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Original Paper

Autologous Mesenchymal Stem Cells in Chronic Stroke

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Key Words
fMRI · Functional imaging · Neurological rehabilitation · Neuronal plasticity · Stem cell transplantation · Stroke

Abstract
Background: Cell transplantation is a 'hype and hope' in the current scenario. It is in the early stage of development with promises to restore function in chronic diseases. Mesenchymal stem cell (MSC) transplantation in stroke patients has shown significant improvement by reducing clinical and functional deficits. They are feasible and multipotent and have homing characteristics. This study evaluates the safety, feasibility and efficacy of autologous MSC transplantation in patients with chronic stroke using clinical scores and functional imaging (blood oxygen level-dependent and diffusion tensor imaging techniques). ***Methods:*** Twelve chronic stroke patients were recruited; inclusion criteria were stroke lasting 3 months to 1 year, motor strength of hand muscles of at least 2, and NIHSS of 4–15, and patients had to be conscious and able to comprehend. Fugl Meyer (FM), modified Barthel index (mBI), MRC, Ashworth tone grade scale scores and functional imaging scans were assessed at baseline, and after 8 and 24 weeks. Bone marrow was aspirated under aseptic conditions and expansion of MSC took 3 weeks with animal serum-free media (Stem Pro SFM). Six patients were administered a mean of 50–60 x 10^6 cells i.v. followed by 8 weeks of physiotherapy. Six patients served as controls. This was a non-ran-

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domized experimental controlled trial. ***Results:*** Clinical and radiological scanning was normal for the stem cell group patients. There was no mortality or cell-related adverse reaction. The laboratory tests on days 1, 3, 5 and 7 were also normal in the MSC group till the last follow-up. The FM and mBI showed a modest increase in the stem cell group compared to controls. There was an increased number of cluster activation of Brodmann areas BA 4 and BA 6 after stem cell infusion compared to controls, indicating neural plasticity. ***Conclusion:*** MSC therapy aiming to restore function in stroke is safe and feasible. Further randomized controlled trials are needed to evaluate its efficacy.
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Introduction

Stroke is the leading cause of morbidity worldwide with a prevalence rate of approximately 250–300/100,000 in the total population [1] in Asian countries, and 28.5 million disability adjusted life years are estimated to be lost [2] due to stroke leaving 60% of stroke survivors dependent on caregivers for their daily activities. Urged by the expectation of functional neuronal replacement, stem cell transplantation has emerged as a 'hope' to cure disease in the last decade. Several studies have evidenced a potential benefit of stem cell grafts in animal models and clinical trials of stroke [3]. It is also postulated that stem cells operate not only through one unidirectional mechanism (e.g. generating neurons) but rather as cellular mediators of a multitude of biological activities that could provide a favorable outcome for neurogenic diseases [4].

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are self-renewing, multipotent cells that can differentiate into bone, cartilage, adipose tissues and neural precursors [5–7]. Intravenously administered MSC have been shown to promote engraftment of hematopoietic lineages in cancers and ameliorate graft-versus-host disease [8–10]. The only published trial with a 5-year follow-up of functional potential in stroke patients receiving autologous MSC transplantation reported significant improvement in the activities of daily living [11]. MSC possess immunomodulatory properties, limit the local inflammatory response by decreasing activation of microglia and macrophages and impair T-lymphocyte maturation [12].

Recovery as Neural Plasticity

Initial recovery following an acute insult/stroke is mediated by spontaneous internal events, and after a late phase this recovery is remodeled by both external and internal perturbations [13, 14]. It has been suggested that 3 months is the time point recognized generally to get the functional status of a stroke victim [15]. Functional neuroimaging investigates the biological mechanism of treatment effects in which blood oxygen level-dependent (BOLD) and diffusion tensor imaging (DTI) techniques are used to study the functionality and integrity of brain areas [16, 17].

Stem Cells as Regenerative Medicine

The emergence of stem cell biology has led to perennial applications in regenerative medicine for stroke aiming to restore plasticity for improving functional recovery [18]. When introduced into the lesioned central nervous system, stem cells can have a positive influence through their intrinsic neuroprotective properties, e.g. production of growth and trophic factors, stimulation of endogenous neurogenesis and modulation of neuroinflammation. They are known to influence the environment by reorganizing the brain, and promoting

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learning in the form of synaptogenesis and dendritic sprouting [19, 20]. Transplanted stem cells also interact with the host tissue by forming connections and by providing 'scaffolds' to an injured brain in order to rescue dysfunctional and dormant cells [21].

Cell therapies are setting new paradigms in regenerative medicine. This research evaluates the safety, tolerance and possible efficacy of intravenous autologous MSC transplantation in chronic stroke assessed clinically and by functional imaging (BOLD and DTI).

Methods

Patients diagnosed with stroke (index event) 3 months to 1 year ago, with MRC (Medical Research Council) grade of muscle power for the wrist and hand extensor or flexor muscles of at least 2, and NIHSS (National Institute of Health Stroke Scale) between 4 and 15 who were conscious and able to comprehend were recruited for this study. We excluded patients with bleeding disorders, chronic liver and/or renal failure, progressive neurological worsening, unilateral neglect, neoplasia and with contraindications to MRI, and immunocompromised and pregnant patients.

The patients were divided into two groups matched for age, disease severity, time of stroke onset and lesion size. All the patients were examined by a neurologist and a neurophysiotherapist regarding muscle power (MRC), tone (modified Ashworth) and Fugl Meyer (FM) scale for upper limbs and modified Barthel index (mBI) at baseline, and the 8- and 24-week follow-ups [22]. We used the Edinburgh handedness inventory to assess hand dominance [23]. The detailed flow chart of the study is explained in figure 1. BOLD and DTI techniques were performed at baseline, and after 8 and 24 weeks of cell therapy.

The trial protocol and informed consent form were approved by the Institute Committee for Stem Cell Research and Therapy. A neurologist helped in treatment allocation but was not part of the study. Only the functional imaging parameters were blinded in this research.

Procedures

Bone Marrow Aspiration, Expansion and Transplantation. Bone marrow was aspirated under aseptic conditions from the posterior superior iliac crest of 6 chronic stroke patients. The aspirate was diluted with phosphate-buffered saline, layered over Ficoll density medium and centrifuged at 1,800 r.p.m. for 25 min. The collected mononuclear cell layer was plated at a density of 1×10^6 cells/cm^2 with Stem Pro MSC SFM basal medium (A-10334, Invitrogen) in a T-25 tissue culture flask and incubated at 37 ° C/5% CO_2. The cells were harvested and seeded at 3,000 or 10,000 cells/cm^2 in triplicate wells of 6-well plates. Throughout the duration of the culture, individual wells remained separate and were propagated individually. On reaching 70–90% confluence, all MSC cultures were harvested using TrypLE™ Express (Invitrogen), counted flow cytometrically and reseeded at the same seeding density till the final required dose of cells was obtained. Nonadherent cells were removed after 24 h and fresh media were again added for incubation [24, 25]. The media were exchanged every 3 days and at confluency, the cells were trypsinized and subcultured. All samples were tested for mycoplasma and endotoxins at every third passage using commercially available kits according to the manufacturer's instructions. MSC expansion took around 23 8 3 days. We used an aseptic infusion technique. Cells were directly dissolved in a 250-ml saline bottle and infused intravenously over 2–3 h using a sterile 50-ml syringe. We used a 20-gauge cannula for cell injection. Patients were evaluated for safety, i.e. laboratory tests (hemoglobin, red and white blood cells, platelets, liver and kidney function tests and partial thromboplastin time) 1, 3 and 7 days and 24 weeks after transplantation. As the patients received an 8-week physiotherapy regime after cell transplantation, they were examined and evaluated daily for any adverse reaction.

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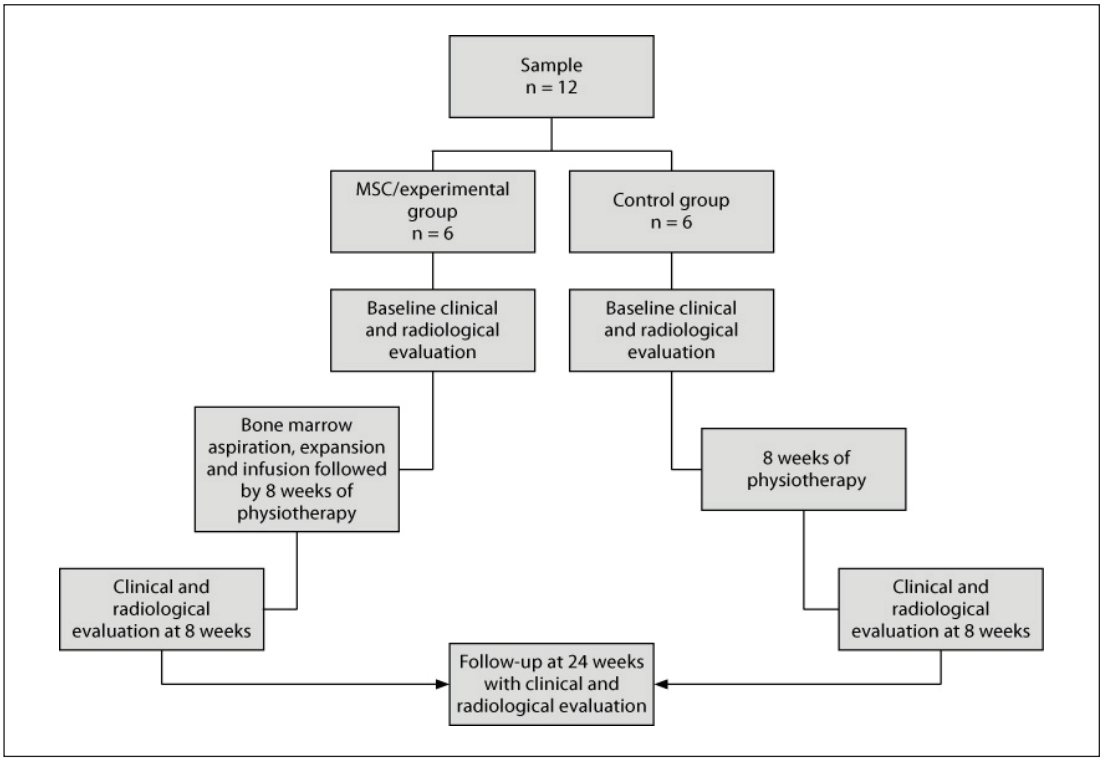

Fig. 1. Flow chart depicting the plan of the study.

Neuromotor Rehabilitation. The physiotherapy regime administered to all 12 patients was based on the motor imagery [26, 27] incorporating learning and repetition of motor learning and lasted 60–90 min 5 days/week for 8 weeks.

fMRI Acquisition. Subjects were asked to perform the motor task with the affected hand, with self-paced (minimum 0.5 Hz) fist clenching/extension of the wrist or metacarpophalangeal joint of the hand. BOLD data were acquired using the gradient echoplanar imaging sequence using a 1.5-tesla MR scanner (Avanto, Siemens, Germany). Block design with alternate baseline and activation cycles was used with a total of 90 whole-brain echoplanar imaging measurements (TR = 4,520 ms, TE = 44 ms, slices = 31 and slice thickness = 4 mm) and MPrage sequence with 176 contiguous slices of 1.0-mm thickness [28, 29].

Diffusion Tensor Images. They were acquired with single-shot echoplanar technique with b values of 0, 400 and 1,000 s/mm^2 in 20 directions, 128 × 128 matrix, field of view: 230 × 230 mm, TE = 76 ms, TR = 10,726 ms, echoplanar imaging factor = 127 and a slice thickness of 2.3 mm. The termination criteria used were fractional anisotropy (FA) !0.2 with an angle change 145°. Seed points as regions of interest (ROI) were drawn in the infarcted area and corticospinal tract in the affected and unaffected hemispheres [30, 31]. The selection of ROI for FA were repeated thrice by one rater, and the average value was regarded as the unit of measurement (intrarater reliability 0.88).

Statistics

Statistical analysis was done by SPSS 11.5. We used parametric paired sample t test/Kruskal-Wallis test for intragroup and 2-sample t test/Mann-Whitney test for intergroup comparisons with p = 0.05. Repeated-measure ANOVA was used to calculate the difference at baseline, and 8 and 24 weeks.

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Table 1. Demographic and clinical data in the MSC and the control group at baseline, and 8 and 24 weeks

No.	Group	Age, years/ sex	Months after stroke	Lesion area all MCA territory	Lesion volume ml	CD90 %	CD73 %	CD105 %	Baseline		8 weeks		24 weeks	
									FM n/66	mBI n/100	FM n/66	mBI n/100	FM n/66	mBI n/100
1	E	28/F	11	R frontoparietal (I)	12	40	40	44	22	52	36	72	44	80
2	E	20/F	12	R frontoparietal (H)	58	52	58	38	11	30	22	42	30	60
3	E	59/F	7	R frontal (I)	34.6	67	65	23	11	40	26	55	32	70
4	E	35/F	8	L internal capsule (H)	13.5	45	43	48	14	32	20	53	28	65
5	E	55/M	9	R frontal (I)	14.2	76	76	52	22	52	38	65	44	78
6	E	55/M	8	R frontal (I)	15.1	86	61	35	20	58	32	70	42	82
Mean		**42**	**9.3**		**24.5**	**61**	**57.1**	**40**	**16.6**	**44**	**29**	**59.5**	**36.6**	**72.5**
1	C	40/M	10	L frontal (I)	55	–	–	–	11	40	20	55	30	65
2	C	28/M	12	R parietal (I)	12.2	–	–	–	20	52	31	62	38	78
3	C	42/M	8	R internal capsule (I)	15.4	–	–	–	12	35	26	52	36	65
4	C	30/M	12	L temporoparietal (I)	45.5	–	–	–	11	42	20	50	30	68
5	C	60/M	7	L caudate (I)	10	–	–	–	24	55	36	65	33	73
6	C	50/M		R frontoparietal (H)	11.2	–	–	–	23	50	30	68	38	72
Mean		**46.5**	**9.3**		**24.8**	**–**	**–**	**–**	**16.8**	**45.6**	**27.1**	**58.6**	**34.1**	**70.1**

C = Control; E = MSC; R = right; L = left; I = ischemia; H = hemorrhage.

Results

Establishment of Safety

The routine laboratory tests 1, 3 and 7 days after the stem cell transplantation were normal for all patients. Flow-cytometric analysis showed phenotype markers which justify these cells as MSC or stromal cells. The cells expressed CD90, CD73 and CD105, and were negative for HLA class II. The mean CD90, CD73 and CD105 were 61, 57.1 and 40%, respectively. The mean cell viability at transplantation was 98% (performed with trypan blue stain); the cells were sterile and endotoxin free during expansion and at the time of injection. There were no early and late adverse reactions observed in patients during and after transplantation. The patients did not report any tumorigenesis, ectopic tissue formation or any behavioral abnormality during the follow-up.

Clinical Results

In the MSC or experimental group (males:females = 2:4), all had right-hand dominance with age = 42 ± 16.4 years (mean ± SD); the mean FM score was 16.6 ± 5.27 at baseline and 29 ± 7.45 after 8 weeks. Patients showed statistically significant improvement when transplanted with stem cells ($p = 0.001$, $t = –8.357$). At the 24-week follow-up, the mean FM score was 36.6 ± 7.4, which was higher than the mean at 8 weeks in these patients exhibiting statistically significant improvement ($p = 0.001$, $t = –8.174$). Repeated-measure ANOVA was found to be statistically significant at all time measurements, i.e. at baseline and after 8 and 24 weeks. The mean mBI in the MSC group were 48.75 ± 10.56 and 68.75 ± 12.27 at baseline and 8 weeks, respectively ($p = 0.0001$), and increased to 78.6 ± 11.34 at 24 weeks ($p < 0.05$). In the control group (all males with right-hand dominance), mean age was 47.08 ± 9.9 years. The mean FM scores were 16.8 ± 6.1 and 27.1 ± 6.4 at baseline and 8 weeks, respectively. These patients also showed statistically significant improvement between baseline and 8 weeks after therapy, and between 8 and 24 weeks ($p < 0.05$) for both FM and mBI scores (table 1).

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BOLD Activation Pattern

The laterality index (LI) was calculated in each subject with a threshold of 10 voxels. It was measured with the formula LI = (CL – I)/(CL + I), where CL = the number of voxels of the contralateral hemisphere to the affected hand and I = the number of voxels for the ipsilateral hemisphere to the affected hand. In the MSC group, the LI of the ipsilesional primary motor cortex (BA 4) did not show statistically significant improvement between 0 and 8 weeks (p = 0.15) and between 8 and 24 weeks (p = 0.98; table 2). The LI of the ipsilesional premotor motor cortex (BA 6) showed statistically significant improvement (p = 0.01) between 0 and 8 weeks but was not significant between 8 and 24 weeks (p 1 0.05). In the control group, the LI for the primary motor and premotor cortex (BA 4 and BA 6, respectively) was not statistically significant when calculated between 0 and 8 weeks and 8 and 24 weeks.

The FA ratio was calculated as FA of the affected hemisphere (ah) divided by the unaffected hemisphere (uh). The FA_{ah} was decreased compared to FA_{uh} in both groups. We also calculated the fiber density by calculating the number of fibers (FN) and the fiber length (FL) in the given ROI in the affected and the unaffected hemispheres. We calculated the FL_{ah}/FL_{uh} ratio, and the FN_{ah}/FN_{uh} ratio. In the MSC group, the mean FL_{ah} (mm) were 0.12 8 0.05 mm at week 0, and 0.14 8 0.05 and 0.15 8 0.06 mm after 8 and 24 weeks, whereas in the control arm they were 0.09 8 0.03, 0.10 8 0.04 and 0.11 8 0.04 mm, respectively. There was no significant change in FL in the MSC and control groups after 8 and 24 weeks. The mean fiber density (number) ratio (FN_{ah}/FN_{uh}) in the MSC group was 0.28, 0.40 and 0.48 at baseline, and 8 and 24 weeks, and 0.25, 0.29 and 0.34, respectively, in the control group (nonsignificant: p 1 0.05).

Comparison between MSC and Control Groups

There was no significant difference in baseline clinical and radiological scores between the MSC and control groups, suggesting that the two groups were comparable to study the effectiveness of therapy after 8 and 24 weeks. There was no significant difference in FM and mBI scores after therapy (8 weeks: p = 0.87, t = 0.161 and p = 0.95, t = 0.065, respectively; fig. 2) and at follow-up (p = 0.65 and p = 0.75, respectively; fig. 3). A meager reduction in the Ashworth tone scale was observed between the two groups (fig. 4).

The LI of BA 4 and 6 between MSC and control groups was also statistically insignificant after 8 and 24 weeks (p 1 0.5). There was no statistically significant (p 1 0.05) change in the FA ratio, FL ratio and FN ratio between the two groups after 8 and 24 weeks.

We compared the results of right-hemispheric stroke with the control arm patients after 8 weeks (table 3). It was found that BA 4 and 6, and the inferior temporal gyrus (fig. 5) of the affected hemisphere were active with a cluster count of 40 and 112 voxels, respectively. The results were similar at 24 weeks (cluster activation of 71 and 112 voxels of BA 4 and BA 6, respectively).

Discussion

This is the first known trial (to our knowledge) that establishes the safety and tolerance of MSC derived using serum-free media for expansion unlike bovine serum used in the earlier study [11, 12, 24, 25]. We were able to procure 50–60 million cells at a mean of 4 passages in all the 6 patients, which made autologous MSC transplantation feasible. No immunosuppressants were required following transplantation, eliminating the risks associated with MSC therapy. The clinical, laboratory and radiological evaluations did not report any deaths, cell-related complications, stroke recurrence and structural changes in imaging up to the 6-month follow-up.

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Table 2. BOLD brain activation pattern and voxel counts in BA 4, BA 6 and cerebellum in the MSC and the control group

Group	Task	Baseline									8 weeks									24 weeks								
		BA 4		LI of CL BA 4	BA 6		LI of CL BA 6	CB		I CB activ. ratio	BA 4		LI of CL BA 4	BA 6		LI of CL BA 6	CB		I CB activ. ratio	BA 4		LI of CL BA 4	BA 6		LI of CL BA 6	CB		I CB activ. ratio
		L	R		L	R		L	R		L	R		L	R		L	R		L	R		L	R		L	R	
MSC	LFM	–	59	1	86	150	0.27	176	–	–	–	390	1	–	250	1	176	–	–	–	–	–	866	1,254	0.98	660	–	1
MSC	LFM	786	–	–1	1,044	–	–1	–	–	–	–	–	–	670	230	–0.6	946	179	0.84	220	220	0	620	3,330	0.66	7,270	7,270	0
MSC	LFM	–	–	–	172	256	0.19	1,012	–	1	–	–	–	13	734	0.96	430	–	1	–	232	1	65	1,544	0.95	640	730	0.46
MSC	RFM	78	–	1	–	–	–	6,490	–	1	513	–	1	513	–	1	540	–	1	–	–	–	543	–	1	634	866	0.57
MSC	LFM	10	24	0.72	98	462	0.65	229	–	1	14	78	0.78	47	1,126	0.91	1,344	–	1	–	770	1	–	1,801	1	–	–	–
MSC	LFM	–	239	1	56	140	0.42	44	142	0.23	–	605	1	–	575	1	221	–	1	–	550	1	110	430	0.59	1,012	572	0.63
C	RFM	–	–	–	499	–	1	–	371	1	–	–	–	643	–	1	329	465	0.41	–	–	–	712	–	–	650	650	–
C	LFM	–	–	–	–	586	1	1,238	748	0.62	–	212	1	–	824	1	1,295	382	0.77	–	350	1	–	724	1	138	461	
C	LFM	–	132	1	221	257	0.11	112	223	0.33	–	650	1	13	730	0.96	230	–	1	–	750	1	–	830	1	212	–	1
C	RFM	–	138	1	1,893	1,462	0.12	–	–	–	–	–	–	712	223	0.49	232	462	0.66	–	–	–	532	126	0.61	512	512	0.5
C	RFM	812	421	0.31	232	–	1	289	631	0.69	1,627	–	1	1,462	–	1	1,128	–	1	1,192	–	1	931	–	1	720	–	–
C	LFM	–	2,861	1	–	2,861	1	2,861	–	1	–	3,542	1	–	4,180	1	3,881	–	1	–	–	–	–	2,921	1	2,691	2,691	0.5

C = Control; L = left; R = right; RFM/LFM = right/left fist making; CB = cerebellum; BA 4 = primary motor cortex; BA 6 = supplementary/premotor cortex; BA 1–3 = sensory motor cortices; LI = (CL – I)/(CL + I); CL = contralateral (to the paretic hand); I = ipsilateral (to the paretic hand); CB ratio = I CB/(I CB + CL CB); cluster: 2*2*2 mm^3.

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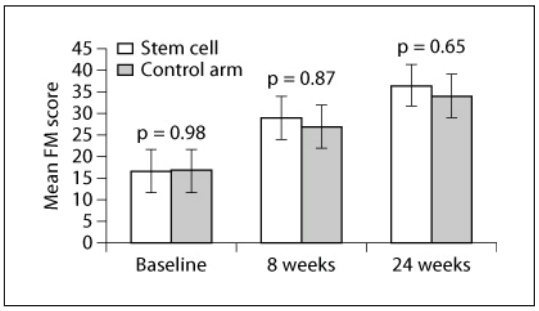

Fig. 2. Mean FM scores at baseline, and at the 8- and 24-week follow-ups with p values in the MSC (stem cell) and control groups.

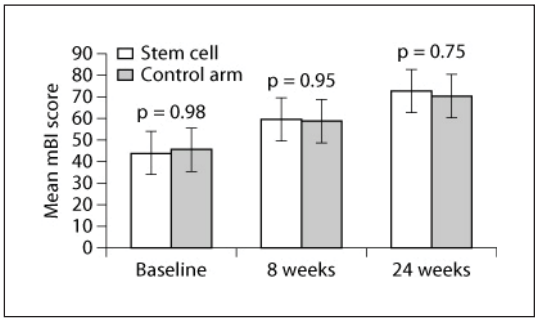

Fig. 3. Mean mBI scores at baseline, and the 8- and 24-week follow-ups with p values in the MSC (stem cell) and control groups.

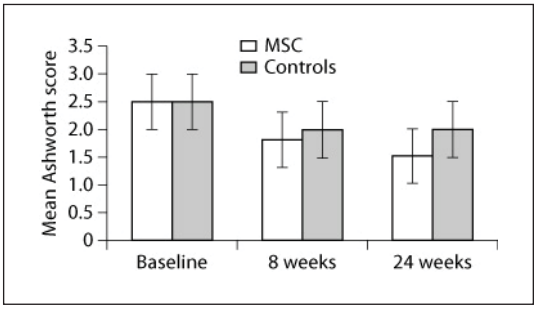

Fig. 4. Mean Ashworth scores between the MSC and control groups.

Fig. 5. Comparison of BOLD activation between the MSC and control groups in right-hemispheric stroke overlaid on rendered images.

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Table 3. Comparison of BOLD activation between the MSC and the control group at 24 weeks in right-hemispheric stroke

Cluster	z score	MNI coordinates (x, y, z), mm	Hemisphere	Area of activation	Brodmann area
71	4.02	16, –,50, 54	right cerebrum	precentral sulcus	BA 4
112	2.95	18, –36, 46	right cerebrum	medial frontal gyrus	BA 6
56	4.05	–54, –36, 26	right cerebrum	inferior parietal lobule	BA 40
40	4.56	–48, 4, –8	left cerebrum	superior temporal gyrus	BA 22, 21
92	3.97	8, –40, 28	right cerebrum	cingulate gyrus	BA 31
95	3.36	–2, 18, 34	left cerebrum	cingulate gyrus	BA 32
87	2.99	–14, –12, 20	left cerebrum	caudate	caudate body
115	2.50	–48, –14, –26	left cerebrum	inferior temporal gyrus	BA 20, 21

One cluster 2*2*2 mm^3. MNI = Montreal Neurologic Institute.

The MSC group had 5 cortical and 1 subcortical lesions, 2 patients (patients 2 and 4) were hemorrhagic, and the remainder was ischemic with a lesion volume of 12–58 ml. All patients in this group showed significant improvement after 8 and 24 weeks versus baseline. The control patients had 4 cortical and 2 subcortical lesions (volume: 10–55 ml). All patients in this group showed significant improvement after 8 and 24 weeks versus baseline. Using the 2-sample t test, we observed no statistically significant (p 1 0.05) difference in FM, mBI, LI and FA ratios between both study groups after 8 and 24 weeks. However, the mean percentage change in FM scores between 8 weeks and baseline levels and between 8 and 24 weeks were 74.6 and 26.2%, respectively, in the MSC group and 61.3 and 25.8% in the control arm, respectively. The change from baseline to the 24-week follow-up was 120% in the MSC group compared to 102% in the control group, suggesting a minor trend to improvement in patients administered MSC. There was only a minor change in the power of wrist and hand muscles (subjective analysis) compared to the control group, though we observed a decrease in tone in spastic muscles, a lower pain threshold and a better functional performance in the MSC group (fig. 4).

In 1 MSC patient (No. 2) who had a large right temporoparietal lesion, we observed a shift in the LI from negative to positive (table 3). At baseline, there was an increased activation in the supplementary motor cortex (BA 6) compared with the primary execution area (BA 4) in nearly all patients (recruitment principle of plasticity) [32, 33]. After an 8-week physiotherapeutic regime, there was an increased number of voxels in BA 6 in both groups. In the MSC group, the premotor and supplementary motor areas (BA 6) had an increased number of voxels active at the 24-week follow-up suggesting the ‘focusing’ principle of neural plasticity although the LI at the 24-week follow-up was not statistically significant (p ! 0.05) between both groups. We noticed a considerable increase in LI and signal intensity [34] from baseline to 8 weeks indicating that a focused exercise regime which involves vigorous training of the hand leads to increased force of activation performing better in the fMRI task compared to the performance at 24 weeks.

We correlated FM scores with FA ratios at 24 weeks and found no significant difference in improvement between the MSC and the control group, but 4 of 6 patients (patients 1, 3, 5 and 6) in the MSC group showed good recovery at follow-up with FA 10.6, whereas in the control group only 3 of 6 patients improved. This minute change in the integrity of the motor tract system might have been due to axonal remodeling imposed by the transplanted MSC [35, 36] although there was no statistical significant change in FL and FN ratios between the groups.

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The dosage of stem cells prescribed in our study was in congruence with previously published trials [11, 12] and still ongoing studies [37, 38]. The earlier research groups administered 2 × 50 [11], and 200–400 [39, 40], 5–10 [41] and 34.6 × 10^6 cells [42]. Our findings were in agreement with those of other clinical trials as adverse reactions, mortality or any other risk factor were not noted in association with MSC administration of up to 50–60 × 10^6 cells in chronic stroke patients.

It has been proved that stem cells given intravenously home in the infarcted regions thus promoting functional recovery in chronic stroke rats [43]. However, cell-enhanced recovery has been reported with chronic delivery of cells even 1 month after ischemia [44, 45]. The best route of transplantation still needs to be established considering the specific cell type or the mechanism of action underlying the beneficial effect.

We did not find any significant change in the pattern of recovery of ischemic and hemorrhagic stroke. Previous clinical trials recruited both ischemic and hemorrhagic stroke patients but could not elucidate the effect of cells on the type of stroke [39–42]. We tried to match the patients with respect to lesion volume but could not find any significant change in the volume and the correlation of the same with MSC therapy.

In our study, the safety and feasibility of expansion of these cells was established in 6 patients. However, our results showed no statistically significant improvement in all clinical scores and functional imaging parameters at 8 and 24 weeks. This could be attributed to a very small sample size and the heterogeneity in MSC group patients (1 patient, No. 2, had a large temporoparietal hemorrhage with a very low potential to recover). We explored infusion with stem cells and physiotherapy as a combination therapy to look into behavioral recovery after stroke. Our aim to administer stem cells intravenously was based on the hypothesis that intravenously administered stem cells will help to upregulate growth factors within the body and brain making the host environment conducive for behavioral recovery [18, 19], as it is known that enriched environment, physical activity, stress or molecules such as BDNF, VEGF and dextroamphetamines lead to reorganization of brain areas [46–48].

Due to the small sample size, non-randomized trial, dose of cells, site and mode of transplantation, cellular milieu and recovery factors after stroke, we could not reach a definite conclusion regarding the potential of MSC in chronic stroke [49, 50]. This study shows, however, that autologous MSC transplantation is safe and feasible. More research is required to evaluate the efficacy of MSC transplantation.

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Essential Workflow and Performance Measures for Optimizing Acute Ischemic Stroke Treatment in India

M.V. Padma Srivastava, MD, DM; Rohit Bhatia, MD, DM; Venugopalan Y. Vishnu, MD, DM; Mayank Goyal, MD, FRCPC

Stroke is a leading cause of death in India, which has one-fifth of the world's population. The approximate age-adjusted prevalence of stroke in India is 84 to 262/100 000 in rural and 334 to 424/100 000 in urban areas, and the age-adjusted incidence of stroke is 135 to 152/100 000 person-years.[1,2] The recent data from the GBD study (Global Burden of Disease) also suggest a high burden of cardiovascular disease in India due to a major epidemiological transition leading to a surge in noncommunicable diseases over the past 2 decades.[3]

See related articles, p 1928, p 1932, p 1941, p 1951, p 1961 and p 1978

Stroke is incorporated in the National Program for Prevention and Control of Diabetes, Cardiovascular Disease and Stroke.[4] The objectives of the program include behavior changes for lifestyle modification, screening, and prevention of noncommunicable diseases, capacity building, optimizing treatment at all levels of health care and surveillance systems for disease burden and monitoring.[5] Stroke Registry program was started in 2012 to collect data about stroke patients and as of 2016, across India 62 institutions have registered with it. This venture was initiated by the Indian Council of Medical Research along with the National Center for disease informatics and research.[6] An Indo-US Collaborative Stroke Registry was started with 5 major teaching institutes from India and one major institute from the United States to develop a registry with high-quality data.[7,8]

However, there are multiple barriers in the implementation of optimized care among patients with stroke at the level of the following:

- patient (late arrival or low awareness of stroke symptoms, denial of stroke, financial incapacity, sociocultural practices or beliefs inhibiting access or seeking optimal stroke care)
- hospital or health system level (personnel with expertise in managing stroke, management will and support, lack of adequate medical facilities or equipment, well-defined protocols and standard operating procedures as also policies, supporting policies, organizational context, or norms, which support the implementation of evidence-based care)
- stroke specialists and professionals (stroke teams, competence, skill, awareness, confidence, and experience in dealing with clinical situations, ability to take timely clinical decisions and confidence to do so, motivations, attitudes, and willingness to provide evidence-based stroke care)
- national health policies (political will, allocation of resources, reimbursement of costs to different health care sectors, to support stroke patients' access to optimal care and the regulatory frameworks or policies to support stroke care).[9,10]

The current article deals with the existing stroke care pathways, its challenges and possible future initiatives to optimize workflow in India.

Key Words: cardiovascular diseases ■ incidence ■ population ■ prevalence ■ workflow

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CURRENT STATUS OF HEALTH CARE AND THE CHALLENGES IN INDIA

Stroke Education

Public awareness of stroke will help in reducing the window period for seeking help from a capable hospital. In a study, which assessed 524 patients in Rajasthan, 12.8% of the patients were taken to a primary care hospital with no stroke management capability.[11] Around 52% knew that the organ involved was brain but only 2% knew about thrombolysis. The mean time of presentation to hospital after stroke onset was 26 hours with a SD of 2.6 hours. The mean distance of the hospital from their residence was 66 km. A majority had heard about stroke but only 7.5% had the information from health professionals. Thus, although the majority had preliminary knowledge about what a stroke was, only a few knew that it can be effectively managed if brought to a capable hospital within a specified time window.

Regional Differences and Rural-Urban Divide

India is nations within a nation which poses a unique challenge with 22 official languages and innumerable ethnic, racial, and geographic variations.[3,12] In Ludhiana Stroke Registry from Northern India, there was a significant difference in risk factors between urban and rural population like hypertension and hyperlipidemia.[13] From Southern India (Trivandrum registry), case fatality rate was 24.5% for urban and 37.1% for rural population.[14] There were higher rates of hemorrhage in the rural population of both Ludhiana and Trivandrum registry. Imaging availability is restricted to urban areas and metropolitan cities where only 30% of Indian population lives, making the provision of thrombolysis unfeasible to 70% of population. These regional differences with rural-urban divide pose great challenges in preparation of a national action plan for stroke.[12]

Health Care Delivery Model in India

India has a hierarchical model of health care delivery with a 3 tier system (primary, secondary, and tertiary).[15] The primary health centers are managed mainly by physicians (with MBBS degree) while many primary health centers in rural areas do not have access to doctors. District hospitals form the second tier which is better equipped with MD physicians and basic facilities. Medical colleges form the tertiary centers where most of the cases get referred to. Various strata of health care availability leads to heterogeneity in the care provided. Added to this complex system, is the predominance of private health care providers, who do so at costs prohibitive to the majority of the Indian population. The public-private divide of health care delivery models, affecting accessibility and affordability, pose enormous challenges for equitable distribution of optimal health care to all.

Lack of Workforce in Acute Stroke Care

Although clinicians are paramount, the stroke team would also require well equipped and swift ambulance services, swift access to radiology, trained paramedical and nursing personnel and rehabilitation facilities. While the above aspects are mandatory, the ground realities in India are lack of uniform nationalized and prompt ambulance services; very few neurologists (2300 neurologists for 1.2 billion population) and an extremely skewed health infrastructure development including radiology services.[16] The small number of neurologists means that most stroke care will have to be provided by physicians and other health care providers. These factors impede access to acute care and ongoing follow-up for primary and secondary prevention. The primary care physician and the physician extender system is not well developed resulting in suboptimal access to the ongoing management of vascular risk factors. These health care providers are not well trained or informed about treating vascular risk factors, the recognition of stroke symptoms/signs and newer developments in management. There is a profound lack of awareness amongst patients and the public about these issues.[17,18]

Lack of Accessible and Affordable Stroke Care

Quintessentially, the challenge is to make optimal stroke care accessible, affordable, and acceptable to all Indians, irrespective of social, economic, and geographic barriers. There is no universal insurance coverage system in India and most of the patients pay from their pocket.

The Way Forward and Meeting the Challenges

Stroke awareness programmes at the national level should be planned by the government and Indian Stroke Association. Physicians and primary health center doctors should be trained in stroke detection and management. While the primary health centers are pivotal for their proximity and acceptability to the interiors of Indian terrain, they can serve only the preventive and educational aspects of health care. In the stroke chain of survival, they can help in stroke recognition and referral, as well as in stroke prevention and rehabilitation. The district level hospitals in India are better equipped in terms of infrastructure and personnel and can serve as primary stroke centers. The medical colleges, institutes, and major public and private chain of hospitals are pillars of tertiary care and referral in all states which can be developed into comprehensive stroke centers. Incorporating the physicians in the national umbrella of the stroke program will help tap their potential in the national fight-stroke program and will be able to generate an adequate work force. Because the physicians practise closer to the community, stroke care would reach closer to the general population.

One of the major aspects in Indian health care delivery is the ratio of public and private sectors. Currently, nearly 70% of health care is managed by the

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private sector. Integrating the private health sector into the nationalized health care chain for holistically improving the access and affordability is a major challenge. One solution could be fostering the public-private partnerships in acceptable terms so as not to jeopardize the sustainability and growth of both sectors. Accessibility and affordability are major factors affecting a successful health care model especially in a resource limited setting like India. The recent launch and enforcement of Modicare for all (Ayushman Bharat) has provided for identifying and ensuring at least 30% of the Indian population with lower socioeconomic status to access and afford advanced health care.[19,20] This programme is actively exploring the public-private partnership and it is hoped that stroke care will be in operational ambit soon.

Ensuring universal access to optimal treatment and health equity remains a big challenge, but a step in the right direction has been taken. A national programme (Pradhan Mantri Bhartiya Janaushadhi Pariyojana) was launched to provide quality generic medicines at affordable Prices.[21,22] A few states have introduced programmes (Mukhya Mantri Nishulk Dawa Yojana) to provide medicines (606 essential and lifesaving medicines, 137 surgical items, and 77 sutures) at no cost for every patient seeking care from any government hospital.[23,24] Food Safety and Standards Authority of India has launched The Eat Right Movement which is built on two broad pillars of Eat Healthy and Eat Safe and aims to engage, excite, and enable citizens to improve their health and well-being.[25] Recently launched public advertisement of Aaj Se Thoda Kam (reduce by little from today) has received wide attention.[26] Lifestyle modifications are promoted nationally by government programmes like International Yoga Day and recently launched Fit India Movement which encourage Indians to embrace fitness activities and sports as part of their daily lives.[27] India has laws that dissuade people from using tobacco and related products in public places. The sale or consumption of tobacco within 100 m of an educational establishment is also banned in India. Political willpower is required for the implementation of all these programmes at ground level to tackle risk factors of stroke.

STROKE SYSTEMS OF CARE

The continuum of stroke care involving the stroke chain of survival is considered as the key for best outcome consisting of prehospital, intrahospital, and post hospital organization of stroke services continuing into secondary prevention, step-down rehabilitation, measures for evaluation of stroke outcome, and a dedicated quality assessment. In India, currently there exists striking disparities across the country in terms of facilities, personnel, and processes.

Prehospital Assessment and Transport

There are very few structured and trained ambulance services in various states of India. Most of the patients use their own/hired vehicle to reach a hospital. 108 is a free telephone number for emergency services in India established in a public-private partnership, which is functioning in 22 states and 2 Union Territories.[28] But the paramedical staff is not trained in prehospital assessment and care of acute stroke. They are trained in transporting trauma injuries, cardiac, and obstetric emergencies. A national or state-level stroke helpline is absent except in few tertiary care/private hospitals.

The Way Forward

An effective nationwide stroke program requires the development of a strong stroke systems of care plan. To improve the prehospital stroke delivery system it is necessary to enhance the effective utilization of existing ambulance services by training the paramedical staff in acute stroke detection, creating a national/state-level stroke help line, creating a state/district level stroke map of stroke ready hospitals, and notifying emergency departments. The emergency ambulance services personnel must be specifically trained to detect stroke, activate the stroke code, and prenotify arrival to the nearest stroke-ready hospital with the help of the available stroke map. Such a system should also include clear pathways and instructions as to where referrals are made for acute stroke victims at specific locations. Catchment areas for each Comprehensive Stroke Center (CSC) and Primary Stroke Center (PSC) should be defined.

Creation of dedicated emergency departments in district hospitals and tertiary centers will help in establishing stroke protocol in the existing systems. Although computed tomography (CT)-equipped mobile stroke units are considered a seminal advancement proven to increase intravenous thrombolysis rates with significantly shorter time to treatment intervals, the provision is expensive and may not be cost productive across a large developing country like India. Nevertheless, in the North-Eastern region of the country, which has a unique terrain, three mobile stroke units have been sanctioned under the aegis of Indian Council of Medical Research, which connect 3 large districts (Guwahati, Dibrugarh, and Tezpur), covering ≈1.2 million population. Educating the general population on how to effectively activate emerging medical services and educating and empowering the district medical personnel and the medical colleges in these 3 districts is being done to ensure prompt reporting of patients in time and to the right place for appropriate management.

India is the second largest and one of the fastest-growing digital markets with 1.2 billion mobile phone subscriptions and 560 million internet subscribers in 2018.[29] The tremendous increase in smartphone availability

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should promote the creation of innovative stroke-Apps which can recognize stroke and direct patients to stroke helpline/stroke ready hospitals.

In Hospital Treatment

Acute Thrombolysis and Mechanical Thrombectomy

Thrombolysis is underutilized in our country. Approximately >12 000 patients were treated with intravenous tissue-type plasminogen activator in year 2016 across the country, and the numbers have steadily increased with temporal trends showing improved rates in tertiary care settings.[30] The approval of biosimilar Tenecteplase and publication of 2 open label multicentric trials in India has also increased the use of Tenecteplase as it is perceived to be cheaper and more practical to use. Debate, however, still exists among the stroke neurologists in the country whether sufficient data exists for its approval.[31,32]

However, the numbers of patients thrombolysed are far low compared with the eligible patients.[33] In the Indo-US registry, 11.5% of the patients with stroke received IV rtPA (recombinant tissue-type plasminogen activator) which was higher than that of China.[34] However, this percentage does not reflect the true national usage of rTPA. These data are only from the 5 major institutes of national importance in the country who admit preferably the severe strokes or those patients who require acute reperfusion strategies on account of limited bed availability. Another source quoted the average thrombolysis rate in India to be 0.5% of all strokes.[35] In China, however, almost every patient who presents with acute stroke is admitted.

Currently, an estimated 100 centers across the country would be stroke ready for thrombolysis. The reasons for the low utilization of thrombolysis are manifold. The awareness among the pubic regarding thrombolysis is poor when compared with what they would do if they had chest pain and suspected a heart attack. Timely access to a stroke ready hospital is difficult, especially to those residing in remote areas, as well as those areas with no dedicated and prompt public ambulance services to ferry patients.[36]

Precious time is also lost due to patients being taken to the nearest primary care center for the first consultation, which may not be stroke ready with time being lost doing investigations and a delay in referral. Many health care facilities lack CT scan and crucial time is lost in obtaining the CT/magnetic resonance imaging from imaging facilities at a distance.[37,38] The cost of medication is also an important factor, and differences in cost of care in public versus private hospitals are another deterrent. Neurologists are limited, mainly centered around the urban communities and physicians are not routinely trained to be confident to make decisions and thrombolyse patients.[1] There is generally an apprehension not to cause a complication and make a patient worse. Also, concerns about legal issues contribute to uncertainty in decision making.

The issue related to endovascular stroke treatment (EVT) is more complex. With the publication of newer data, tissue window therapies are slowly replacing time sensitive boundaries in stroke treatment and an increasing need for centers equipped with infrastructure and manpower to provide EVT. The effectiveness of reperfusion therapies is highly time-dependent; the promptness of the patient's presentation to the hospital will determine the outcome. The proportion of patients treated with EVT has increased in recent years in high-income countries mainly in CSC, where EVT is provided. With the advent of evidence for EVT, there has been an increase in centers providing stroke intervention to patients with large vessel occlusions in India. It is estimated that about 40 to 50 centers across the country have the facility for EVT. However, many factors are likely to contribute to the limitations of performing or setting up of this service. These include very limited number of neurointerventionists, cost of setting up the service, and high cost of therapy. Whereas in the West, there are concerns of setting up protocols and sensitive means of detecting large vessel occlusions and deciding to bypass PSC for CSC, these goals are not the priority for India as it is extremely important that timely acute stroke care at least for thrombolysis and in-hospital supportive care is provided and set up in most government-aided hospitals even in smaller cities.[39,40]

The Way Forward

Increasing public awareness of stroke symptoms and therapeutic advances, political interventions for the availability of necessary treatment in public hospitals and reducing costs of treatments both at the industry and hospital level are desired steps to increase eligible patients receiving thrombolysis or timely supportive treatment. In-hospital delays should be minimized with highly organized workflows to achieve the desired/ideal door to needle times and door to groin puncture times.[41] Stroke guidelines were put forward by the Indian Stroke Association in 2018, which covered the broad aspects, including thrombolysis and thrombectomy.[42] The national stroke guidelines have also been released recently to encompass different levels of stroke care.[43] However, many unmet needs and challenges remain.

Effective strategies need to be instilled as a well-oiled machinery to reduce critical time delays. Some strategic interventions include education to the emergency staff, direct transfer to CT scan room from emergency and direct thrombolysis in the CT room etc which are eminently possible even in a primary stroke center in India.[41] It is also imperative that vascular imaging using CT angiography is routinely performed in the acute phase to plan for EVT or consider shipping to a higher center after starting thrombolysis.

EVT, however, needs a far more rigorous intervention both in terms of training the skilled personnel as well as the development of infrastructure. In the developed world,

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there has been a rethinking of the systems of stroke care at a national and regional level to optimize the hub and spoke transfer networks. In India, with very few CSCs capable of EVT, a direct transfer may not be time-efficient, unless the concerned geography has the stroke-map showing sufficient proximity to do so (Figure 1). Enhancing the capability and affordability for EVT and the measures required to do so are apparently more important than reorganizing the transfer networks. Capability for EVT will mean enhancing the number of CSCs, whether they are strictly under public or private set ups. The National Boards of Education, Government of India has recently launched a fellowship/training program for Neurointerventions including stroke interventions, broadening the ambit of entry with inclusion of neurologists, neurosurgeons, and radiologists.[44] With this certified training and expertise, there is hope to enhance the number of CSCs across India. Demand for neurointervention in coming years will grow with increased number of EVT-capable centers. The government should establish a national certification programme in consultation with national stroke agency which will certify and recertify centers as stroke-ready, primary, thrombectomy capable, and

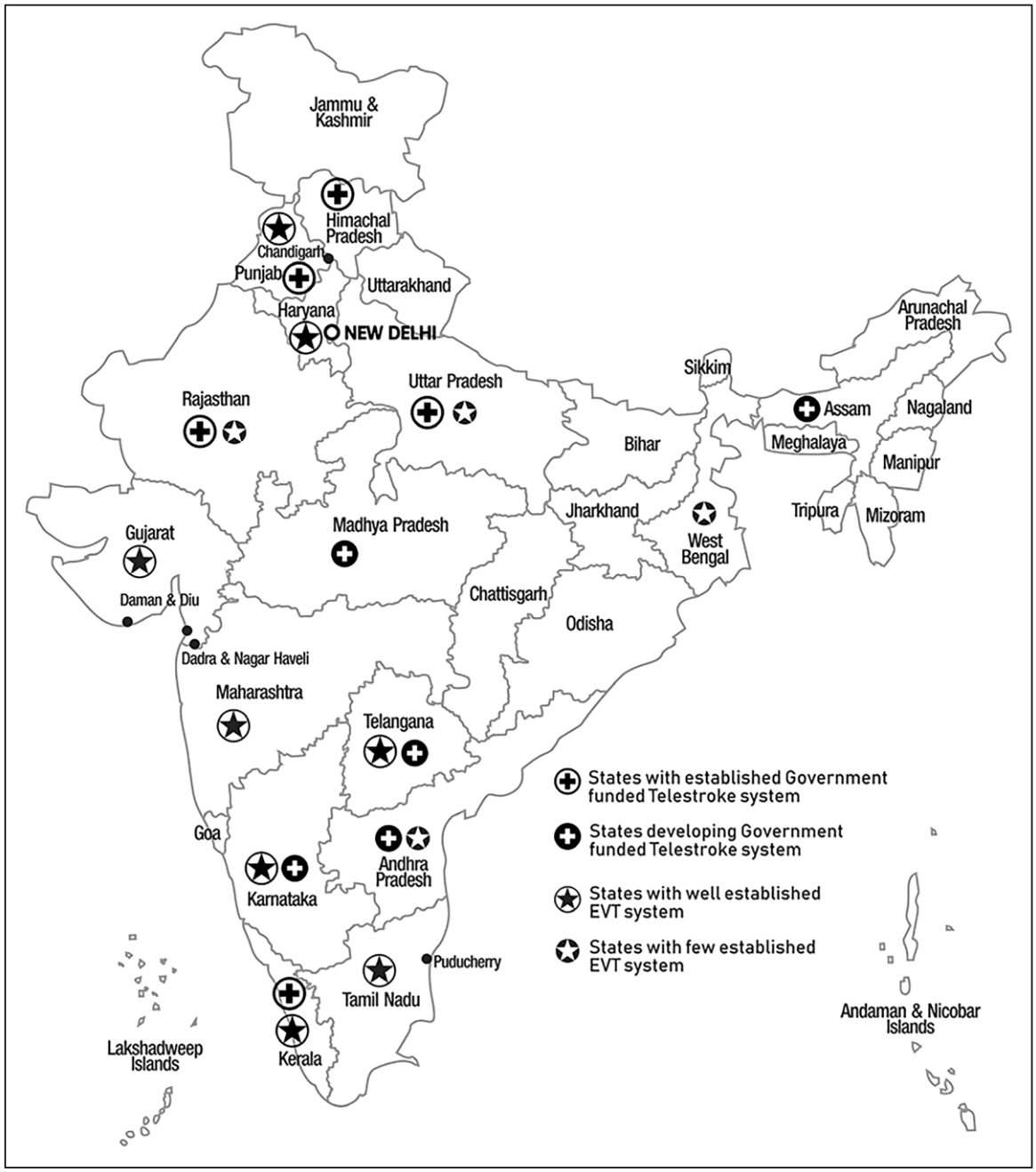

Figure 1. Stroke map of endovascular workflow available states in India and states running government-funded telestroke systems (Dr Vikram Huded, Head of Interventional Neurology and Stroke, NH Institute of Neurosciences, personal communication).

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comprehensive stroke centers. This can be integrated with the existing governmental agencies for accreditation of hospitals like National Accreditation Board for Hospitals and Healthcare Providers. Specific funding may be provided to these hospitals especially those situated in rural areas that achieve the resources and qualifications required for certification thus fostering their growth and sustainability.

Telestroke facilities through telemedicine seems to be the promise, which has the potential to optimize stroke care across all strata bridging the economic and geographic barriers in the country.[45,46] The decrease in price and complexity of this technology over last decade makes it economically viable for India. Telestroke can serve to address the problems of both insufficient numbers of stroke specialists as well as the narrow therapeutic time for treatment with rtPA and stroke can be diagnosed expediently and remotely.[47] In addition to enhancing the delivery of intravenous rtPA within 4.5 hours of symptom onset, telestroke is of immense value to guide physicians in spoke hospitals in the decision making process to emergently transfer a patient to the hub hospital for advanced recanalization therapies including EVT.

There is sufficient evidence to suggest that thrombolysis, when given using telestroke consultation, is as safe and effective as when it is given in a stroke center.[5–7] Telemedicine for stroke management is a level I, class A recommendation when a vascular neurologist is absent.[48,49] However, current telestroke networks require exorbitant start-up costs, which are prohibitive for the resource poor countries in which they are needed most. To deliver this treatment in resource poor settings, therefore, becomes all the more challenging. Telemedicine in acute ischemic stroke has been practiced by a number of technological devices less sophisticated than videoconferencing, including telephones, Multimedia Messaging Service, email, or some combination methods.[47]

Indian telestroke model consists of WhatsApp-technology over a smart phone which is entirely a no-cost design. Having accrued experience over past 5 years in a single small hilly state in the Northern region of India (Himachal Pradesh), this design has now been implemented under the National Program for Prevention and Control of Diabetes, Cardiovascular Disease and Stroke program across several states in the country[47] (Figure 1).

The first ever telestroke program was started in March, 2014, in Himachal Pradesh.[46] Till 2017, around 150 patients have received thrombolysis through the telestroke program in Himachal Pradesh without any additional utilization of infrastructure. Innovative programs like telestroke should be encouraged and enhanced to increase the stroke care in remote areas.

Stroke Unit Care

Stroke units provide more effective management than management in general wards. In India, around 35 stroke units are present, mostly in private sectors and in metropolitan cities primarily catering to an urban population. Stroke unit implementation remains a major challenge in India. A dedicated team and a place to manage stroke patients are also suboptimal in substantial number of hospitals.[50] The barriers for the development of stroke units are many. Stroke unit requires a geographically separate location with

	Challenges		Solutions
	Major	Minor	
Patient level	• Lack of awareness • Poverty • Quacks/Fraudulent practice	• Alternative Medicine • Regional differences • Rural-Urban divide	• Stroke and risk factor awareness programmes at national and regional levels • "The Eat Right Movement" • "Fit India Movement"
Transport	• Lack of ambulance services • Lack of training of paramedical staff in stroke • Poor roads and Traffic	• Lack of stroke helpline • Lack of Stroke map	• Creating a National Ambulance service in public-private partnership (108 ambulance service) • Creation of stroke map of stroke ready hospitals in both public and private settings • CT-equipped mobile stroke units in remote difficult to access areas • Low-cost innovative Telestroke system
In-hospital	• Lack of Neurologists • Lack of Interventional Neuroradiologists/Neurologists • Lack of stroke units	• Delay in triage • Delay in recognizing stroke • Cost of drugs/intervention	• Creating Emergency medicine cadre and department in all district hospitals • Training physicians in acute stroke management • Fellowship programmes in Neuro-intervention • Affordable and Accessible health care to low socioeconomic strata (Ayushman Bharat) • Free emergency drugs/intervention procedures in public hospitals (Pradhan Mantri Bhartiya Janaushadhi Pariyojana) • Administrative and policy changes to find dedicated space in emergency for stroke ("stroke unit")

Figure 2. Challenges and solutions for stroke workflow in India.

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required number of beds, nurses, stroke physicians, physiotherapists, with necessary pharmacopeia for stroke care, critical care set up, and neurosurgical support if required. The cost involved in establishing a stroke unit is the prime stumbling block in most developing countries, including India. Regular audit of performance measures, with monitoring of the care given and regular quality improvement drives are mandatory to meet international standards.

The Way Forward

It is imperative to set up more stroke units in the country. As a part of the National Program for Prevention and Control of Diabetes, Cardiovascular Disease and Stroke program, each district hospital with stroke care facility should mark space for stroke patients where they can be specifically cared for by a group of dedicated personnel. Setting up of stroke care pathways with well-specified guidelines and algorithms helps in improving outcomes.[51] The monitoring of fever, swallowing, and sugar levels in any poststroke patient are critical and is associated with a significantly improved outcome. Currently, research for implementation is being performed across few hospitals in India (CTRI/2017/08/009411). With limited nursing personnel for the number of stroke patients, steps are being taken to improve care giver knowledge and understanding about caring for acute and chronic needs. There is a likely potential that this intervention will reduce in-hospital complications, reduce patient stay, and improve long-term outcomes (ECCOS trial [Evaluating the Role of Structured Education to Care Givers in Reducing Complications in Hospitalized Stroke Patients and Improving Their Outcomes - A Cluster Randomized Trial] CTRI/2018/11/016312).

STROKE RESEARCH IN INDIA

The INSTRuCT (Indian Stroke Clinical Trial Network) was established by the Indian Council of Medical Research to create a network for conducting clinical trials on stroke in India. Currently, 24 centers across India are part of this network who are participating in 2 ongoing multicenter trials (RESTORE [Ayurvedic Treatment in the Rehabilitation of Ischemicstroke Patients In India: A Randomized Controlled Trial] and SPRINT INDIA trial [Secondary Prevention by Structured Semi-Interactive Stroke Prevention Package in India]). INSTRuCT is collaborating with National Institutes of Health to create

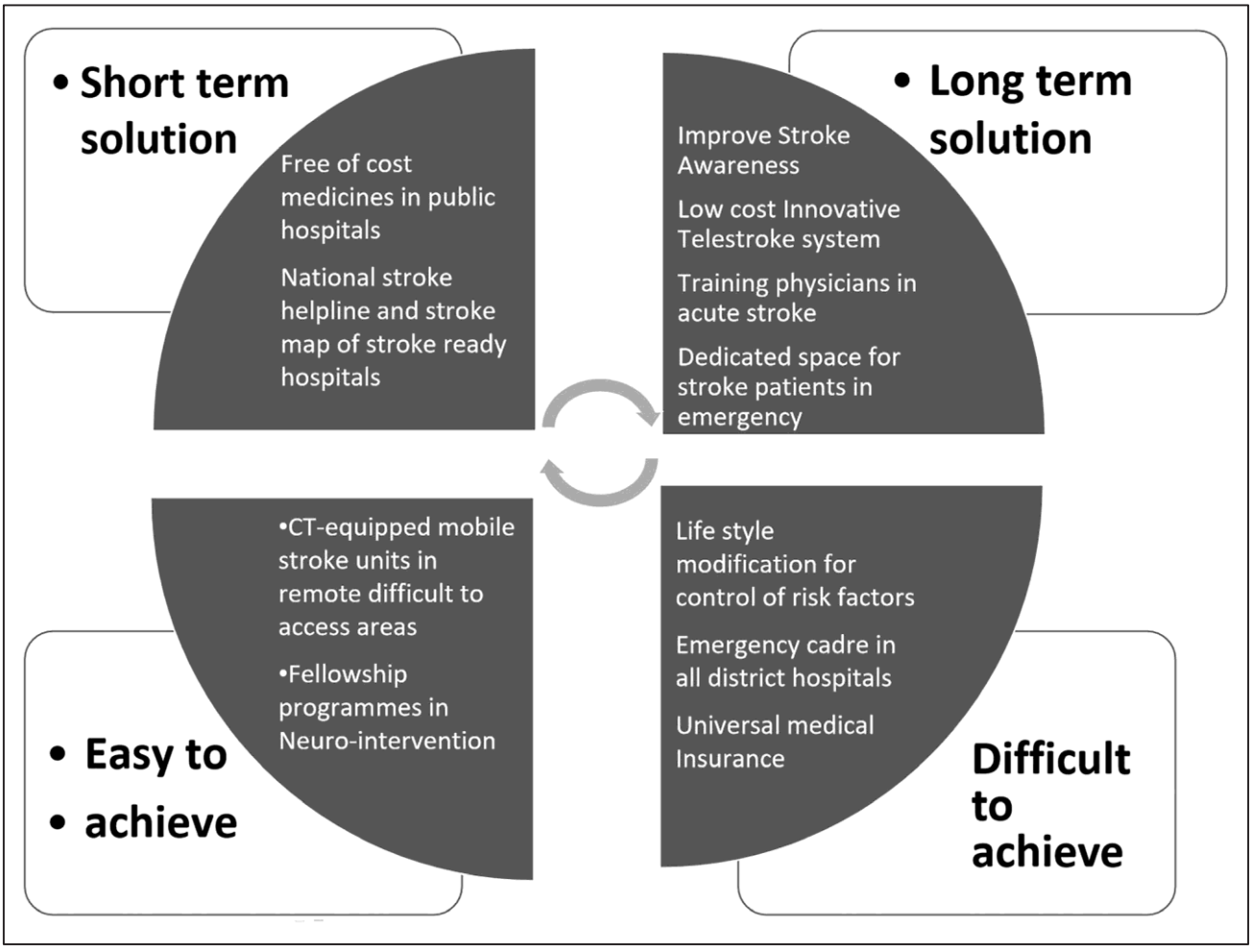

Figure 3. **Short-term and long-term solutions in stroke care in India.**

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INSTRuCT-National Institutes of Health network which will further advance international collaboration and make India a launchpad for major clinical trials.

STROKE IN INDIA: GLASS HALF FULL AND HALF EMPTY

Glass Half Full

There is no ambiguity in claiming that a tremendous amount of thrust and increment has happened in stroke care in India, essentially in past 2 decades (Figures 2 and 3). Progression, from a sparse and negligible number of intravenous thrombolysis at the beginning of the decade to nearly 16 000 per year (personal communication from Boehringer Ingelheim) is by no means a meager achievement. EVT has improved in numbers in terms of personnel, infrastructure, and centers. Stroke awareness, stroke unit care, and development of PSCs and CSCs have improved over the last decade. We now have a dedicated national association for stroke, a stroke journal (Journal of Stroke Medicine), developed and published Indian Stroke guidelines, developed national and international stroke network for research and integrated Stroke into the national priority in health care.

Glass Half Empty

India is a huge developing country with unique social, economic, cultural, ethnic, and geographic heterogeneity leading to barriers in health care delivery system which includes stroke; thereby, posing innumerable challenges and road blocks in endeavors to optimize stroke care across the length and breadth of the country. Meeting these challenges continues to be a herculean task in terms of attitudes, policy, finances, expertise, knowledge, know-how, implementation, and audit. However, accepting these challenges, learning from experience, and moving forward should be the plan for achieving the target of best stroke care for all in India.

CONCLUSIONS

To deal with the huge burden of Stroke in India, innovative stroke systems of care which are India-centric and cost-effective are mandatory. A National Stroke Plan to fight-stroke needs to be developed and implemented. Integral to this plan is the singularly important aspect of providing the best treatment to all patients eligible for reperfusion therapies. Other initiatives such as involvement of public-sector health care personnel, hospital preparedness, legislative, and economic factors remain keys to success in improving access to optimal stroke care. The different aspects of stroke systems of care will need to be refined for India-specific health-care delivery model and made robust enough to weather the storms of resistance to changes. Implementing strategies to address this bottleneck falls within the gambit of public health and education but is prone to marked local and regional variability. With its great diversity, including innumerable ethnic, racial, and geographic variations, India poses a unique challenge. But is mandatory to overcome this bottleneck for any success in achieving optimal stroke care.

ARTICLE INFORMATION

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