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Research Article
Role of Levetiracetam in the Rehabilitation of Dysphagia due to Stroke

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Abstract

Background and Objective: Cerebral apoplexy may develop infarcts in cerebral, cerebellar, or brain stem lesions.It may lead to developing dysphagia-a physiological complication. The objective of the study was to explore the effect of levetiracetam in the rehabilitation of dysphagia due to cerebral apoplexy. **Materials and Methods:** There were 638 patients with dysphagia due cerebral apoplexy enrolled for the study. Each patient of placebo, treatment and control groups was received placebo tablets, levetiracetam 500 mg film coated tablets and levodopa (in combination with carbidopa in 10:1 ratio) tablets twice daily for eight weeks respectively. Qualitative, quantitative measures of video fluorographic study, electroencephalography and mu rhythm of all patients were evaluated at theinitial stage and at the end of successful treatment of 8 weeks. The one-way ANOVA and the Wilcoxon test were used for all parameters to show a significant difference between groups and within the group at the 95% level of confidence. **Results:** There was a reduction in aberrant bolus movement, dorsal head compensation, abnormal posture and cough/gag at the end of treatment of in treatment group and control group with respectto theplacebo group. There was a significant improvement in bolus speed, mastication speed, jaw excursion, bolus area, alpha, beta and gamma oscillations after eight weeks of treatmentbetween placebo group and treatment group and placebo group and control group ($p<0.05$ for all). After 8 weeks of treatment, there was a significant improvement in alpha, beta and gamma oscillations between control group and treatment group ($p<0.05$). **Conclusion:** This study identified significant effect of levetiracetam in the rehabilitation treatments of dysphagia due to stroke.

Key words: Cerebral apoplexy, dysphagia, electroencephalography, levetiracetam, video fluorographic studies

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

After cerebral apoplexy (Stroke), there could be chances of several and multiple physiological complications like dysphagia (DP) and complications of the other neurological functions[1]. Cerebral, cerebellar, or brain stem lesions of thebrain are attached with thephysiology of swallowing[2]. Due cerebral apoplexy, there could be thedevelopment of infarcts in posterior brain areas which resultinswelling of cortex, lesions of the insula, the frontal operculum and the primary sensorimotor cortex, damage to posterior limb of the internal capsule and the other parts of thebrain. These anatomical changes may lead to DP (Fig. 1)[3].

Swallowing is the complex biomechanical process[4]. The most frequent occurred complication after cerebral apoplexy is a DP. The advanced DP patients receive food via nasogastric or percutaneous gastrostomy tubes but it is not patients' compliance technique of feeding, one nursing should engage in the procedure per patient and costly too[5].

At present levodopa in combination with carbidopa (LC) is the drug of choice of physicians for DP[6]. Levetiracetam (LET) is chemically (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide. Till date, LET is used as antiepileptic, anticonvulsive and anti-ictogenic[7]. The LET modulates glycoprotein that interacts with synaptotagmin and regulates exocytosis of synaptic vesicle[8]. Till date, no any three-arm studies that showing LET significantly effective as compared to placebo and LC (10:1 ratio) treatments in the rehabilitation of DP iscarried out.

The present study tested hypothesis that LET is effective and is superior to placebo and LC in the rehabilitation of DP due to cerebral apoplexyof a mild, moderate and advanced category of severity. The finding was validated by Video Fluorographic Swallowing (VFS) studies and electroencephalography (EEG).

MATERIALS AND METHODS

Keppar® (Levetiracetam) 500 mg film-coated tablets were purchased from UCBPharma, Belgium. Scored Sinemet (anhydrous carbidopa 25 mg and levodopa 250 mg) tablets were purchased from Bristol-Myers SquibbShanghai China. Placebo (sugar or inert cellulose) tablets were purchased from Shandong Luoxin Ltd, Weifang, China.

The Ethics Committee for Human Experiments of the Second Clinical College of the Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China approved the experimental protocol under thereference number ofChiCTR-TRC-14004955 and the Ethical Guidelines for biomedical research on human participants in accordance with Chinese law was followed[9].

Inclusion criteria: There were 638 patients who were enrolled for the study. They were age older than 35 years, time of treatment was 2-7 days after onset of advanced, moderate or mild symptoms of DP. The cortical infarction of DP was documented by imaging. The patients of the Second Clinical College, Nanjing, China, Gaochun Hospital of

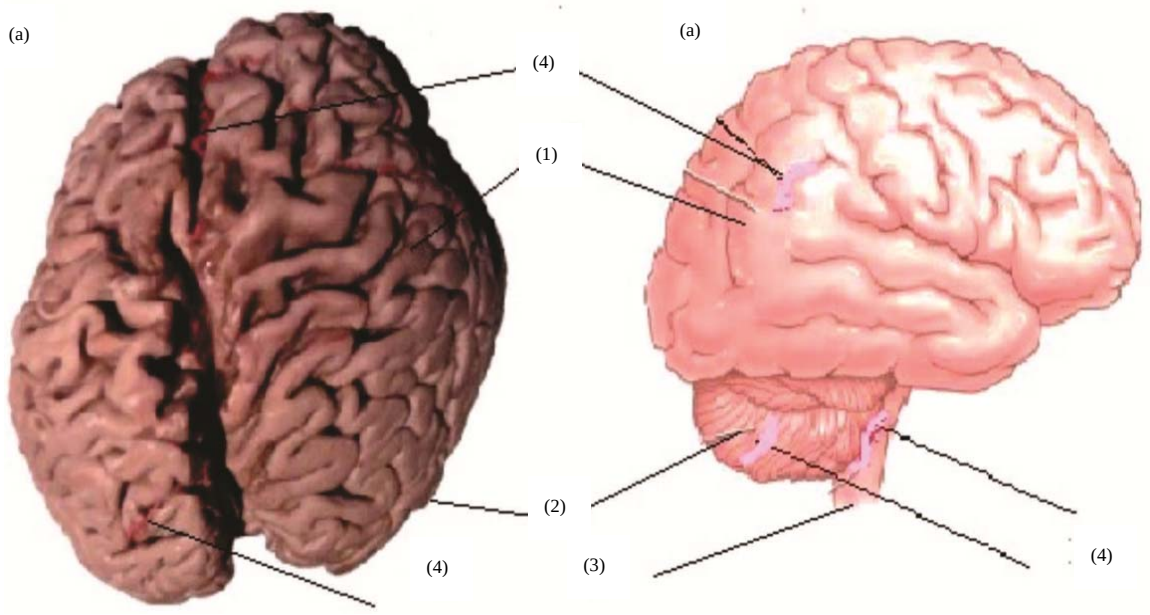

Fig. 1(a-b): Anatomy of brain portion damage that responsible for dysphagia after cerebral apoplexy (a) Side view and (b) Top view
1: Cerebrum, 2: Cerebellum, 3: Brainstem, 4: Infarcts due to cerebral apoplexy

Table 1: Demographic data of patients enrolled for the study

	Groups		
Diagnosis and anatomical characters	Placebo group	Treatment group	Control group
Drugs	Placebo	LET	LC
Patients[#] n (%)	205 (100)	225 (100)	208 (100)
Male	131 (64)	139 (68)	112 (54)
Female	74 (36)	116 (52)	96 (46)
Mean±SD	67.32±4.77	65.71±6.89	66.38±6.44
Age (years)			
65<	21 (10)	44 (20)	35 (17)
≥65	184 (90)	181 (80)	173 (83)
TT	15 (7)	22 (10)	9 (83)
Pharyngeal phase abnormalities at BL	187 (91)	178 (79)	174 (84)
Stroke episodes			
First event	200 (98)	218 (97)	200 (96)
Previous stroke history	5 (2)	7 (3)	8 (4)
Symptoms of dysphagia			
Mild	155 (76)	159 (71)	139 (67)
Moderate	45 (22)	58 (26)	62 (30)
Advanced	5 (2)	8 (3)	7 (3)
Laryngeal neuropathy	189 (92)	173 (77)	172 (83)
Cervical myelopathy	8 (4)	9 (4)	11 (5)
Head and neck cancer	2 (1)	2 (1)	2 (1)
Dementia	11 (5)	15 (7)	17 (8)
Cervical dystonia	2 (1)	2 (1)	2 (1)
Myopathy	2 (1)	2 (1)	2 (1)

Data are represented as No. (%), LET: Levetiracetam, LC: Levodopa (in combination with carbidopa in 10:1 ratio), All patients are of China PR origin, [#]Expressive and receptive both type of dysphagia patients were included, TT: Patient was on tracheostomy at BL , BL: Baseline: Baseline after two days of symptoms of dysphagia noticed

Traditional Chinese Medicine, China, the People's Hospital of Xuancheng city, China and China-Japan friendship Hospital, China during January 2013 to January 2016 were enrolled in the study. All were signed the informed consent form before enrollment. They were randomly divided as per theneed of study into three groups (Table 1).

Exclusion criteria: The patients who were refused to sign informed consent form, did not follow study procedure, DP caused by dementia, neurological diseases, head and neck cancer, participated in the other clinical trial(s), with strong epilepsy, with the advanced congestive heart failure, history of loss of consciousness were excluded from the study.

Each patient of placebo, treatment and control groups were received placebo tablets, LET 500 mg film coated tablets and LC tablets twice daily after or within meal for 8 weeks after 2 days of onset of DP.

Video fluorographic swallowing studies: Bothqualitative and quantitative measures were evaluated by Video Fluorographic Swallowing (VFS) studies. A fluoroscope (OEC 9800, GE Medical Systems-OEC, Salt Lake City, UT) was fixed at the bed of each patient at a rate of 31 frames sec^{-1}. All patients were provided cooked pasta three times a day for eating. Video images were digitized for frame-by-frame analysis and measured using HC image (Compix, Sewickley, PA). A 1.795 cm disk was placed into the field of view for calibration purposes. One viewer blind for the study was selected for viewing of all videos. The qualitative measures and quantitative measures were evaluated at after two days of symptoms of dysphagia noticed that was considered as abaseline (BL) and at the end eight weeks of successful treatment (EP).

Qualitative measures

Aberrant bolus movement: It is provided tongue movement without successful bolus transport and was used for detection of aproblem in oral processing.

Dorsal head compensation: The head movement during bolus transport was used to judge during swallowing process.

Abnormal posture: It is the inability of the properly position of the body during swallowing.

Cough/gag: It was noted immediately after or during the pharyngeal swallow. Radiology is not differentiated cough and gag. Therefore, both were put into the same category.

Among three videos, the best image was considered for qualitative measures.

Quantitative measures

Bolus speed: It is the rate at which the head of the bolus moved from the initiation point to the fourth cervical vertebra (C_4). It was measured in mm sec^{-1}.

Mastication speed: The number of cycles for complete jaw opened and closed over a period of at least five seconds during mastication of the bolus. It was measured in cycles sec^{-1}.

Jaw excursion: It is the maximum jaw was opened during chewing. It was measured in mm.

Bolus area: It was the bolus size measured after swallow initiation and before the head of the bolus reached to and was measured in mm^2 [10].

Electroencephalography (EEG): The EEG is the method used to measure brain activity during rehabilitation of DP. Distinctive EEG waves are disturbed in DP[11]. Slowing of alpha, beta and gamma (α, β and γ) oscillations are associated with DP due to cerebral apoplexy[12]. The electrode scrubbed with conductive paste (Chuangian Electronics component group Co, Ltd, Mainland, China), placed on scalp and face and measured the EEGand mu rhythm of all patients using wireless EEG equipment (Arc, Cadwell Industries Inc, US) of each patient at BL and EP[13].

Post-study observations: All patients after the study came for followed-up and after one year time period, the baseline data were further evaluated for the post-study observations.

Statistical analysis: All quantitative measures were mean of five video images. Statistical Analysis was performed by SAS (SAS Institute, Inc, Cary, NC). The one-way ANOVA (Microsoft Excel Worksheet®, 2013, Microsoft Corporation, Redmond, USA) was used for all parameters to show a difference between vehicle group and treatment group, between vehicle group and control group and treatment group and control group. The difference was considered significant statistically at the 95% level of confidence[14]. The Wilcoxon test was used to compare asymmetry at BL and EP. Fisher's protected least significant difference test was used for comparisons of groups[10]. ANOVA was used to overcome confounding effect.

RESULTS

The patrician's enrollment, allocation, follow-up and analysis is presented in Fig. 2.

The significant reduction was found in aberrant bolus movement, dorsal head compensation, abnormal posture and cough/gag at EP between treatment groupand placebo groupand control group and placebo group ($p<0.05$ for all). Moreover, the in significant differences between treatment group and control group for a berrant bolus movement, dorsal head compensation, abnormal posture ($p<0.05$ for all, Table 2) at EP.

The statistical analysis showed significant improvement of bolus speed, mastication cycles, jaw excursion (mm) and bolus area (mm^2) at EP between placebo group and treatment group and placebo group and control group ($p<0.05$ for all). However, there was insignificant difference in improvement bolus speed, mastication speed and bolus area between BL and EP levels of placebo group ($p<0.05$, for all). Moreover, there was a significant difference in improvement of quantitative measures between BL and EP levels of treatment and control group ($p< 0.05$ for all). There was insignificant difference in improvement quantitative measures between treatment group and control group at EP ($p <0.05$ for all, Table 3).

Table 4 shows the insignificant difference for the placebo group ($p<0.05$) and significant improvement for treatment group and control group ($p<0.05$ for both) for α, β and γ oscillations between BL and EP. The control group showed epileptic form activity in the gamma oscillation and treatment group showed better quality of gamma oscillation at EP (Fig. 3).

Table 2: Qualitative measures of video fluorographic studies

	Groups								
	Placebo group		Treatment group			Control group			
Qualitative measures	BL (n = 205)	EP (n = 197)	BL (n = 225)	EP (n = 216)	*p-value	BL (n = 208)	EP (n = 200)	p-value	#p-value
Aberrant bolus movement	194 (95)	193 (98)	192 (85)	185 (86)	0.031	194 (93)	187 (93.5)	0.032	0.984
Dorsal head compensation	193 (94)	191 (97)	177 (79)	169 (78)	0.022	195 (94)	186 (93)	0.034	0.834
Abnormal posture	153 (75)	135 (66)	162 (72)	141 (65)	0.029	145 (70)	127 (63.5)	0.046	0.868
Cough/gag	115 (56)	108 (55)	116 (52)	110 (51)	0.031	113 (54)	112 (56)	0.0001	0.004

BL: Baseline after two days of symptoms of dysphagia noticed, EP: End point, after successful treatment of eight weeks, Data are represented as No. (%), *p-value between EP of placebo group and EP of treatment group for one-way ANOVA, for statistical analysis, quantitative measures and recovered conditions were considered as 1 and 0, p-value between EP of placebo group and EP of control group for one-way ANOVA, #p-value between EP of treatment group and EP of control group for one-way ANOVA

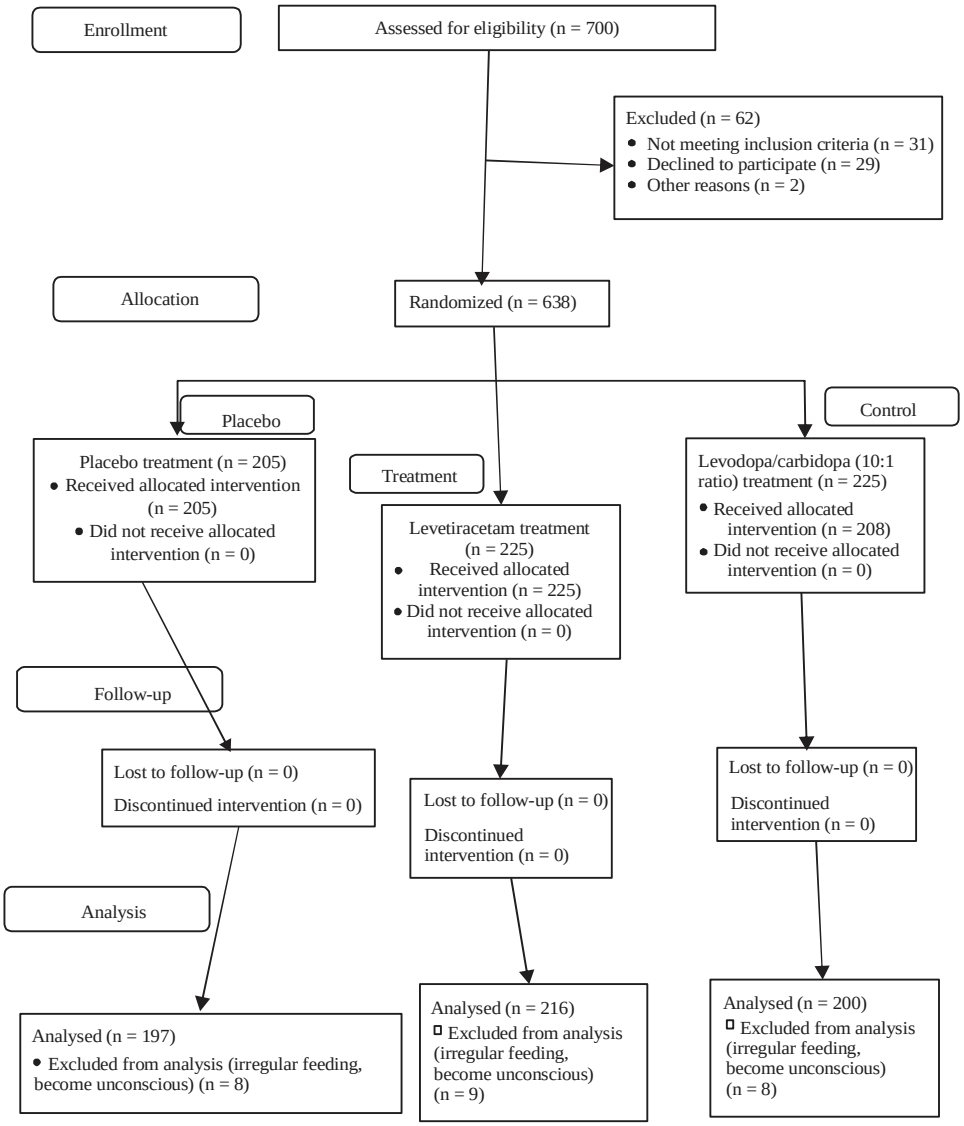

Fig. 2: Study tree

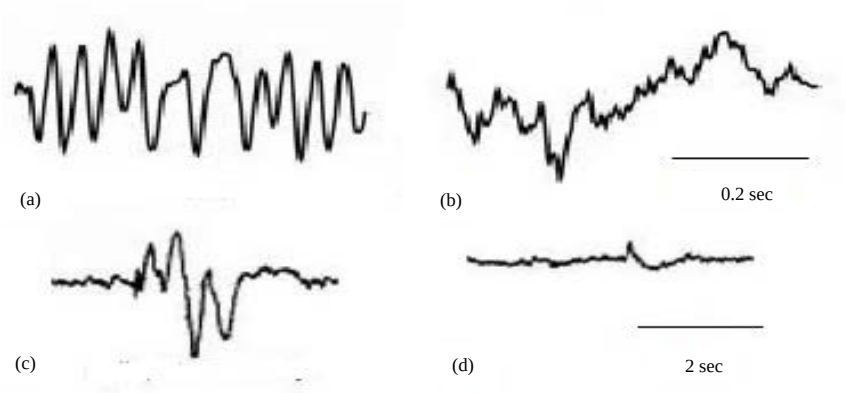

Fig. 3(a-d): Gamma oscillations of dysphasia patients at the end of successful treatment (a) Gamma oscillations of nondysplastic person, (b) Gamma oscillations at EP of patient belongs to treatment group, (c) Gamma oscillations at EP of patient belongs to control group and (d) Gamma oscillations at EP of patient belongs to placebo group

EP: EP: End point; After successful treatment of eight weeks

Table 3: Quantitative measures of video fluorographic studies

	Groups											
	Placebo group			Treatment group				Control group				
Quantitative measures	BL (n = 205)	EP (n = 197)	¶p-value	BL (n = 225)	EP (n = 216)	¶p-value	*p-value	BL (n = 208)	EP (n = 200)	¶p-value	p-value	#p-value
Bolus speed (mm sec^{-1})	66.07±2.71	66.55±2.51	0.063	70.78±5.97	72.01±6.04	0.0001	0.032	70.30±5.66	72.25±4.14	0.00013	0.0001	0.652
Mastication speed (cycle sec^{-1})	6.99±1.65	7.01±1.63	0.903	7.02±1.75	7.39±1.70	0.026	0.021	7.14±1.32	7.40±1.29	0.049	0.008	0.9
Jaw excursion (mm)	18.24±1.04	18.25±1.03	0.924	18.23±1.04	18.52±1.12	0.005	0.013	18.17±1.22	18.41±1.17	0.044	0.172	0.313
Bolus area (mm^2)	88.91±4.77	88.89±4.71	0.969	89.23±4.72	90.68±5.68	0.003	0.0006	89.94±4.89	89.90±4.91	0.049	0.038	0.139

BL: Baseline after two days of symptoms of dysphagia noticed, EP: End point, after successful treatment of eight weeks, data are represented as Mean±SD of five independent variables, *p-value between EP of placebo group and EP of treatment group for one-way ANOVA, for statistical analysis, quantitative measures and recovered condition were considered as 1 and 0, p-value between EP of placebo group and EP of control group for one-way ANOVA, #p-value between EP of placebo group and EP of control group for one-way ANOVA, ¶p-value between BL and EP within group for the Wilcoxon test

Table 4: Electroencephalography alpha, beta and gamma oscillations measure results

	Group											
	Placebo group			Treatment group				Control group				
Quantitative measures	BL (n = 205)	EP (n = 197)	¶p-value	BL (n = 225)	EP (n = 216)	¶p-value	*p-value	BL (n = 208)	EP (n = 200)	¶p-value	p-value	#p-value
Slow alpha, beta and gamma oscillations	205 (100)	195 (99)	0.153	225 (99)	202 (94)	0.0001	0.0041	208 (100)	196 (98)	0.04	0.426	0.025
Improvement in alpha, beta and gamma oscillations	0 (0)	2 (1)		0 (0)	13 (6)			0 (0)	4 (2)			

BL: Baseline after two days of symptoms of dysphagia noticed, EP: End point, after successful treatment of eight weeks, four electrodes on the left side and the right side, *p-value between EP of placebo group and EP of treatment group for one-way ANOVA, for statistical analysis, quantitative measures and recovered condition were considered as 1 and 0, p-value between EP of placebo group and EP of control group for one-way ANOVA, #p-value between EP of treatment group and EP of control group for one-way ANOVA, ¶p-value between BL and EP within group for the Wilcoxon test, For statistical analysis slow α, β and γ oscillations and improvement in α, β and γ oscillations were considered as 1 and 0, Data are represented as No. (%)

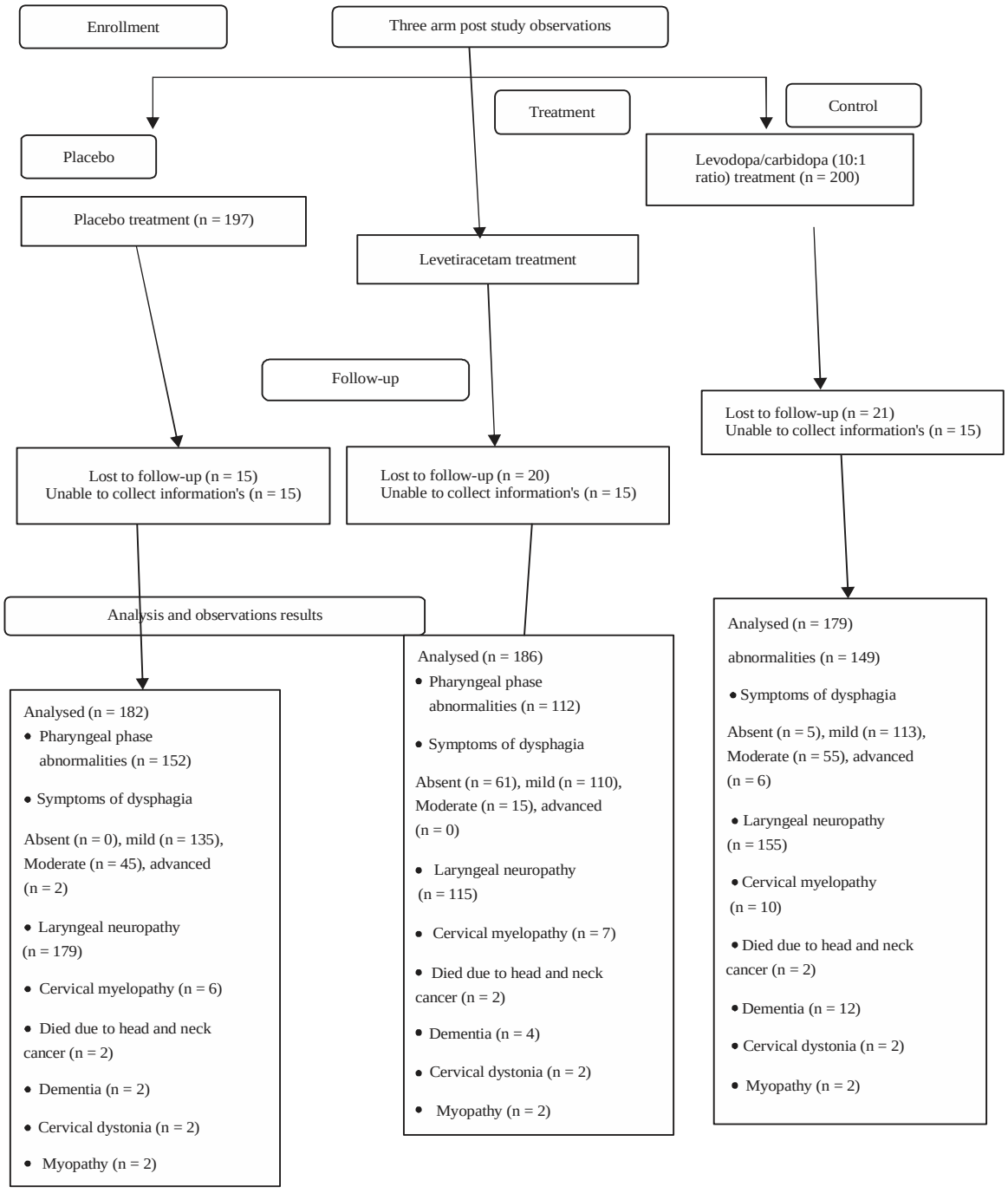

Fig. 4: Three arm post study observations after one year of successful treatment

The clinical characteristics of participants in the post-study after one year are shown in Fig. 4.

DISCUSSION

The current study, first time provided use of LET in the rehabilitation of patients with advanced, moderate or mild DP after stroke when patients swallowed semisolid materials i.e. pasta. The treatments reported in the previous studies for moderate or mild DP areby use of LC[6], by use of traditional or not–traditional nutrient supplements[15,16], by use of motor rehabilitative training and the compensatory strategies of those[17], along with use of viscosity increasing agents in thin drinks to increase the thickness of theliquid[18]. In agreement to

the selection of situations and conditions, the current finding was more effective in the rehabilitation of patients with all conditions of DP after stroke.

The effects of LET as antiepileptic[8], anticonvulsive, anti-ictogenic[7] and seizure suppression are reported by previous studies. But researchers were failed to report theeffect of LET in the rehabilitation of DP[19]. In correction to the results of the current present study, the finding was anew development for neuroscience in the rehabilitation of DP due to cerebral apoplexy.

The previous study provided a significant effect of the LC (10:1 ratio) in the rehabilitation of DP after stroke[6]. In the agreements of the results of the current study, the finding was evidenced that LC had almost the same like placebo effect in the rehabilitation of DP due to cerebral apoplexy.

The previous study reported that DP patient has adequate oropharyngeal pressure which results into swallowing difficulties[20]. With the reference to the EEG data of the present study, the study provided evidence that LET improves oropharyngeal pressure in the rehabilitation of DP due to stroke.

The present study was based on the latest studies of EEGand VFS[21]. In the study, one-way ANOVA was used for all measures to show a significant difference ($p<0.05$). Till date studies on DP are available for functional Magnetic Resonance Imaging (fMRI) and diffusion weighted imaging dataset[22]. These are difficult diagnosis tests, expensive and complicated studies. Moreover, statistical analysis is hard to apply for fMRI[23]. In reference to methods and the statistical analysis usedin the study, the finding was more authentic for the hypothesis.

There are several parameters for evaluation of rehabilitation of DP by VFS studies[24].The present VFS studies were on a human in DP. However, The reported VFS studies are for animals only[10]. The previous findings are more concentrated on qualitative measures of VFS studies[21]. The present finding used qualitative measures and quantitative measures of VFS study. With the agreement of the results of VFS studies, the study was provided amore realistic approach for the rehabilitation of DP due to stroke.

The present study revealed that there was a strong improvement of γ oscillationsin DP patients at EP in the treatment group. The available studies of EEG are less concentrate on mu rhythm and α, β and γ oscillations associated with DP[12]. In association with the results of EEG oscillations, the study showed that LET was more effective as compared to placebo and LC in the rehabilitation of DP due to stroke.

The current study first time provided rehabilitation of DP when patients swallowed semisolid materials i.e. pasta. Till date, human clinical studies available for rehabilitation of DP are based on Newtonian or non-Newtonian fluids only[25].The study provided a more realistic approach in the rehabilitation of DP.

CONCLUSION

The present human clinical study concluded that levetiracetam was significantly effective as compared to placebo and levodopa treatments in there habilitation of dysphagia. The significant effect of levetiracetam was validated by new diagnostic tools electroencephalography and video fluorographic swallowing studies for the quantification of rehabilitation of dysphagia. However, rehabilitation of DP was not evaluated by fiberoptic endoscopic evaluation of swallowing disorder. Researchers do not know the exact mechanism of action regarding this significant effect ($p<0.05$). The mechanism of action is required to disclose.

SIGNIFICANCE STATEMENT

This study discover the significant role of levetiracetam in the rehabilitation of dysphagia that can be beneficial for dysphagia due to stroke. This study will help the researcher to uncover the critical areas of neuroscience that many researchers were not able to explore.

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REFERENCES

1. Cohen, D.L., C. Roffe, J. Beavan, B. Blackett and C.A. Fairfield *et al*., 2016. Post-stroke dysphagia: A review and design considerations for future trials. Int. J. Stroke, 11: 399-411.
2. Martino, R., N. Foley, S. Bhogal, N. Diamant, M. Speechley and R. Teasell, 2005. Dysphagia after stroke: Incidence, diagnosis and pulmonary complications. Stroke, 36: 2756-2763.

3. Cuellar, M., A.W. Harkrider, D. Jenson, D. Thornton, A. Bowers and T. Saltuklaroglu, 2016. Time-frequency analysis of the EEG mu rhythm as a measure of sensorimotor integration in the later stages of swallowing. Clin. Neurophysiol., 127: 2625-2635.
4. Kikuchi, T., Y. Michiwaki, S. Koshizuka, T. Kamiya and Y. Toyama, 2017. Numerical simulation of interaction between organs and food bolus during swallowing and aspiration. Comput. Biol. Med., 80: 114-123.
5. Marchina, S., G. Schlaug and S. Kumar, 2015. Study design for the FEASt trial: A randomized controlled intervention for improving dysphagia after acute ischemic stroke. J. Stroke Cerebrovasc. Dis., 24: 511-520.
6. Mancopes, R., A.R. Busanello-Stella, L.S. Finger, A.P. Neu, A.D.B. Pacheco and M.S. Torriani, 2013. Influence of levodopa on the oral phase of swallowing in patients with Parkinson's disease. Rev. CEFAC, 15: 707-712.
7. Vinogradova, L.V. and C.M. Van Rijn, 2008. Anticonvulsive and antiepileptogenic effects of levetiracetam in the audiogenic kindling model. Epilepsia, 49: 1160-1168.
8. Levesque, M., C. Behr and M. Avoli, 2015. The anti-ictogenic effects of levetiracetam are mirrored by interictal spiking and high-frequency oscillation changes in a model of temporal lobe epilepsy. Seizure, 25: 18-25.
9. The University of Hong Kong, 2010. Reviewing Clinical Trials: A Guide for the Ethics Committee. Clinical Trials Centre, Hong Kong, China.
10. Russell, J.A., M.R. Ciucci, M.J. Hammer and N.P. Connor, 2013. Videofluorographic assessment of deglutitive behaviors in a rat model of aging and Parkinson disease. Dysphagia, 28: 94-104.
11. Jestrovic, I., J.L. Coyle and E. Sejdic, 2015. Decoding human swallowing via electroencephalography: A state-of-the-art review. J. Neural Eng., Vol. 12.
12. Rabiller, G., J.W. He, Y. Nishijima, A. Wong and J. Liu, 2015. Perturbation of brain oscillations after ischemic stroke: A potential biomarker for post-stroke function and therapy. Int. J. Mol. Sci., 16: 25605-25640.
13. Light, G.A., L.E. Williams, F. Minow, J. Sprock and A. Rissling *et al*., 2010. UNIT 6.25 electroencephalography (EEG) and Event-Related Potentials (ERPs) with human participants. Current Protocols Neurosci., Vol. 6.
14. Mahajan, B.K., 2006. Methods in Biostatistics. 6th Edn., Jaypee Brothers Medical Publishers (P) Ltd., India, pp: 152-155.
15. Venketasubramanian, N., C.L.H. Chen, R.N. Gan, B.P.L. Chan and H.M. Chang *et al*., 2009. A double blind, placebo controlled, randomized, multicenter study to investigate CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES Study). Int. J. Stroke, 4: 54-60.
16. Venketasubramanian, N., C.L.H. Chen, R.N. Gan, B.P.L. Chan and H.M. Chang *et al*., 2009. A double blind, placebo controlled, randomized, multicenter study to investigate CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES Study). Int. J. Stroke, 4: 54-60.
17. Jones, T.A., 2017. Motor compensation and its effects on neural reorganization after stroke. Nature Rev. Neurosci., 18: 267-280.
18. Mowlavi, S., J. Engmann, A. Burbidge, R. Lloyd, P. Hayoun, B. Le Reverend and M. Ramaioli, 2016. *In vivo* observations and *in vitro* experiments on the oral phase of swallowing of Newtonian and shear-thinning liquids. J. Biomech., 49: 3788-3795.
19. Klitgaard, H., A. Matagne, R. Grimee, J. Vanneste-Goemaere and D.G. Margineanu, 2003. Electrophysiological, neurochemical and regional effects of levetiracetam in the rat pilocarpine model of temporal lobe epilepsy. Seizure, 12: 92-100.
20. Park, D., Y. Oh and J.S. Ryu, 2016. Findings of abnormal videofluoroscopic swallowing study identified by high-resolution manometry parameters. Arch. Phys. Med. Rehabil., 97: 421-428.
21. Baijens, L.W., R. Speyer, V.L. Passos, W. Pilz, N. Roodenburg and P. Clave, 2011. Swallowing in Parkinson patients versus healthy controls: Reliability of measurements in videofluoroscopy. Gastroenterol. Res. Pract., Vol. 2011. 10.1155/2011/380682.
22. Mihai, P.G., M. Otto, M. Domin, T. Platz, S. Hamdy and M. Lotze, 2016. Brain imaging correlates of recovered swallowing after dysphagic stroke: A fMRI and DWI study. NeuroImage: Clin., 12: 1013-1021.
23. Fattori, B., G. Siciliano, V. Mancini, L. Bastiani and P. Bongioanni *et al*., 2016. Dysphagia in amyotrophic lateral sclerosis: Relationships between disease progression and fiberoptic endoscopic evaluation of swallowing. Auris Nasus Larynx, 44: 306-312.
24. Martin-Harris, B. and B. Jones, 2008. The videofluorographic swallowing study. Phys. Med. Rehabil. Clin. N. Am., 19: 769-785.
25. Burbidge, A., J. Cichero, J. Engmann and C. Steele, 2016. A day in the life of the fluid bolus: An introduction to fluid mechanics of the oropharyngeal phase of swallowing with particular focus on dysphagia. Applied Rheol, Vol. 26.