**	**37**
Mean age in years		65.8
Location of infarct	Supracapsular	21(57%)
	Capsular	16(43%)
Infarct type	Moderate supracapsular	30%
	Small capsular	20%
DTI metrics	FA	0.36
	ADC	0.54
	Voxels	675±412
	rFA	0.5
	rADC	0.67
	rVoxels	0.5
MRS > 4	Day 7	37(100%)
	Day 30	19(51%)
	Day 90	8(9%)
Barthel score < 60	Day 7	37(100%)
	Day 30	22(60%)
	Day 90	10(12%)

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Table 5: Comparison with Puig et al study.

	Puig et al [12]	Our study
Number of patients	70	86
Age (median) in years	72	63
NIHSS score at presentation	12	14
FA(median)	0.38	0.36
rFA(median)	0.59	0.51
RFA cut off for severe motor deficit	<0.689 based on motoricity index	<0.323 based on MRS, Barthelscore

Table 6: Comparison with Thomalla study.

	Thomalla et al [14]	**Our study**
Number of patients	9	86
Age in year	61	63
Infarct location	Capsular (77%)	Capsular (40%)
NIHSS Mean	10(moderate)	15(moderate)
FA(Infarct)	0.39	0.36
rFA	0.77	0.5
rFA vs NIHSS	Negative correlation	Weak positive correlation
rFA vs motor indices	Positive correlation	Weak positive correlation

Table 7: Comparison with Chunshui et al study.

	Chunshui et al [15]	**Our's**
Number of patients	9	86
Age in year	47,7	63
Infarct location	Capsular (100%)	Capsular (40%)
NIHSS Mean	10.9	15
Mean MI	20.8	-
FA(Infarct)	0.42	0.39
rFA	0.96	0.5
Correlation of rFA with clinical scores	Correlated with MI and NIHSS after 1 year	Weak positive correlation with various scores at different time periods.

Figure legends:

FIGURE 1: NIHSS Scoring system.

Score 0: No stroke, 1-4 : Minor stroke, 5-15: Moderate stroke, 16-20: Moderate to severe stroke 21-42: Severe stroke.

FIGURE 2: Modified Rankin Scale

FIGURE 3: Barthel Index

Score 0-20: Total dependency, 21-60: Severe dependency, 61-90: Moderate dependency, 91-100: Slight dependency.

FIGURE 4: Protocol Of The Study

FIGURE 5: Distribution of patients with respect to infarct location.(n=86)

FIGURE 6: Distribution of patients with respect to infarct location and size n=86

FIGURE 7: Scatter plot No 1, 2, 3: Correlation between NIHSS vs FA, ADC and voxels of infarct n=86

FIGURE 8: Scatter plots: Correlation with MRS day 7, Correlation with Barthel score day 30, Correlation with MRS day 90.

FIGURE 9: Correlation between rADC and clinical scores

FIGURE 10: FA cut off by ROC curve.