Challenges Faced for Botulinum Toxin Injection in the Treatment of Hemifacial Spasm and Blepharospasm: Our Experience in Tribhuvan University Teaching Hospital during COVID-19 Pandemic

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ABSTRACT

Introduction: Hemi facial spasm (HFS) and Blepharospasm (BS) is a chronic distressing condition. Botulinum toxin (BoNT) injection is one of its treatment modality. Acquiring the injection and treating the patients overcoming the lockdown hurdles of COVID pandemic has been a major challenge.

Methods: Patients who were treated at Tribhuvan University Teaching Hospital (TUTH) Outpatient Department (OPD) during the COVID pandemic in 2020 and 2021 were included in this study.

Results: Out of 30 patients, 77% were female. 47% were diagnosed with BS whereas the rest with HFS. About 50% of them have had symptoms for an average of 2-5 years before receiving botulinum toxin injection. The mean Jankovic score for patients before BoNT was 2.31(SD: 0.66 range 1-4). 26 patients experienced a decrease in spasm within one week of BoNT injection and had symptomatic relief. The mean Jankovic score at week 1 was 0.63(SD: 1.09 range 1-3) and the difference was statistically significant ($p<0.001$). After 2 weeks of BoNT therapy, all patients experienced a decrease in spasm with symptomatic improvement. The mean Jankovic score at week 2 was 0.26(SD: 0.44 range 0-1) and the difference was statistically significant ($p<0.001$). In terms of side effects, 4 patients experienced paresis while 26 patients experienced no side effects. No other systemic side effects were reported.

Conclusion: BoNT injection has a good outcome for HFS and BS, despite its cost and the need for frequent injection. Importing the BoNT from India during the lockdown period of COVID pandemic and patients travelling within the country were challenges that were faced by the patients and doctors to achieve the result.

Keywords: Blepharospasm; Botulinum Toxin; COVID-19 Pandemic; Hemifacial Spasm.

INTRODUCTION

Hemi facial spasm (HFS) and blepharospasm (BS) are two of the most common craniofacial movement disorders. HFS is a rare neuromuscular disorder characterized by irregular, involuntary muscle contractions on one side of the face whereas BS is a form of dystonia involving orbicularis muscle in which muscle contractions cause sustained eye closure, twitching or repetitive eye movements often resulting in functional blindness. The incidence of HFS is approximately 0.8 per 100,000 persons and more common in females than males with prevalence of 14.5 per 100,000 compared to 7.5 per 100,000 in males[1]. Though HFS and BS are two different conditions, they are often chronic, progressive and spontaneous remission is very rare. The earliest description of HFS dates back to 1899 and since then many treatment modalities have been tried and tested including neurolysis, stretching of facial nerve and high-pressure irrigation of nerve with lactate ringer's solution.[2,3] However, treatment has evolved over time. Cases can be often managed with anticonvulsants like carbamazepine, BoNT, to microvascular decompression (MVD) for HFS.[4]

On a botulinum toxinA (Allergan) BoNT has been used for the treatment of HFS and BS in Nepal for almost two decades now. Tribhuvan University Teaching Hospital (TUTH) is a tertiary teaching hospital situated in

Kathmandu, Nepal which is among very few specialized treatment centers which offer BoNT therapy. The cost of single injection is NRs 20000 (approx. 170 USD) and many patients will often require 2-4 shots of BoNT per year, amounting to USD 640 per year to the cost of injection alone. Further, this cost goes up due to travel and other logistics issues. The high treatment cost means that many patients often choose to go under MVD instead of BoNT . Nepal detected its 1st coronavirus case in January 2020 and since then thousands of cases have been reported.[5] All sectors have been affected including healthcare due to prolonged travel restrictions. Patients seeking specialized care including those suffering from HFS and BS were deprived of care during both the first and second wave of the coronavirus pandemic. Further, the delay in procurement of medical supplies because of lockdown including drugs resulted in shortage of medicines. This halted many outpatient procedures including the BoNT therapy for HFS and BS. In this study, we aim to retrospectively analyze the data among HFS and BS cases who received treatment with BoNT therapy.

METHODS

Relevant data of BS and HFS diagnosis based on detailed clinical history, neurological examination, and patients treated with BoNT in the outpatient department was retrospectively extracted from the medical record department of TUTH. However, patient follow up was done virtually due to travel restrictions. Informed consent was taken for the study. Information on patient's age, sex, address, presenting symptoms, time since onset of symptoms, comorbidity including recent coronavirus infection, relevant neurological examination findings, routine blood investigations, COVID vaccination history, Magnetic Resonance Imaging (MRI) in Siemens 1.5 Tesla was extracted from medical record. The pre-treatment and post-treatment severity of HFS and BS was graded by the Jankovic Rating Scale (JRS) and was extracted from the records. JRS includes two subscales that measure intensity and frequency of eyelid spasms, both based on a 5-point grading system.[6] The doses of BoNT and specific muscle injected, the duration of effectiveness, the frequency of injection, the complications encountered, and its management. Patients' data were also extracted fpr the purpose of the study by making audio phone calls and viber video calls, to avoid hospital follow up in a pandemic. Pre and post procedure videos of patients were also collected.

50 Units frigid Onabotulinum toxin A was prepared by mixing well with 0.9% Normal saline in proper ratio and injecting it carefully at proper dosage within four hours of preparation. Cold chain was maintained during the procedure of acquiring BoNT. Double N95 mask and surgical mask with facial visor was worn during the procedure. Aseptic measures were taken while injecting BoNT into specific muscle and observed for contraction by doing maneuvers like whistling if required. The most commonly injected muscles were the orbicularis oculi (upper and lower eyelids), corrugator, frontalis, zygomaticus major, buccinators, and masseter mentalis. Precautionary measures were taken to avoid bleeding, by staying away from the mid-pupillary line and going laterally as far as possible, especially in the case of eyelids and eyebrows.

Data were retrospectively collected from patients of both sexes, age > 18 years old, who arrived at the outpatient neurology department of TUTH with signs and symptoms consistent with HFS and BS and had received BoNT injection between march 2020 and April 2021. All cases of HFS and BS with secondary diagnosis were excluded from the study. Patients who did not consent to be part of this study were also excluded from the study. All the statistical analyses were performed using SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Pre-test, post-test Jankovic score analysis was carried out by Wilcoxon signed rank test. P-value was calculated and p-value < 0.05 was considered as statistically significant.

RESULTS

A total 30 patients were enrolled in our study after meeting exclusion and inclusion criteria, of which 23 (77%) were female (Table 1). 47% were diagnosed with BS whereas rest with HFS. Left eye was involved in 43% cases whereas there was bilateral involvement in 40% cases. About 50% of them have had symptoms for an average of 2-5 years. 11 (37%) patients were from outside of province 3 where the capital city and study site TUTH is located(Figure 1).

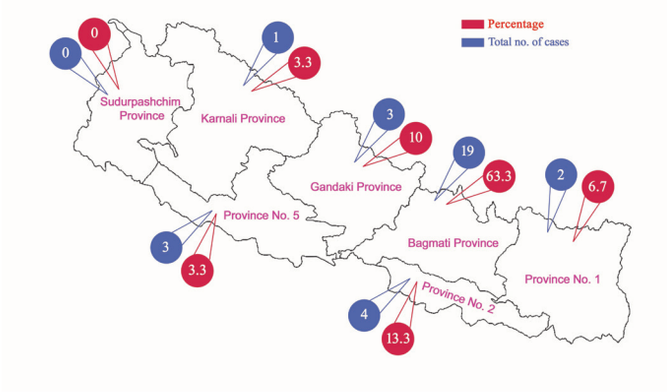
43% patients had one or more comorbidity in the form of diabetes or hypertension. At the time of the study, 80% of patients included in the study were not vaccinated. 70% patients had tried medications for a period of less than 2 years before opting for BoNT injection. Most of our patients (57%) prior to BoNT injection were classified as grade 2 according to the Jankovic severity score while 34% were grade 3 or grade 4 patients(table 1). Most of our patients (70%) had tried conventional medications including anticonvulsants before opting for BoNT. The mean Jankovic score for patients before BoNT was 2.31(SD: 0.66 range 1-4). 26 patients experienced a decrease in spasm within one week of BoNT injection and

Table 1 : Distribution of Participants according to Demographic and Clinical Profile

Category	Frequency	Percentage
Age		
31-40 years	4	13%
41-50 years	5	16%
51-60 years	8	27%
61-70 years	8	27%
71-80 years	5	17%
Sex		
Male	7	23%
Female	23	77%
Side Affected		
Left	13	43.3%
Right	5	16.7%
Both	12	40%
Duration of Illness		
2 years	5	16.7%
2-5 years	15	50%
5-10 years	4	13.3%
10-15 years	4	13.3%
15-20 days	2	6.7%
Diagnosis		
Bhlepherospasm	14	46.7%
Hemi Facial Spasm	16	53.3%
Co-morbid Condition		
Hypertension	10	33.3%
Hypertension +Diabetes Miletus	3	10.1%
None	17	56.7%
Onset of action of BONT		
<7 days	26	86.7%
7-14 days	4	13.3%
Age of Onset		
<40 years	9	30%
40-50 years	9	30 %
50-60 years	6	20%
60-70 years	4	13.3%

had symptomatic relief. The mean Jankovic score at week 1 was 0.63(SD: 1.09 range 1-3) and the difference was statistically significant (p<0.001). After 2 weeks of BoNT therapy, all patients experienced a decrease in spasm with

Figure 1: Case Distribution in different Provinces



symptomatic improvement. The mean Jankovic score at week 2 was 0.26(SD: 0.44 range 0-1) and the difference was statistically significant (p<0.001) (table 3). In terms of side effects, 4 patients experienced paresis while 26 patients experienced no side effects. No other systemic side effects were reported.

Table 2:Baseline data of study participants

Side effect	**None**	**26(86.7)**
	Paresis	04(13.3)
Jankovic scoring before BoNT	Grade 1	02(06.7)
	Grade 2	17(56.7)
	Grade 3	09(30.0)
	Grade 4	01(03.3)
Duration of medication	< 2 years	21(70.0)
	2-5 years	05(16.7)
	5-8 years	04(13.3)
Covid vaccination status	1st dose only	02(6.66)

Table 2: Functional improvement in Jankovic score during study period

Jankovic score	Number	Grade (Range)	Mean	Standard deviation	Z value	p-value
Day 1 before injection	30	1-4	2.31	0.66		
Week 1 after injection	30	1-3	0.63	1.09	-4.179	<0.001
Day 1 before injection	30	1-4	2.31	0.66		
Week 2 after injection	30	0-1	0.26	0.44	-4.697	<0.001

DISCUSSION

One of the most dangerous food poisoning botulism is due to the exotoxins released by spores forming Clostridium Botulinum, an anaerobic gram-positive bacteria.[7] It acts by binding in presynaptic cholinergic nerve ending, decreasing acetylcholine at neuromuscular junction causing flaccid paralysis. Its therapeutic effect was established first by Dr. Scott who used it to treat strabismus. Since then, BoNT has been extensively used for cosmetic and therapeutic purposes. Its therapeutic effect leads to reducing muscle tension and increasing muscle relaxation. Out of the seven serotypes (A-G), three A serotypes and one B Serotype is approved globally for treating spasmodic torticollis. The three serotype A products have been approved for focal dystonia like BS and HFS. [8] In Nepal, we use Onabotulinumtoxin A (Allergan) which comes in 50 units or 100 Units.[9] Once applied in the respective muscles, it takes 7 to 10 days to be effective and its full efficacy will be seen for five to six months leading from flaccid paralysis to muscle relaxation. Among the many complications, temporary facial paralysis is most commonly witnessed. [10] However, BoNT is contraindicated in patients suffering from neuromuscular disorder, prior history allergies to BoNT, Amyotrophic lateral sclerosis and other myopathies.

Our study participants had a mean age of 64.3 years with a range of 28 to 81 years for patients suffering from BS while the mean age was 54.1 years with a range of 39 to 80 years for those suffering from HFS. Studies have shown that both HFS and BS usually arises in fifth or sixth decade. Though HFS does have not have any gender predisposition, BS tends to occur more commonly in women than men in ratio of 2.8:1.[11,12] Most of the patients (86%) became symptom free as evidenced clinically and Jankovic score within 7 days whereas remaining 4 patients responded within 2 weeks. The mean Jankovic score for patients before BoNT was 2.31(SD: 0.66 range 1-4). The mean Jankovic score at week 1 was 0.63(SD: 1.09 range 1-3) and the difference was statistically significant ($p<0.001$). After 2 weeks of BoNT therapy, all patients experienced a decrease in spasm with symptomatic improvement. The mean Jankovic score at week 2 was 0.26(SD: 0.44 range 0-1) and the difference was statistically significant ($p<0.001$). Studies have shown that over 90% patients with BS improve with BoNT and magnitude of benefit exceeds 90% (0% -"no improvement, 100% -"complete resolution"). Further, it has been shown that a stable dose or small gradual increase in dose over time maintains high level of benefit.[13,14] Hence, the need for regular follow up cannot be undermined and coronavirus pandemic forced us to explore alternative means for follow up with telemedicine. With regards to HFS, there is limited data from randomized clinical trials. Studies have shown that 76 to 100% patients with HFS report around 75% improvement in clinical symptoms with effect lasting upto 3 to 4 months. Similar response has been noticed with regards to long term benefit BoNT in HFS with gradual increase in dose required over time.[14,5,6]

In our study, side effects of injection were reported among 4 HFS patients (13%), all of them developed facial paresis. Side effects from BoNT injection may occur in upto 20% patients with HFS and may include paresis of lower facial muscles and ocular side effect such as irritation. BoNT injection related side effects in BS have been reported in 3 to 25% patients and includes ptosis, bruising, tearing, dry eyes, diplopia and keratitis. However, these are rarely severe and are reversible.[14 17] No serious side effects have been reported with long term use.[18]

Several rating scale has been developed to assess the severity of blepharospasm. The Jankovic rating scale (JRS) has been preferred over others due to high internal consistency. However, it is not without demerits. These include lack of a clear definition of spasms regarding the degree of rim closure, the combination of examiner-based and patient-based information, and the lack of attention to clinical features. However, it is not used clinically and physician often rely on observation, patient reported benefit and side effects.[19] However, assessing JRS via virtual consultation was challenging and can be considered one of the limitations of the study. There are several other limitations of the study. First, the study might overestimate the effect of BoNT due to small sample size. However, only patients who consented and received BoNT at TUTH during the pandemic were considered for this study, accounting for small sample size. Second, in this study, we have assessed effectiveness of BoNT at the end of week 1 and week 2 only. So the duration for which effect of BoNT lasts could not be accounted for at the time of publication of this study. This is an important thing to consider as many patients choose MVD over BoNT in the long term if the effect of BoNT is short lived as the yearly cost of BoNT is high.

CHALLENGES

BoNT therapy was only possible during the period when lockdown was eased for COVID. Further, we largely depend on India for drugs such as BoNT. However, BoNT could not be imported due to travel restrictions. So patients suffered due to lack of timely treatment and affected their quality of life. Further, Polymerase Chain Reaction (PCR) for coronavirus was not mandatory until recently for patients undergoing outpatient procedures which posed significant

risk for treating physicians and staff. Social distancing could not be achieved as the procedure had to be informed.

CONCLUSION

Despite the cost and the difficulty in acquiring BoNT during COVID pandemic, the result of injecting BS and HFS was as par to the international results. Although it works temporarily it improves the quality of life of such patients and the success rate is very good. Our study has shown that telemedicine can be a viable option for follow up in such patients as we can communicate with video chat and see the improvement of the symptoms

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