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Efficacy of Ultrasound Guided Botulinum Toxin Injection for Cricopharyngeal Dysphagia in Post-Stroke Patients: A Randomized Controlled Pilot Study

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ABSTRACT

Dysphagia means difficulty in swallowing is a common symptom following stroke. Most of these patients usually recover within two months of their cerebrovascular accident. But some of them suffer from dysphagia for a longer period which can lead to malnutrition, dehydration and in more severe case aspiration pneumonia. Rehabilitative swallowing therapy (RST), Neuromuscular Electrical Stimulation over anterior neck musculature, Endoscopic Pharyngeal stimulation, Transcranial magnetic stimulation, EMG biofeedback, Botulinum toxin (BTX) injection in cricopharyngeus muscle etc were the mainstay of treatment. We have tried to assess any improvement in video fluoroscopic dysphagia scale(VDS) after Botulinum toxin injection along with swallowing techniques, maneuvers and videofluroscopic improvement of swallowing in post stroke dysphagia patients in both-botulinum toxin injection and conservative management group and compared the improvement of swallowing between them. The present study was randomized controlled pilot study. This study was conducted from 18 months at Department of Physical Medicine and Rehabilitation, IPGME and R, SSKM Hospital, Kolkata. Total 16 patients were included in this study. Mean Baseline VDS score was 82.5±3.12 in Group A and 83.0±4.07 in Group B. There is no statistically significant difference in Mean Baseline VDS score as p-value is >0.05. Mean VDS score after 1 month of intervention was 78.5±7.23 in Group A and 79.75±6.54 in Group B. There is no statistically significant difference in Mean VDS score after 1 month of intervention as p-value is >0.05. Mean VDS score after 3 months of intervention was 70.75±7.85 Group A and 49.75±6.63 in Group B. There is statistically significant difference in Mean VDS score after 3 months of intervention as p-value <0.0001. Mean VDS score was more or less same in both Group A and Group B in Baseline data and after 1 month Data. But after 3 months of Intervention mean VDS score showed sharp decline in graphs. This reveals that intervention group had similar outcome after one month (p-value>0.05) but statistically significant better out come after 3 months of intervention (p<0.0001).The majority of PSD patients have ischemia comorbidities. After one month and three months of follow-up both the conservative management (RST) group (A) and the RST with Botulinum toxin (BTX) injection group (B) have clearly improved. Improvement was comparable across the two groups after a month of follow-up. But after that group A's progress was not sufficient compared to group B's considerable recovery between one month and three months following the injection of botulinum toxin.

INTRODUCTION

Dysphagia means difficulty in swallowing is a common symptom following stroke. Most of these patients usually recover within two months of their cerebrovascular accident. But some of them suffer from dysphagia for a longer period which can lead to malnutrition, dehydration and in more severe case aspiration pneumonia. It is one of the clinical condition seen in post stroke patients in PMR OPD and IPD. It usually happens in CVA involving brain stem or in case of multiple cerebrovascular accident involving bilateral cerebral hemisphere.

Patients typically exhibit a variety of symptoms including difficulty passing food down, food becoming stuck in the mouth, coughing during, before or after swallowing, nasal regurgitation, something getting lodged in the neck when swallowing, excessive eating, etc.

Patients underwent extensive examinations with special attention paid to the cranial nerves and bedside swallowing tests. Then a videofluroscopic swallowing study (VFSS) was conducted to determine which stage of swallowing was aberrant. Specific methods were used in this investigation and progress was seen.

Most managements lacked initiative. In those who need surgery it is also advised that you try some conservative therapy. However there is debate over what constitutes an effective conservative and/or non-operative treatment. Rehabilitative swallowing therapy (RST), neuromuscular electrical stimulation over the muscles of the anterior neck, endoscopic pharyngeal stimulation, transcranial magnetic stimulation, EMG biofeedback and injections of botulinum toxin (BTX) into the cricopharyngeus muscle are just a few examples of the conservative treatments available. To increase neck muscle strength and swallowing physiology, various approaches and procedures were used in rehabilitative swallowing therapy. The strength of the muscles in the front of the neck is increased by neuromuscular electrical stimulation. Improved muscle strength and sensory stimulation are other ways that pharyngeal stimulation works. EMG biofeedback and transcranial magnetic stimulation are thought to function by accelerating neuroplasticity. In patients with lateral medullary syndrome the cricopharyngeal muscle is primarily relaxed by the effects of botulinum toxin. Among these, Botulinum toxin (BTX) in the cricopharyngeus muscle in posterior circulation stroke is frequently used nowadays but its efficacy in improving dysphagia on both a subjective and an objective level is in question.

After a thorough search of the literature we were unable to locate sufficient data to support the superiority of rehabilitative swallowing therapy for the treatment of post-stroke dysphagia versus ultrasonography (USG) guided Botulinum toxin injection for cricopharyngeal dysphagia. Determining the effectiveness of USG-guided Botulinum toxin in the cricopharynx in post-stroke patients is hence our modest endeavour.

MATERIALS AND METHODS

Institutional ethics committee clearance was obtained for the study (IPGMER Research Oversight Committee. IPGME and R/IEC/2021/419). Individual informed consent was taken from the patients to include in this study group.

Study area: Department of Physical Medicine and Rehabilitation, IPGME and R, SSKM Hospital, Kolkata.

Study population: Patients with clinical symptoms of post stroke dysphagia attending the OPD and IPD of the Department of Physical Medicine and Rehabilitation and Department of Neuromedicine, BIN, Kolkata.

Study period: 18 months.

Study design: Parallel group open label randomized controlled pilot study.

Sample size: For the purpose of sample size calculation, Videofluroscopic Dysphagia Scale (VDS) score based on VFSS was considered as primary outcome measure. As it was a pilot study we did not went into a formal sample size calculation protocol. However considering time and case load at our disposal we included total sixteen patients in our study (n = 16). They were allocated into two groups by computer generated randomization consisting eight patients in each group. Patients in group-A were managed with conservative management only. Patients in group-B were managed with botulinum toxin injection along with conservative management.

Inclusion criteria:

- Clinical dysphagia with confirmed posterior circulation stroke
- Normal hyolaryngeal elevation with pyriform fossa
- Only pharyngeal phase involvement
- Patients with >18 years of age with dysphagia for >2 months after cerebrovascular accident
- First incident of cerebrovascular disease
- Patients able to communicate

Exclusion criteria:

- Anterior circulation stroke
- Significant oro-pharyngeal incoordination
- Oral phase involvement
- Patients with progressive neurovascular disorder

and neoplastic disease undergone radiotherapy to the neck, H/O any surgery to swallowing apparatus, local inflammation, infection, injury over anterior neck.

The patients who attended Department of Physical Medicine and Rehabilitation, IPGME and R, SSKM Hospital, Kolkata were clinically screened for post stroke dysphagia. Those patients who fulfilled above criteria were selected for study. Detailed history and thorough clinical examinations were conducted for each and every patient after taking written informed consent. Following baseline blood investigations and the imaging were done to rule out comorbidities and contraindication and to prevent treatment complications.

After that Videofluroscopic swallowing study (VFSS) was done on every patient to confirm the diagnosis.

RESULTS

Among total 8 participants in Group A 12.5% less than 40 years 25% in 51-60 years 25% in 61-70 years and 37.5% in >70 years age groups. Among total 8 participants in Group B, 12.5% less than 40 years, 37.5% in 41-50 years 12.5% in 51-60 years 25% in 61-70 years and 12.5% in >70 years age groups. Mean Age of Group A was 62.25±13.23 years, median age 66.5 years ranging from 37-78 years. While in Group B, Mean age was 55.88±12.17 median age 54 years ranging from 40-77 years. Among the Group A 75% were male and 25% were female while in Group B 62.5% were male and 37.5% were female. Among the Group A 87.5% had ischemic CVA and 12.5% had hemorrhagic CVA while in Group B 62.5% had ischemic CVA and 37.5% had hemorrhagic CVA.

Mean Baseline VDS score was 82.5±3.12 in Group A and 83.0±4.07 in Group B. There is no statistically significant difference in Mean Baseline VDS score as p-value is >0.05. Mean VDS score after 1 month of intervention was 78.5±7.23 in Group A and 79.75±6.54 in Group B. There is no statistically significant difference in Mean VDS score after 1 month of intervention as p-value is >0.05. Mean VDS score after 3 months of intervention was 70.75±7.85 Group A and 49.75±6.63 in Group B. There is statistically significant difference in Mean VDS score after 3 months of intervention as p-value is <0.0001. Mean VDS score was more or less same in both Group A and Group B in Baseline data and after 1 month Data. But after 3 months of Intervention mean VDS score showed sharp decline in graphs. This reveals that intervention group had similar outcome after one month (p-value>0.05) but statistically significant better out come after 3 months of intervention (p-value<0.0001) (Table 1-2).

DISCUSSION

This study was conducted in department of Physical Medicine and Rehabilitation, IPGMER, Kolkata with the study duration of 18 months and sample size of 16 to assess the efficacy of ultrasound guided Botulinum toxin injection for cricopharyngeal dysphagia in post stroke patients.After randomization of sample and statistical analysis there are different observations has been noticed. The main finding of this study was that both rehabilitation swallowing therapy (RST) and rehabilitation swallowing therapy with ultrasound guided botulinum toxin injection in

Table 1: Distribution of the study population according to age group (n = 16)

	Group A (n = 8)		Group B (n = 8)	
Age groups (years)	Frequency	Percent	Frequency	Percent
≤40	1	12.5	1	12.5
41-50	0	0.0	3	37.5
51-60	2	25.0	1	12.5
61-70	2	25.0	2	25.
>70	3	37.5	1	12.5
Total	8	100.0	8	100.0
Sample size	8		8	
Mean±SD	62.25± 13.23		55.88± 12.17	
Median	66.5		54	
Range	37-78		40-77	

Table 2: Comparison of VDS score baseline, 1 month, 3 month of intervention and all VDS scores between two groups (n = 16).

	Age in years	Group A	Group B	p-value
Baseline VDS score	Sample size	8	8	0.787
	Mean±SD	82.5±3.12	83.0±4.07	
	Median	82.5	83.5	
	Range	78-86	76-89	
VDS score after 1 month of intervention	Sample size	8	8	
	Mean±SD	78.5±7.23	79.75±6.54	
	Median	77	81	
	Range	70-90	70-88	
VDS score after 3 month of intervention	Sample size	8	8	<0.0001
	Mean±SD	70.75±7.85	49.75±6.63	
	Range	62-84	40-60	
ll VDS scores	Baseline VDS	82.5±3.12	83.0±4.07	
	VDS at 1 month	78.5±7.23	79.75±6.54	
	VDS at 3 month	70.75±7.85	49.75±6.63	

cricopharynx showed significant improvement. But added benefit was found by giving botulinum toxin injection in cricopharynx with RST.

Dysphagia is a very common complication after stroke. At the very beginning we have not included early cases of CVA as reported by Gordon *et al.*[1] that after stroke 86% patients could swallow normally and those who are having symptoms after 14 days may develop chronic dysphagia. In this study we included those patient having swallowing difficulty more than 2 months after stroke. Permsirivanich *et al.*[2] considered similar inclusion criteria in their study with the cases of PSD persisting for more than 3 months where we included patients of PSD persisting more than 2 months.

In the present study we included only those patients who had their 1st ever stroke .We did not include patients with history of multiple stroke.

It has been reported by Arnold *et al*.[3] that both anterior and posterior circulation stroke can cause significant dysphagia and stroke location did not have any association with the dysphagia. Priya CM *et al.*[4] compared Left Lateral medullary syndrome and Left MCA infarct and concluded that in the Lateral medullary syndrome mainly pharyngeal phase of swallowing is affected. Terre *et al*.[5] reported that the patients with lesion in posterior territory have higher risk of aspiration. Cough, change in voice, altered gag reflex has been described as three main clinical parameters to predict swallowing disorders.

With the Videofluroscopic swallowing study we found 10 patients (62.5%) having entry of food in airway. We found some clinical correlation of change in voice quality with the Videofluroscopy findings. Otherwise, clinical finding was inaccurate to diagnose aspiration or silent aspiration, finding similar to some previous studies. The baseline VDS score was 82.5+3.12 in group A and 83+4.07 in group B quite higher than a study done by J.W. Park *et al.*[6] who included unilateral hemispheric stroke and post 1 month stroke. Pyriform fossa residue has been given a higher value (13.5) in the VDS score. So, the mean VDS in our study was higher probably because all the patient of our study had posterior circulation stroke.

For rehabilitation swallowing therapy (RST) different swallowing techniques and maneuvers are used as per the patients' requirement. Patients are taught to do direct techniques regarding swallowing, and indirect techniques multiple times a day with 45 minutes to 1 hrs gap in between similar to McCullough *et al*.[7]. The compensatory swallowing techniques provide immediate effect not long term effect. In our study we included compensatory strategy of Head turning to weaker side of pharynx, found to be beneficial in closuring in paretic hemipharynx at hyoid level. Studies have reported improved bolus clearence in lateral medullary syndrome. In patients with the reduced upper esophageal sphincter opening head rotation to either side reported beneficial. Swallowing exercises change physiology and eliminate need for compensation. In our study we included Shaker exercise which increases hyolaryngeal movement by strengthening suprahyoid muscles and demonstrated significant improvement in patients of chronic dysphagia with tube feeding. Effortful swallow improves base of tongue retraction and reduce the vallecular residue and demonstrated increased duration of UES opening and maximum anterior movement. Mendelsohn maneuver has been reported to increase UES opening duration and reduced pyriform fossa residue and McCullough *et al*.[7] reported significant improvement.

We used Botulinum toxin Type A injection in cricopharynx in one group of 8 patients along with rehabilitation swallowing therapy. We found significant improvement in swallowing with this combined therapy and statistically significant difference found between RST and RST Botulinum toxin injection group. There are many studies that compared between these two treatment options described above. There are different studies where Injection Botulinum toxin was given in different ways. One of them given under EMG guidance for the treatment of long standing post-stroke dysphagia with 25 U of botulinum toxin injection under EMG guidance along with rehabilitation like Stefano Masiero *et al*.[8] and Domenico De Grandis *et al*.[9] reported Botulinum toxin treatment of severe dysphagia following brainstem stroke under the EMG guidance. Deong Young Kim *et al.*[10] reported successful treatment by endoscopic guided 100 U Botulinum toxin injection in cricopharynx for post stroke cricopharyngeal muscle dysfunction. But for CT guidance and endoscopic guidance, EMG guidance we need larger OT set-up more facilities and the treatment will become costly. But in case of only USG guidance it will reqire minimum OT set-up minium facilities and treatment will become cost effective.

Enrico Alfonsi *et al.*[11] reported that Botulinum toxin is effective in the management of neurogenic dysphagia due to hyperactivity and relaxation failure of upper esophageal sphincture. The effect of the first treatment usually lasted longer than 4 months and in some cases upto a year. We followed up the patients for 3 months to see the long term effectiveness of Botulinum toxin injection like Rosa Terre *et al*.[12] who reported effectiveness of one single injection of Botulium injection in the upper esophageal sphincture has long lasting effectiveness in patients with neurological dysphagia caused by alteration in the upper esophageal sphincture opening and with pharyngeal contraction.

An intramuscular injection of a botulinum toxin preparation blocks acetylcholine release from the nerve endings at the neuromuscular junction (i.e. the

motor endplate) of the muscle. Different botulinum toxin products, such as Botox (Allergan, Irvine, CA, USA), Dysport (Ipsen, Slough, UK), Xeomin (Merz Pharma, Frankfurt am Main, Germany) and Hengli (Lanzhou Biological Products Institute, Lanzhou, China), have various manufacturing processes and formulations. Such differences lead to various interactions between the product and the tissue injected. Thus the dosing and performance of these products are uninterchangeable and it should be cautious to use these products in simple dose ratios. The local spread/diffusion characteristics of the botulinum toxin may affect the botulinum toxin injected into the UES, cricopharynx and UES are synonymous here.

Several termsincluding diffusion, spread and migration have been used to describe the physical movements of the toxin from the injected site to other areas of the body. Botulinum toxin moves to areas other than the injected site, resulting in the local, distal and systemic effects of the therapy through mechanisms including molecular dispersion, neuro-axonal transport, or hematogenous transport. Here, local spread/diffusion refers to a passive dispersion process by which botulinum toxin moves to adjacent areas from the injected site. Usually a more limited extent of local spread/diffusion is preferred because the injected toxin has a lower chance of paralyzing muscle fibers near the injection site. However a greater extent of spread/diffusion of botulinum toxin may effectively relieve UES narrowing. For instance if an injection presents a 10 mm^{-1} radius scope of spread/diffusion around the injected site it can lead to greater inhibition of the hyperactive UES activities than an injection leading to 5 mm^{-1} radius spread/diffusion. More localized effects (less extent of spread/diffusion) of a product are favorable for large muscles to avoid influencing untargeted muscles near the injection sites. However a higher extent of spread/diffusion is preferred for UES injection of botulinum toxin. The role of spread/diffusion in UES botulinum toxin injection is more important than the injection into large-volume muscles. For UES dysfunction the injection targets the circular muscle layers of the UES wall. Such circular muscle layers are much smaller than limb muscles and a higher degree of spread/diffusion can result in a more extensive distribution of botulinum toxin inside the UES wall. In the cricopharyngeus and cervical esophagus portions of the UES the distribution of motor endplates does not form a motor endplate band but presents a scattered pattern. Instead of toward motor endplate enriched zones the injection sites are usually selected on the basis of the local anatomy of the UES. Under normal conditions the uppermost part of the esophagus inclines slightly to the left side of the neck. When transcutaneous ultrasonography is used for scanning the majority of the cervical esophagus can be seen from the left side rather than from the right side (left lateral 2-3 vs. right lateral 1-3).Thus, for percutaneous botulinum toxin injection an approach through the left side of the neck is easier to reach the target muscle layer in the anterolateral wall of the UES. Under such conditions the injected toxin needs to spread to reach as many scattered motor endplates as possible and thus effectively inhibit UES hyperactivity. Therefore, spread/diffusion is important for UES botulinum toxin injection in comparison with large-volume muscles.

Real-time ultrasound guiding allows for the visualization of the injection site and nearby anatomical structures without the requirement for ionizing radiation like that from X-rays or CT scans. The cricopharyngeus is typically seen from the left side of the neck during an ultrasound scan in a transverse or longitudinal perspective. The left lateral 2-3 portion of the cervical esophagus can be seen when scanning from the left neck while the right lateral 1-3 portion can be seen when scanning from the right side when using a slightly flexed neck position with a pillow under the head and turning 45 degrees to the opposite side. While connective tissues and fat exhibit bright/hyperechoic signals, muscular tissues exhibit dark/hypoechoic signals. From outside to inside the cricopharyngeus is seen to have an outermost hyperechoic layer (adventitia) a hypoechoic muscle layer and an innermost mixed-echoic layer made up of the mucosa and submucosa. In an outside-inside order the cervical esophagus shows five echo layers on ultrasonography. The outermost hyperechoic layer the hypoechoic esophageal longitudinal muscle layer the hyperechoic intermuscular connective tissue layer the hypoechoic esophageal circular muscle layer and the innermost mixed-echoic layer made up of the mucosa and submucosa.

Four layers of the cervical esophagus are also recorded, notwithstanding the disparity in the tools and descriptions. The downward passage of air during a dry swallow creates a prominent echogenic appearance crossing the UES lumen, similar to a comet-tail artifact which aids in locating the cricopharyngeus among adjacent structures.

In order to reach the cricopharyngeal muscle the needle can be inserted either long-axis in plane (i.e., the needle moves along the long axis of the probe/image plane) or short-axis out-of-plane. Either the left or right side of the neck may be probed. The insertion location should be on the lateral side of the neck rather than the anteromedial side if the operator chooses to employ a needle approach to avoid the thyroid gland and major blood vessels. It is possible to inject the UES at places that are dispersed longitudinally or the anterior and posterior walls of the cricopharyngeal muscle. The UES's dark/hypoechoic muscle layers are the needle tip's intended target. In

light of this I should highlight that no participant experienced a serious issue throughout the trial. Additionally we wish to point out that neither group had any dropouts. Last but not least I want to point out that every study has some limitations and our study is no different.

CONCLUSION

Most of the PSD patients are ischemic in origin. There is definite improvement in both conservative management (RST) group (A) and RST with Botulinum toxin (BTX) injection group (B) after 1 month and 3 month of follow-up.

In both the groups, improvement was comparable upto 1 month of follow up. But thereafter the improvement in group A was not satisfactory unlike group B where marked recovery was seen between 1 month to 3 months after Botulinum toxin injection.

REFERENCES

1. Gordon, C., R.L. Hewer and D.T. Wade, 1987. Dysphagia in acute stroke.. BMJ., 295: 411-414.
2. Permsirivanich, W., S. Tipchatyotin, M. Wongchai, V. Leelamanit and S. Setthawatcharawanich, 2009. Comparing the effects of rehabilitation swallowing therapy vs. neuromuscular electrical stimulation therapy among stroke patients with persistent pharyngeal dysphagia: A randomized controlled study. J. Med. Assoc. Thai., 92: 259-265.
3. Arnold, M., K. Liesirova, A. Broeg-Morvay, J. Meisterernst and M. Schlager *et al*., 2016. Dysphagia in acute stroke: Incidence, burden and impact on clinical outcome. PLOS One., Vol. 11. 10.1371/journal.pone.0148424.
4. Priya, C.S.M. and J. Menon, 2014. Cricopharyngeal dysfunction in lateral medullary syndrome. J. Laryngol. Voice., 4: 21-27.
5. Terré, R. and F. Mearin, 2006. Oropharyngeal dysphagia after the acute phase of stroke: Predictors of aspiration. Neurogastroenterol. Motility., 18: 200-205.
6. Park, J., J. ,C Oh, J. ,W Lee, J. ,S Yeo and K.H. Ryu, 2012. The effect of 5HZ high-frequency rtms over contralesional pharyngeal motor cortex in post-stroke oropharyngeal dysphagia: A randomized controlled study. Neurogastroenterol. Motility., 25: 324-0.
7. McCullough, G.H., E. Kamarunas, G.C. Mann, J.W. Schmidley, J.A. Robbins and M.A. Crary, 2012. Effects of mendelsohn maneuver on measures of swallowing duration post stroke. Topics. Stroke. Rehabilitation., 19: 234-243.
8. Masiero, S., C. Briani, R. Marchese-Ragona, P. Giacometti, M. Costantini and G. Zaninotto, 2006. Successful treatment of long-standing post-stroke dysphagia with botulinum toxin and rehabilitation. J. Rehabilitation. Med., 38: 201-203.
9. Grandis, D.D., S. Faletti, F. Pirali and G. Santus, 2013. Botulinum toxin treatment of severe dysphagia following brainstem stroke. World J. Neurosci., 3: 275-281.
10. Kim, D.Y., C.I. Park, S.H. Ohn, J.Y. Moon, W.H. Chang and S.W. Park, 2006. Botulinum toxin type a for poststroke cricopharyngeal muscle dysfunction. Arch. Phys. Med. Rehabilitation., 87: 1346-1351.
11. Alfonsi, E., D.A. Restivo, G. Cosentino, R.D. Icco and G. Bertino et al., 2017. Botulinum toxin is effective in the management of neurogenic dysphagia. clinical-electrophysiological findings and tips on safety in different neurological disorders. Front. Pharmacol., Vol. 8 .10.3389/fphar.2017.00080.
12. Terré, R., M. Vallès, A. Panadés and F. Mearin, 2008. Long-lasting effect of a single botulinum toxin injection in the treatment of oropharyngeal dysphagia secondary to upper esophageal sphincter dysfunction: A pilot study. Scand. J. Gastroenterol., 43: 1296-1303.