

**SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL
SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM, KERALA**



**Clinical presentation and evolution of isolated focal and
segmental dystonia in adults treated with botulinum toxin
injection– A retrospective study from a tertiary care center in
India**

Dissertation submitted in partial fulfillment of the rules and
regulations for

Post-Doctoral Fellowship in Movement Disorders

By

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DECLARATION

I, Dr. Asish Vijayaraghavan, hereby declare that this project was undertaken by me under the supervision of Dr Syam K, Professor and In-Charge, Comprehensive Care Centre for Movement Disorders , Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram,
Date: 15-12-2021.

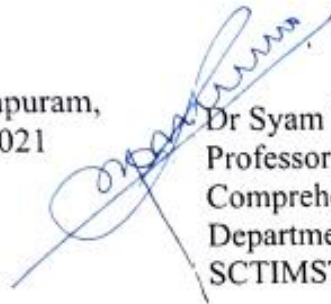


Dr. Asish Vijayaraghavan

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The candidate, Dr. Asish Vijayaraghavan, has completed the project under my guidance.

Thiruvananthapuram,
Date: 15-12-2021



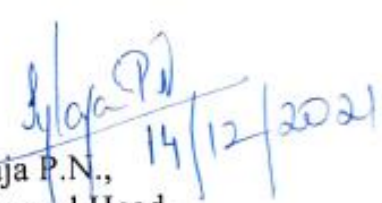
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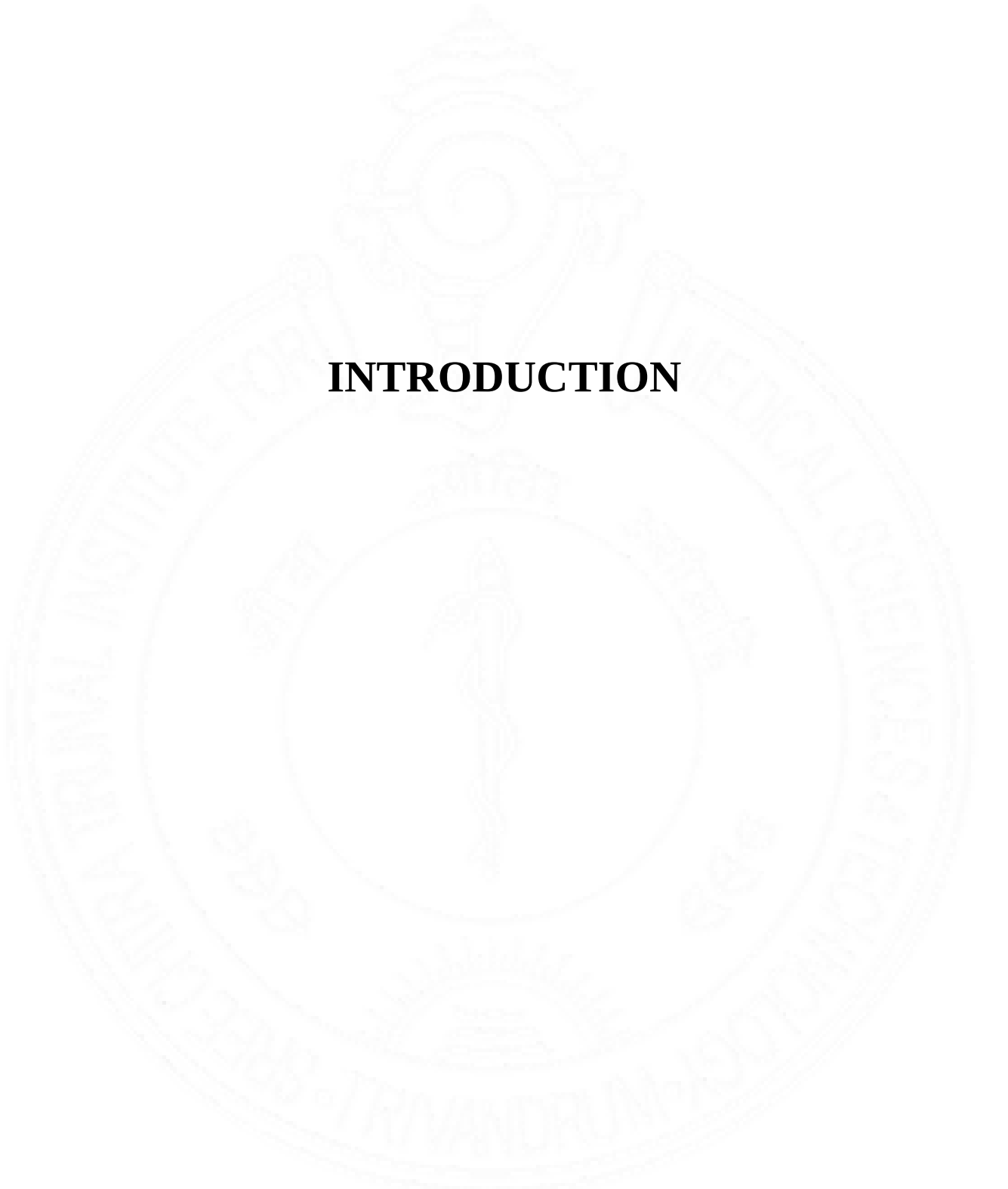
The candidate, Dr. Asish Vijayaraghavan, has carried out the minimum required project for completion of Post Doctoral Fellowship in Movement Disorder.

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INTRODUCTION

Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. The dystonia is "focal" when it affects a single body region and "segmental" when it affects two or more contiguous body regions(1). Botulinum toxin treatment is the standard of care for patients with focal and segmental dystonia(2–4).

Most of the literature on botulinum toxin in focal dystonia is from European or American centres and predominantly Caucasian populations (5–8). In India, the use of botulinum toxin injections is limited essentially by the lack of expertise in this method and the cost of the treatment. Despite India's vast population and high prevalence of focal dystonia, there are only a few studies on botulinum toxin injections in focal dystonia from India. This large retrospective study describes the clinical and demographic profile of patients who underwent botulinum toxin injection treatment in the dedicated clinic of a tertiary care center. The study presents the self-reported benefit and weakness after botulinum toxin injections in different types of isolated focal or segmental dystonia. This study aims to provide unique data on the common patterns of muscles selected for injection and time course of benefit and weakness for BoNT injections in a real-life setting outside of a clinical trial. The study also provides information on the clinical evolution of isolated dystonia over time.



REVIEW OF LITERATURE

Review of literature

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting and may be tremulous. It is often initiated or worsened by voluntary action and associated with overflow muscle activation. Dystonia is currently classified along two axes- the clinical axes and etiology(1). In the clinical axes, dystonia is classified as “isolated” if it occurs as the sole manifestation, without any other movement disorders, neurological signs, or systemic involvement clinically. Isolated dystonia generally results from genetic defects, which do not cause neurodegeneration or structural brain damage. The overall prevalence of primary dystonia is approximately 16.43 per 100,000(9). It is the second most common hyperkinetic movement disorder after tremor.

When combined with other movement disorders (such as myoclonus or parkinsonism), dystonia is classified as “combined dystonia.” The upper or lower cranial region, the cervical region, the larynx, the trunk, the upper limbs, or the lower limbs can be affected by dystonia. These territories may be involved individually or in various combinations.

Based on the body distribution, dystonia may be classified as focal (single body part), segmental (two or more contiguous body parts), multifocal (two or more non-contiguous body parts), hemi-dystonia (one side of the body), and generalized (trunk and at least 2 other sites are involved). According to European studies, cervical dystonia is the most common cause of primary focal dystonia (10,11). However, recent Indian studies have shown focal hand dystonia as the most common isolated focal dystonia(12,13). At the same time, studies from Japan and Italy showed blepharospasm (BSP) being more frequent than other focal dystonia(14,15).

A meta-analysis of major series of patients published in English literature in the past few decades showed that the mean age of onset is 38 years for focal hand dystonia (FHD), 41 years for cervical dystonia (CD), 43 years for laryngeal dystonia (LD), and 56 years for blepharospasm (BSP)(16). Most studies have shown female predominance in focal dystonia, except for focal upper limb dystonia(17,18).

Sensory tricks are voluntary actions that specifically alleviate the dystonic movements. These are usually simple movements (“gestes”) involving, or directed to, the body region affected by

dystonia, but not consisting of a forceful opposition to the phenomenology of dystonia. Sensory tricks are common in CD and less common in cranial and hand dystonia(19). Effective sensory trick, when present, maybe a hallmark of idiopathic dystonia.

Evolution of dystonia

Dystonia usually affects only one body region at first, but it can spread to additional contiguous or distant body regions over time, resulting in higher disability depending on which body region or regions are involved. Data suggest that blepharospasm (BSP) has a higher rate of spread than other forms of focal dystonia. Most common regions for first spread were the oromandibular region and neck(20). In more than half of patients presenting with blepharospasm, dystonia usually spreads during the initial five years and then stabilizes. In contrast, patients presenting with CD, laryngeal dystonia, or FHD experience significantly less spread to adjacent body regions within five years(21).

Botulinum toxin injection treatment in dystonia

Treatment of dystonia usually consists of medical management, surgical interventions, and botulinum toxin injection(22–25). Botulinum toxin treatment is the accepted standard of care for patients with focal and segmental dystonia. The success of the treatment depends on meticulous muscle selection and the appropriate dosage of the toxin. Usually, botulinum toxin is injected according to clinical experience of surface anatomy and clinical location. Injection techniques with ultrasonic or EMG guidance help in better identification of the dystonic muscles.

Botulinum neurotoxin (BoNT), produced by spore-forming anaerobic bacteria, is the most potent biologic toxin and is a powerful therapeutic tool for a vast number of clinical indications in neurology and beyond. BoNT inhibits the release of acetylcholine from the presynaptic terminals of the neuromuscular junction by interfering with normal process of vesicle–plasma membrane fusion. The turn of the century has witnessed the use of BoNT to treat various ailments in neurology, ophthalmology, gastroenterology, urology, autonomic disorders, and dermatology. The major indications for BoNT are hyperkinetic movement disorders. Because BoNT must be injected locally, neurologists must possess the appropriate expertise to deliver the therapy effectively.

BoNT was initially approved by the Food and Drug Administration (FDA) in 1989 for strabismus, blepharospasm, and hemifacial spasm following ten years of experimental treatment on human volunteers. Over the next few years, BoNT was gradually introduced in the treatment of other movement disorders, including tremors, tics, myoclonus, and spasticity (Table-1).

Although considered effective and safe, there are still many limitations, such as discomfort associated with the injection, a relatively short duration of response, the possibility of immunogenicity, and high cost. The technical aspects are of utmost importance and play a significant role in the outcome. With advancing research into novel formulations, mechanisms of action, improved methods of administration, the field of therapeutic BoNT will continue to grow.

Literature is scarce on the long-term follow-up of patients receiving botulinum toxin injections in India. Even though there are studies on the efficacy of botulinum toxin in focal dystonia, there are no large long-term follow-up studies. In India, the routine use of botulinum toxin in clinics is far from standardized. Reduced use of EMG, difficulty in muscle localization, and cost of the toxin are important limitations.

Types of toxin

While all types of BoNT are composed of two peptide chains linked through a disulfide linkage, the amino acid sequence of various peptide chains found in each subtype of BoNT differs. The entire protein comprises three domains—two in the heavy chain and one in the light chain, and each domain performs a specific function at the molecular level. The molecular weight of the heavy and light chains are 100 and 50 k Dalton, respectively. The C-terminal of heavy chain is involved in binding the toxin to receptor site, whereas the N-terminal is responsible for "translocation." The light chain contains the catalytic unit. Based on the serological typing of the BoNT, eight types, from A to H, are described in the literature. The specific neutralizing anti-sera determines the type. The serotypes and subtypes not only differ structurally, but significant differences are also apparent in their toxo-pharmacological properties (26).

Types A and B, because of their prolonged mode of action, are approved by FDA for clinical use. They have a substantially different affinity to the motor and the autonomic nervous system. The three types of A toxin approved consist of onabotulinumtoxinA (Botox; Allergan, CA,

USA), abobotulinumtoxinA (Dysport; Ipsen-Pharma, UK), and incobotulinumtoxinA (Xeomin; Merz Pharma, Germany). RimabotulinumtoxinB (Myobloc in the USA;) is a BoNTB preparation. Novel preparations of BoNTA include LanbotulinumtoxinA (Prosigne; Shanghai, China), marketed primarily in Asia, and Daxibotulinumtoxin A, which was evaluated in a phase 3 trial (ASPEN-1) in cervical dystonia(27).

The biological activity of therapeutic BoNT preparations is given in mouse units (MU), shortened to units (U). One MU is the calculated median lethal intraperitoneal dose (LD50) injected in a 20gm Swiss-Webster mouse (which would kill 50% of a BoNT-intoxicated mouse population). Therefore, MU or U describes the biological activity and – according to the amount of inactivated botulinum toxin contained – correspond to different mass units. Comparable units for various commercial preparations is 1-U Botox = 1-U Xeomin = 2.5–3-U Dysport = 50-U Myobloc.

Mechanism of Action of BoNT

BoNT inhibits the release of acetylcholine(ACh) from the presynaptic terminals of the neuromuscular junction (NMJ) by interfering with the normal process of vesicle–plasma membrane fusion. This is achieved by inhibition of synaptic SNARE proteins (soluble N-ethylmaleimide-sensitive factor-activating protein receptor)(28). Because of the molecular turnover within the neuromuscular junction and neuronal sprouting, neuronal activity begins to return at 3 months, with the restoration of complete function at around 6 months(29).

BoNT also prevents the release of other neurotransmitters, namely substance P, adenosine triphosphate, and calcitonin-gene-related peptide. In addition, it also negatively regulates the sensory receptors involved in the pain pathways, such as transient receptor potential cation channel subfamily V member 1 (TRPV1), commonly termed as the capsaicin receptor and vanilloid receptor1, and purinergic (P2X3) receptors(30). The effects of BoNT on these transmitters and receptors are being explored in managing autonomic and pain syndromes such as those associated with cancer(31).

Non-responsiveness to BoNT

Neutralizing antibodies (NAbs), jeopardizes sustained response to the toxin(29). Larger protein content in specific toxin formulations, higher individual and cumulative toxin doses, the narrow

interval between injections and booster doses have been implicated in exalted risk of resistance to BoNT(32,33). The risk of developing NABs varies with BoNT formulations, with immunogenicity varying from 0% for incobotulinumtoxinA to 42.4% for rimabotulinumtoxinB(33). Non-responsiveness is rare for incoBoNTA, which has a molecule free from antigenic proteins. For onaBoNTA, the low rate (approximately <1%) is due to the reduction in albumin content from 25 ng present in the formulations prior to 1997 to only 5 ng in the current one(34).

Table 1 Level of evidence for various indications of BoNT

Indications for BoNT	Onabot-A	Abobot-A	Incobot-A	Rimabot-A
a) Movement disorders				
Cervical Dystonia	B	A	B	A
Blepharospasm	B	C	B	U
Writer's cramp	C	C	-	-
Spasmodic dysphonia	B	-	-	-
Oromandibular dystonia	U	U	-	-
Hemifacial spasm	C	C	C	U
Palatal TREMOR	U	-	-	-
Tics	C	-	-	-
Essential tremor	C	U	B	-
PD tremor	C	-	C	-
PD Camptocormia	U	U	-	-
Restless leg syndrome	U	U	C	-
b) b. Other Neurological indications				
Upper limb spasticity	A	A	A	B
Lower limb spasticity	A	A	-	U

Level A- effective, Level B- probably effective, Level C-possibly effective, Level U- insufficient evidence

Clinical use in specific conditons

Cervical Dystonia

Cervical dystonia (CD) is the most frequently encountered form of adult-onset focal dystonia(35), with a prevalence of 5/100,000(9). In the Cervical Dystonia Patient Registry for

Observation of OnabotulinumtoxinA Efficacy (CD-PROBE) study, an extensive registry of CD patients, the mean age of onset was 49 years, and 74% were females(36). Major abnormal neck postures seen in CD according to traditional classification are - head rotation (torticollis), head tilt (laterocollis), head bent forward (anterocollis), and head bent backward (retrocollis). Torticollis is the most common form of abnormal head and neck posture in CD, followed by laterocollis. The most common combination in CD is torticollis with laterocollis. The list of common muscles injected in CD is given in table-2.

Combinations of complex cervical dystonias have recently been classified depending on the head (caput) and neck(collis) movements(37). In CD, two levels of movement of head-neck complex can be defined: upper – between the skull and C2, lower – between C2 and C7, with C2 vertebra being a fixed point. Depending on their insertions, the cervical muscles involved in CD can also be divided into muscles acting mainly on the head or mainly on the neck. Based on this caput-collis concept, the CD can be classified into 11 fundamental types - anterocollis, antecaput, rotacollis, rotacaput, laterocollis, laterocaput, retrocollis, retrocaput, anterior sagittal shift, posterior sagittal shift and lateral shift.

Approximately 70% of the patients with CD have associated neck pain(38). In addition, torticollis is sometimes associated with head jerks when the patient attempts to rotate the head opposite the sustained abnormal rotation. The emerging data regarding deep brain stimulation (bilateral GPi) efficacy in CD(39) is encouraging, but the procedure is expensive and not devoid of complications. Therefore, BoNT remains the treatment of choice.

BoNT has longstanding and widespread use in CD treatment, a condition without effective alternative medical therapies. Based on existing literature, the Guideline Development Subcommittee of the American Academy of Neurology (AAN) in 2016 has given rima- and aboBoNT toxins a level A efficacy (established) and ona- and incoBoNT toxins a level B efficacy (one class I study each probably effective) for treatment for CD(40). Several studies have supported the conclusion that BoNT is a safe and effective CD treatment(41–45). The long-term response rate in open and double-blind studies is between 60% and 80%(46). BoNTs also improve the associated neck pain of CD substantially. Peak benefit occurred at 6 weeks following injection, improving functional capacity, head-turning, pain, and subjective assessment(47). Neck weakness and dysphagia are the two most common side effects. Dysphagia may be less common in onaBoNT-A therapy (3.4%) compared to the other neurotoxins (12.6, 15.6, and 19.6% with inco-, rima-, and aboBoNTs, respectively)(48).

Bilateral injections of sternocleidomastoid muscles and higher doses of BoNT into the anterior neck muscles have been associated with a higher incidence of dysphagia. Dysphagia is usually mild and disappears after several weeks. BoNT improves symptoms associated with cervical dystonia and favorably alters the natural course of the disease. In addition, it helps in the prevention of contractures.

Table 2- Common muscles for BoNT injection

Muscle	Action	Dose range (in units*)
Sternocleidomastoid	Contralateral rotation Ipsilateral flexion Anteroflexion	40-100
Splenius capitis	Ipsilateral rotation Ipsilateral flexion Head extension	40-100
Scalenus medius	Ipsilateral flexion Anteroflexion	10-20
Levator scapulae	Ipsilateral flexion	40-60
Trapezius	Ipsilateral flexion Ipsilateral shoulder elevation Head extension	40-80
Longus colli	Ipsilateral flexion Anteroflexion	10

*Dosage in units for onabotulinum (Botox) / incobotulinum (Xeomin) toxin. Abobotulinum toxin (Dysport) dose to be calculated with a multiplication factor of 2.5-3

Oromandibular dystonia(OMD)

Oromandibular dystonia (OMD) is a rare focal form of dystonia characterized by repetitive, involuntary jaw movements. OMD affects women more commonly than men, and the range of mean age at onset varies from 50 to 60 years. The dystonic jaw movements can present as intermittent jaw opening, jaw closure, jaw deviation, protrusion, retraction, or a combination. Often there are associated lingual movements that take the form of dystonic rolling, tongue retraction, or protrusion. The etiology includes drug-induced dyskinesias, tardive dyskinesias, and neurodegenerative disorders such as neuroacanthocytosis, neurodegeneration of brain with iron accumulation and Wilson's disease. Specific genetically determined dystonias (DYT6 dystonia(THAP 1), Lubag; DYT3 dystonia of the Philippines, ATP1A3 mutation also demonstrate mandibular dystonia. Symptoms often interfere with essential daily living activities, such as feeding, chewing, swallowing, and speaking(49–51). OMDs, especially the primary ones may be ameliorated by different proprioceptive sensory inputs ("sensory trick"), such as touching the lips or chin, chewing gum, or biting a toothpick. This type of dystonia is often associated with blepharospasm(defining Meige's syndrome) and cervical dystonia (referred to as cranial-cervical dystonia).

A retrospective chart review from 1995–2011 included 59 OMD patients and showed inter-BoNT injection intervals of 3.8 months; 47.5% had jaw closing, 35.6% opening dystonia, and 16.9% jaw lateral deviation OMD(52).

Jaw Opening Dystonia (JOD) -OMD is caused by dystonic contractions of lateral pterygoids, anterior belly of the digastric muscle, and submental (geniohyoid, digastric, mylohyoid) muscles. Jaw Closing Dystonia (JCD) -OMD is caused by dystonic spasms of the masseter and temporalis muscles, leading to trismus and bruxism.

A retrospective study of 172 patients divided lingual dystonia into four types: protrusion(68.6%), curling (7.6%), retraction (16.9%), and laterotrusion (7%)(53).

OMD, especially JOD, remains one of the most challenging forms of dystonia to treat. Pharmacological treatment of orofacial and OMD is generally unsuccessful.

BoNT therapy is now considered the first line of treatment for OMD despite paucity of high-quality clinical trials. Tan and Jankovic reported a mean total duration of response upto 16.4

±7.1 weeks in a large prospective open study(49). The best response is obtained with jaw-closing OMD. The most common side effect reported is transient mild dysphagia, which occurred in 60% of patients(54).

BoNT has been shown to be as effective in the treatment of tardive OMD as in the treatment of idiopathic OMD using the same general principles(55).

Blepharospasm

Blepharospasm(BSP) is focal cranial dystonia caused by excessive involuntary closure of the eyelids, usually bilateral, although it may sometimes be briefly unilateral at onset(56). The initial symptoms include unpleasant sensations, eyelid fluttering, or increased blink rate to stimuli, which progresses to chronic involuntary bilateral spasms of the eyes(57). The muscle most often involved in BSP is orbicularis oculi, a sphincter muscle around the eye which consists of an orbital, preseptal, and pretarsal part. BSP can also affect the levator palpebrae superioris, corrugator, procerus, and frontalis. Typically, both eyes are involved. The mean age of onset of BSP is in the fifth and sixth decades, and women are more commonly affected, with a female to male ratio of 2.8/1(58,59). BSP is usually an isolated finding (essential BSP). Secondary BSP, related to brain stem pathology, represents less than 10% of the cases. The differential diagnosis of blepharospasm includes eyelid opening apraxia(elderly), tics of Tourette syndrome, and psychogenic blinking (young patients).

In 1989, Onabotulinum toxin- A (Botox) received FDA approval for BSP, including benign essential BSP or VII nerve disorders, in patients older than 12 years. BoNT injections are now considered the first line for the management of BSP(60). Onabot-A, abobotulinumtoxinA (Abobot-A), and incobotulinumtoxinA (Incobot-A) can be considered as therapeutic options. Ptosis, visual blurring, and local oedema are the usual side effects. The American Academy of Neurology (AAN) in 2016 published updated practice guidelines regarding the use of BoNT in multiple movement and neurologic disorders and found that (i) onabotulinumtoxinA and incobotulinumtoxinA were probably effective for blepharospasm treatment (Level B), and (ii) abobotulinumtoxinA was possibly effective (Level C).

Focal hand dystonia and task-specific dystonia (TSD)

We often see patients with dystonia specific to a particular task. For example, they may have dystonia when using their hand for writing but not for other tasks such as eating or typing. Writer's cramp (WC) and musician's cramp are the two most common occupational dystonia.

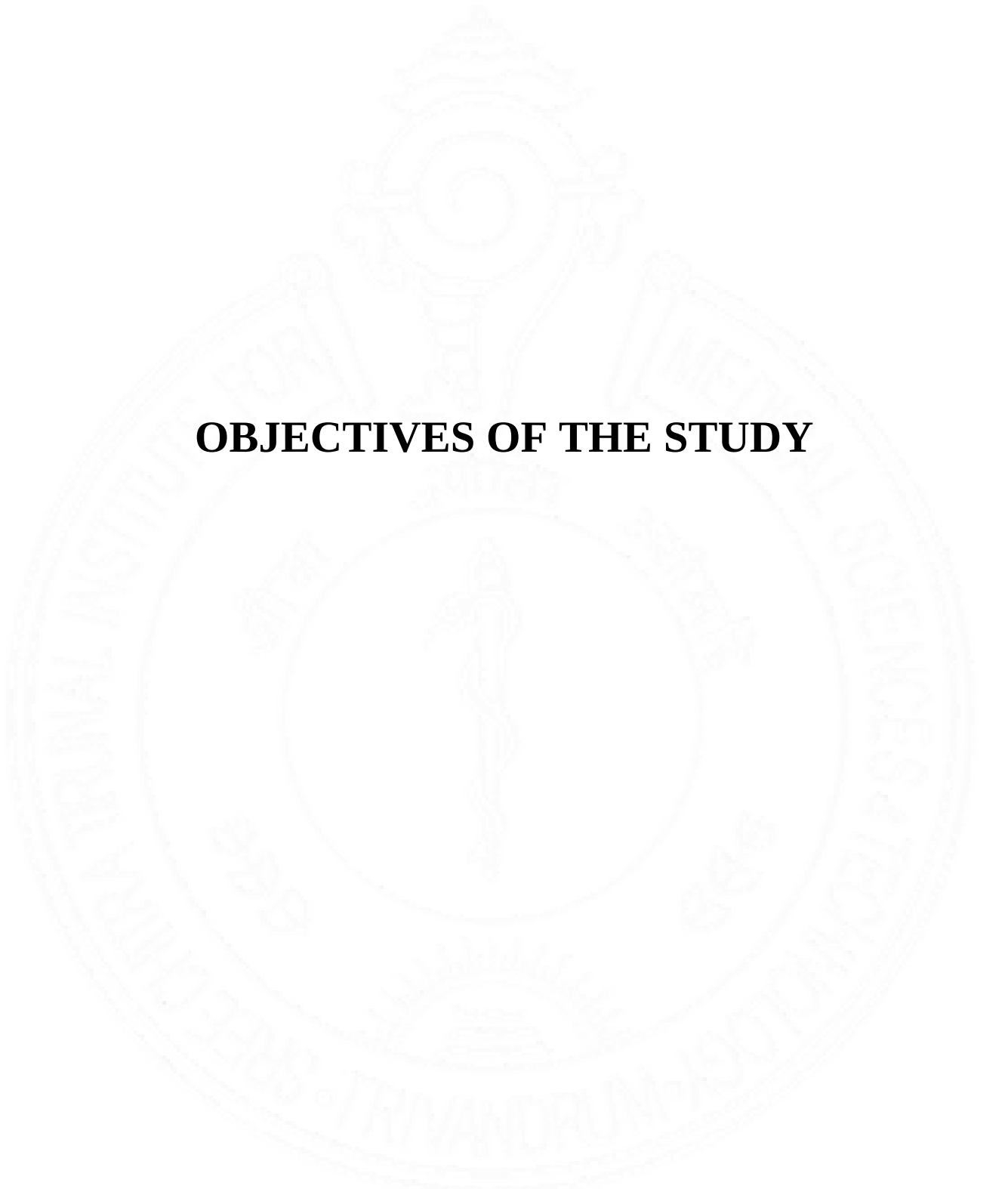
An interaction of proprioceptive, behavioral, gestural, environmental, genetic, and psychological factors plays a role in their etiology.

Writer's Cramp

Writer's cramp (WC) can be – simple or complex. "Simple writer's cramp" is when other acts of dexterity, such as buttoning of clothes, are unimpaired. It can be flexion or extension type depending upon the type of abnormal finger movements. The presence of difficulties with tasks other than writing is said to have a "complex writer's cramp." WC can be divided into various subtypes depending on the hypothesized muscle group. Most common muscles involved include the flexors and extensors of the fingers and wrist.

Writing with the non-dominant hand can evoke dystonia in the dominant, resting hand (mirror dystonia). Mirror dystonia can help identify dystonic muscle activity and distinguish dystonia from compensatory muscle activity(61).

Injections should be done under careful EMG guidance to locate the specific muscle(s) of interest since the muscles are tightly clustered together in the forearm. The recommended mean total dose for onaBoNT-A is 24.9 units, and for aboBoNT-A, 82 units for WC(62). Weakness of the injected muscle is the most frequent side effect(63). Writer's Cramp Rating Scale(WCRS) and Burke-Fahn-Marsden scale are the rating scales used to assess clinical response after BoNT injection.



OBJECTIVES OF THE STUDY

Aims and Objectives:

- 1) To analyze the demographic and clinical profile of patients presenting with isolated focal and segmental dystonia to the botulinum toxin clinic, the patterns of dystonia in them, and the injected muscles
- 2) To investigate the self-reported benefit, duration of benefit, and complications after botulinum toxin injections in these patients
- 3) To assess the predictors of good clinical outcome
- 4) To evaluate the temporal evolution of the dystonic symptoms over time

MATERIALS AND METHODS

Methods:

Study setting : Botulinum toxin injection clinic, Comprehensive Care Center for Movement Disorders, Department of Neurology, Sri Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram

Study design: Retrospective, single-center study

Inclusion criteria

- 1) Patients with a clinical diagnosis of isolated focal or segmental dystonia at presentation to the botulinum toxin injection clinic
- 2) Patients who have undergone botulinum toxin injection treatment at least twice

Exclusion criteria

- 1) Presence of additional movement disorders (with the exception of tremor), neurological signs, or systemic signs associated with dystonia, making it a “combined” dystonia syndrome
- 2) Dystonia resulting from birth injury, head trauma, stroke, or other acquired causes
- 3) Patients who have taken botulinum toxin injection only once

Sample size – Five hundred and fifty charts were screened. Two hundred were excluded due to multifocal or generalized dystonia and other secondary dystonia. One hundred and eight were excluded for having fewer than two visits. Questionnaires from 242 patients were selected for final analysis.

Study Duration – The data collection and analysis was done over six months(June 2021 to December 2021)

Method

Data was extracted from our prospectively maintained Botulinum Toxin Injection files as well as the case files in the electronic database(EMR). Data on clinical and demographic profiles, family history, relevant investigations, medications received, patterns of dystonia, muscles selected for injection, and doses for each muscle were collected. The response reported by the patients and the duration and side effects reported were documented. As part of routine clinical care in our Botulinum toxin clinic, the patients complete a structured questionnaire at each visit about their immediately previous BoNT injection, rating benefit, and weakness on a visual

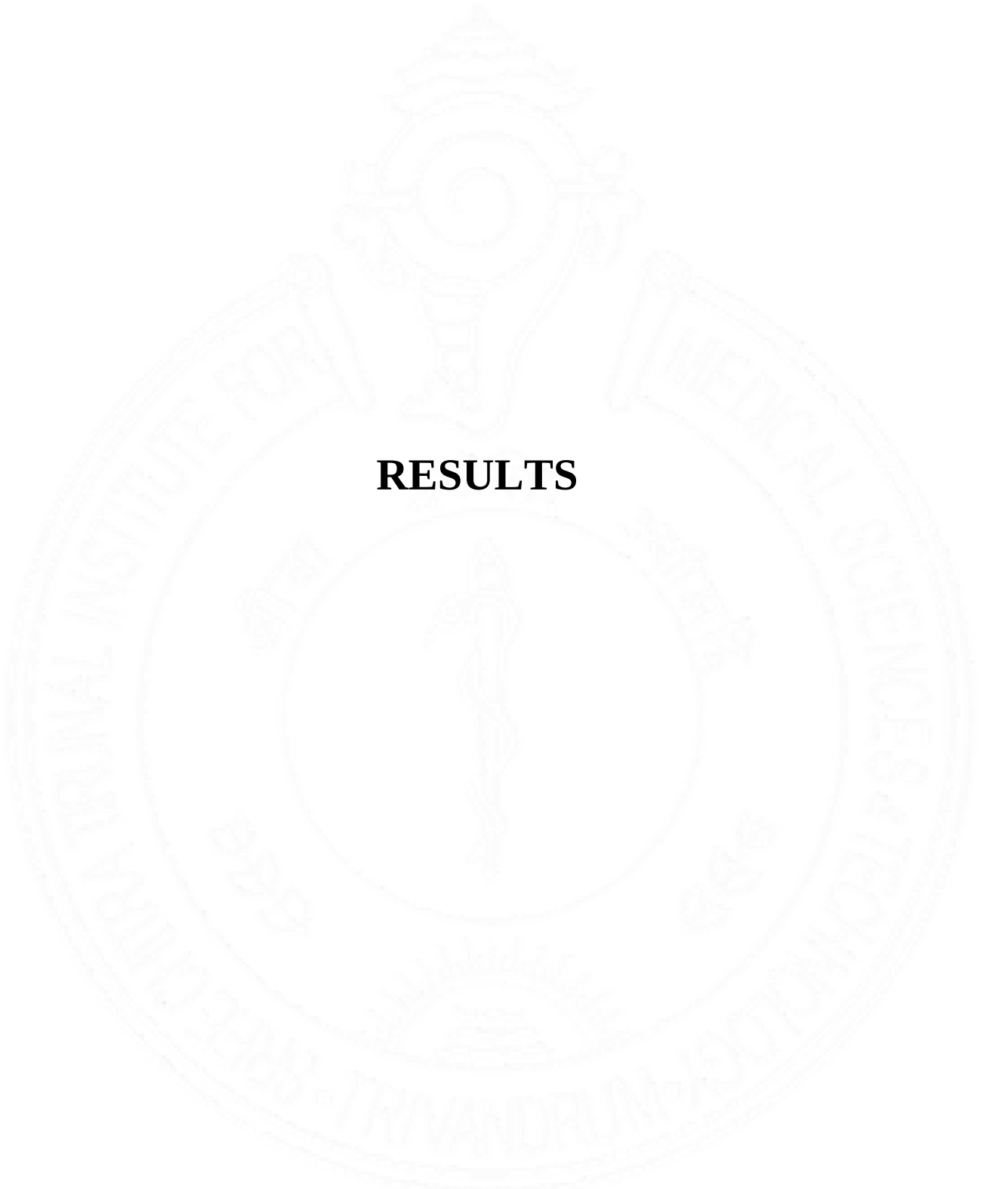
analog scale ranging from 0 to 100% (for benefit: 0 = no benefit; 100% = complete relief; for weakness: 0 = no weakness; 100% = no voluntary movement). They also recorded the time-to-onset of any benefit/weakness, time-to maximal benefit/weakness, and maximal benefit/weakness duration. Patients were followed up every 3-6 months. We extracted data on timing variables from the most recent questionnaires for patients receiving injections for blepharospasm (BSP), cervical dystonia (CD), focal hand dystonia (FHD), and oromandibular dystonia (OMD) between 2000–2020. A “good outcome” was defined as a 70% or more self-reported benefit for more than or equal to 3 months. We reported the predictors of outcome in various focal dystonia. This study provides unique data on the course of benefit and weakness for BoNT injections in a real-life setting outside of a clinical trial. In addition, we also described the evolution of dystonia over time (changes in the pattern of muscles involved, the spread of dystonia to other regions, the appearance of additional neurological signs on follow-up).

Statistical analysis

For statistical analysis, we used proportion as a descriptive statistic for categorical and ordinal variables, median and interquartile range for ordinal and continuous variables, and mean (SD) for continuous variables. Categorical variables were analyzed using the Chi-square test. Univariate models were used to determine the relationship between different variables and outcomes. Analyses was performed using statistical software IBM SPSS Version 22.

IEC approval

The study was approved by the Institutional Ethics Committee (SCT/IEC/17021AUGUST-2021).



RESULTS

Results

Five hundred and fifty charts were screened. Two hundred were excluded due to multifocal or generalized dystonia and other secondary dystonia. One hundred and eight were excluded as they had less than two visits. Questionnaires from 242 patients (mean age 41 years, SD = 15.7; 61.2% males) were eligible.

Isolated focal dystonia was seen in 223(92.1%), whereas only 19 patients(7.1 %) had segmental dystonia. Cervical dystonia (41.3%) was the most common focal dystonia, followed by focal hand dystonia(29.1%), blepharospasm(21.1%), and oromandibular dystonia(8.5%)(figure-1). Among patients with segmental dystonia, the combination of cervicobrachial was the most common(42.1%).

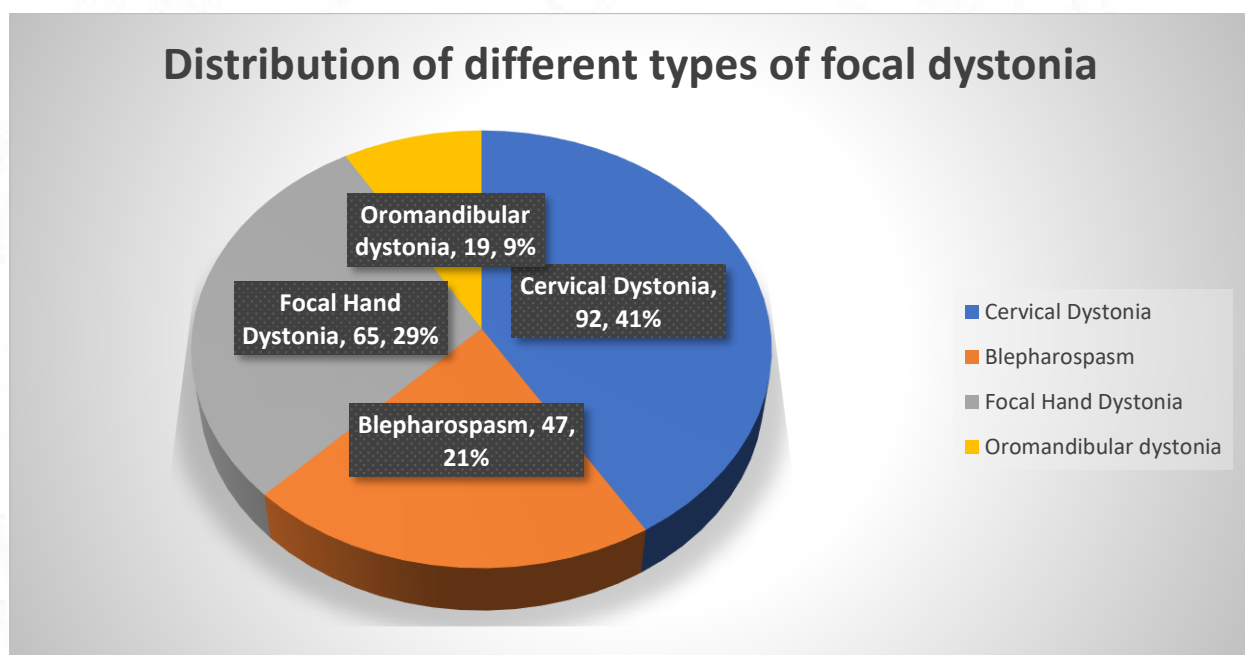


Figure 1- Distribution of focal dystonia

The mean age at onset of dystonia was 41 ± 15.75 years; 38.45 (SD-15.26) for males and 45.02 (SD-15.65) for females. Overall, males with primary dystonia were noted to have an earlier age of onset. Of the focal dystonia subtypes, age of onset was lowest in patients with focal hand dystonia (28.23, SD-12.14) compared to those with other focal dystonia ($p < 0.001$). Positive family history was reported in 18 (7.4%) patients. The group of patients with family history

showed a mean age at onset significantly lower (30.83 ± 11.78) than in patients without a family history ($p=0.004$). A male predominance was noted overall with a male to female ratio (M : F) of 1.57: 1. Most patients were in the late adulthood onset dystonia category ($n=130, 53.7\%$). The mean duration of illness before the first injection was 4.99 (SD – 6.99) years.

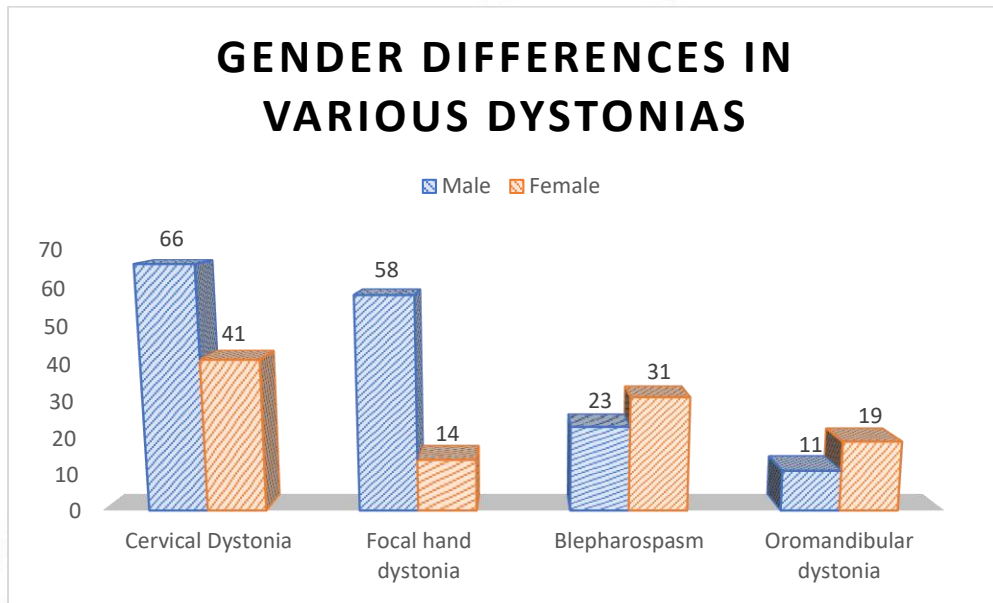


Figure 2 Gender differences in various dystonia

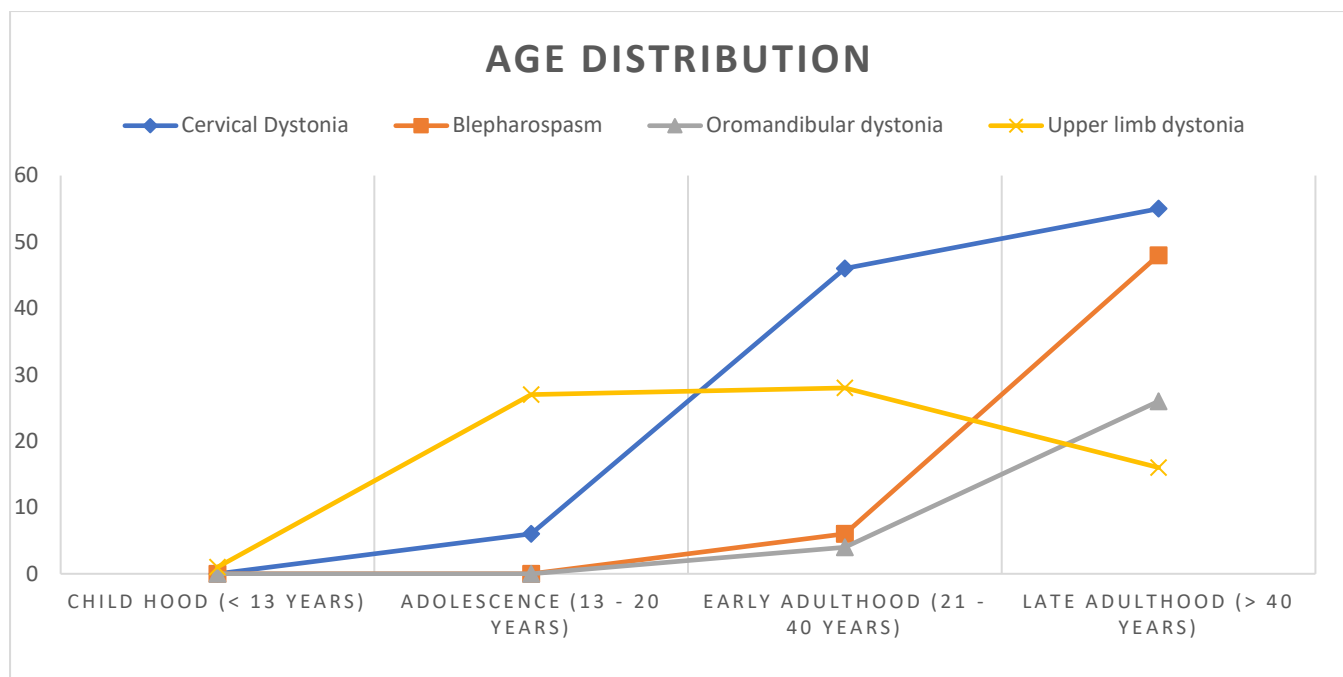


Figure 3- Age distribution

The mean benefit from BoNT for the entire population was 65.87%(SD-23.26), and the mean duration of benefit was 3.79 months(SD-2.49). The mean duration of follow-up was 3.89 years(SD-4.11). Adverse events occurred in 17.8% of patients, and the mean duration of weakness was 15.05 days(SD-13.35). The mean number of injections was 4.96(SD-4.94). BoNT type A (Dysport- abobotulinumtoxinA) was used in this survey.

Cervical dystonia

In our study, CD was seen in 107(44.21%) of the total population. CD was the most common cause of isolated focal dystonia 92(41.3%) and was also involved in a major proportion(78.9%) of the segmental dystonia, where it was mainly associated with brachial dystonia(46.6%) and oromandibular dystonia(46.6%). The mean age of onset was 40.9 ± 13.12 years (Range 13-71). The majority of the subjects were males (61.7%). Only five patients(4.7%) had a positive family history. The mean disease duration before the first botulinum toxin injection was 5.02 years(SD-8.25). There was a sensory trick in 39.25% of patients (n=42). In 30.8% of patients, neck pain was prevalent(n=23). Head tremor was observed in 29.9% of CD(n=32), and tremor elsewhere was found in 3.7%. Right rotacollis was the most common pattern of CD(46.7%). Right rotacollis with left laterocollis was the most common combination of CD(21.6%). The most common muscle injected were right splenius capitis(n=73), left sterno-cleido-

mastoid(n=67), right sterno-cleido-mastoid(n=54) and left splenius capitis(n=53). The mean dose was 204.26 units of abobotulinum toxin-A for splenius capitis, and 140.38 units for sternocleidomastoid. The mean dose of BoNT injection for isolated focal dystonia was 531.85 (SD-145.77) units of Abobotulinum toxin. The mean self-reported benefit was 69.53%(SD-17.27), and the duration of benefit was 4.02 (SD-2.66) months. Adverse events were noted in 32 out of 542 injections(5.9%), and the mean duration of adverse events was 9.11(SD-8.75) days. The mean duration of follow-up for the group was 4.22 (SD-4.32) years, and the mean number of injections was 5.07(SD-4.6). A good outcome was seen in 77(72%) patients.

Table 3-Comparison of various focal dystonia

Variables	Cervical Dystonia	Blepharospasm	Focal hand dystonia	Oromandibular dystonia
Age at onset (Years), Mean/SD	40.9 ± 13.12	53.2 ± 11.27	28.24 ±12.14	54.9 ± 11.68
Gender(M/F)	66/41	23/31	58/14	11/19
Duration of illness before BoNT injection (years), Mean/SD	5.02 (8.25)	4.53 (5.63)	6.41 (7.29)	2.97 (2.87)
Family history (n / %)	5 (4.7%)	1 (1.9%)	14 (19.4%)	0%
Sensory trick	42 (39.2%)	8(14.8%)	6 (8.5%)	4(13.3%)
Benefit(%), Mean/SD	69.53 ± 17.27	76.67 ± 21.16	51.67 ± 26.97	65.17 ± 23.5
Duration of benefit (months)	4.02 (2.66)	4.24 (1.81)	3.32 (3.56)	3.57 (1.54)
Good therapeutic outcome(n/ %)	77(72%)	46(85.2%)	26 (36.1%)	19(63.3%)
Duration of follow up (years)	4.22 (4.32)	4.15 (3.96)	3.22 (3.74)	3.33 (3.01)
Adverse events (%)	5.9%	5.6%	29.92%	13.3%
Duration of adverse events(days/SD)	9.11 (8.75)	10.21 (7.68)	20.33(15.79)	6.75 (5.25)
Number of injections (Mean/SD)	5.07 (4.61)	6.54 (6.25)	3.67 (4.00)	4.26 (3.73)
Total dose (units)(Mean/SD)	531.8 (145.7)	306.1 (45.61)	159.3 (80.06)	319.7 (130.9)

Blepharospasm

BSP was seen in 54(22.3%) patients. It was focal in 47(87.04%) and formed a part of segmental dystonia in 7(12.96%) subjects. The mean age of onset was 53.2 ± 11.27 years (range, 22 -80 years). There was a female preponderance—31 of 54 (57.4%) patients were women. A sensory trick was present in 8(14.8%) patients. The mean duration of illness of 4.53 (SD-5.63) years. The mean dose of abobotulinum toxin A was 306.17 (SD-45.61) units, the mean self-reported benefit was 76.67%(SD-21.16), and the duration of benefit was 4.24 ± 1.81 months. Orbicularis oculi muscle was injected in all patients. Among 353 injections, adverse events occurred 20 times (5.6%), with no severe sequelae, and the mean duration of adverse effects was 10.21 days (7.67). The mean duration of follow-up was 4.15 (SD-3.96) years, and the mean number of injections received was 6.54 (SD-6.24). The dystonia spread to other areas in 18(33.3%) overall. The dystonia spread in 15(31.91%) of the focal BSP(Table-4) and 3 out of 7(42.8%) of segmental dystonia involving BSP. The most common area of spread was to the oromandibular region(73.3%).

Focal hand dystonia

Seventy-two patients (58 men and 14 women) with FHD were studied. Sixty-nine patients had writer's cramp, whereas the remaining 3 had other task-specific dystonia. Their mean age at onset was 28.24 ± 12.14 (range 10-67) years, and the mean duration of symptoms was 6.41 (range 0.5-35) years. Positive family history was noted in 14 (19.4%) patients. All patients were right-handed. Superimposed on dystonic posturing, 17 patients (23.6%) showed a mild intermittent writing tremor, and in four patients(5.5%), writing tremor was the dominant complaint. Pain was present in 13(18.1%) patients. Mirror dystonia was observed in 40(55.5%) patients, and sensory trick was present in 6 (8.3%). Among the 69 patients with WC, 53(76.8%) had a simple WC, and 16 (23.1%) had a complex one. Thirty-one patients(44.94%) had extension type, 19(27.53%) had flexion type, and 19(27.53%) had mixed type of WC.

Out of the 15 treated forearm muscles, the most commonly injected muscles were the extensor indicis (n = 34), extensor pollicis longus (n =33), flexor pollicis longus (n =23), flexor digitorum superficialis digitorum II and III (n = 21), extensor pollicis brevis (n = 23) and flexor carpi ulnaris(n=19). The average doses in individual muscles were 63.3units in flexor digitorum superficialis, 62.1 units in flexor carpi ulnaris, 54.7 units in flexor pollicis longus, 47.1 units in extensor pollicis longus, and 36.3 units in extensor indicis.

The mean benefit was 51.67%(SD -26.97%), and duration of benefit was 3.32 months(SD-3.56). Adverse effects occurred in 79 out of 264 injections(29.92%), and the mean duration of

adverse events were 20.33 days(SD-15.79). This was significantly higher compared to other subgroups ($p=0.009$). The mean duration of follow-up was 3.22 years (SD-3.742). The mean dose was 159.38(SD-80.06) units of Abobotulinum toxin A, and the mean number of injections was 3.78(SD-4.18).

Oromandibular Dystonia

Thirty patients(12.4 %) had OMD in our study. OMD was focal in 19(63.3%) and formed a part of segmental dystonia in 11(36.7%) subjects. The segmental form included BSP (Meige syndrome) and CD in 54.5% and 45.5% of patients, respectively. The mean age of onset was 54.9 years (range, 29 -73 years; SD = 11.68 years). There was a significant female preponderance—19 of 30 (63.3%) patients were women. A total of 15 out of 30 (50%) patients had JOD, 13 (43.3%) patients had JCD, and 16 (53.3%) had tongue involvement. Lingual dystonia was more associated with JOD than JCD (62.5%, and 31.25%, respectively). Dystonic movements impaired speech in 12 (40%) patients, swallowing in 12(40%) patients, chewing in 11 (36.6%) patients, and bruxism in 8(26.7%). A sensory trick was present in 8 (26.7%) patients. The mean duration of illness before the first BoNT injection was 2.96 years. The lateral pterygoid muscles were the most common injected muscle($n=18$) followed by genioglossus($n=16$), masseter($n=14$) and temporalis($n=6$). The mean dose injected was 122.5 units in the lateral pterygoid muscle, 53 units in the genioglossus, and 113.2 units in the masseter muscle. The mean self-reported benefit after BoNT injection was 65.17%(SD-23.5), and the mean duration of benefit was 3.57 months(SD-1.54). A good outcome was seen in 19(63.3%) patients. Adverse events were seen in 13.3% of injections, and the mean duration of adverse events was 6.7 (SD-5.25) days. The mean total injection dose for OMD was 319.74(SD-130.98), and the mean number of injections was 4.26(SD -3.73). The mean duration of follow-up was 3.47 years. The dystonia spread to other areas in 3(10%) patients (blepharospasm in 2 and cervical dystonia in 1 patient).

Evolution of dystonia

Dystonia spread to other regions in 36(14.9%) patients(34 patients with focal dystonias and 2 patients with segmental dystonia spread to other regions). Among the focal dystonias, the risk

of dystonia spread was higher in patients with BSP(31.91%) than in the other three groups(Table-4). The dystonia spread towards oromandibular(73.3%) and cervical(26.7%) in case of blepharospasm. In cervical dystonia of focal onset at the time of presentation, the dystonia had spread to other regions in 11.96% of subjects. The most common areas of spread were oromandibular region(36.6%) followed by blepharospasm(27.27%), and upper limb(27.27%).

Table 4 Dystonia spread characteristics in focal dystonias based on onset site

	Cervical dystonia(n=92)	Blepharospasm (n= 47)	Hand dystonia(n=65)	Oromandibular dystonia (n=19)
Spread, n=34 (%)	11(11.96%)	15(31.91%)	6(9.23%)	2(10.52%)
Region of first spread, n=34 (% of those who spread)				
Cervical	-	4(26.7%)	3(50%)	1(50%)
Blepharospasm	3(27.27%)	-	2(33.3%)	1(50%)
Hand	3(27.27%)	0(0)	-	0(0)
Oromandibular	4(36.36%)	11(73.3%)	1(16.7%)	-
Laryngeal	1(9.1%)	0(0)	0(0)	0(0)
Second region of spread, (n=5)	(n=1)	(n=3)	(n=1)	(n=0)
Cervical	-	n=1	n=1	-
Blepharospasm	-	-	-	-
Hand	-	-	-	-
Oromandibular	-	n=1	-	-
Laryngeal	n=1	n=1	-	-

Table 5-Predictors of good outcome

Predictors of a good outcome	Odds Ratio (95% Confidence interval)	P-Value
Age >40 years	0.78 (0.64 – 0.97)	0.014
Females	0.901 (0.74 – 1.09)	0.19
Duration of illness < 3 years	1.01 (0.82 – 1.24)	0.55
Positive Family history	1.12 (0.73 – 1.72)	0.37
Sensory trick	0.74 (0.62 – 0.903)	0.006
Absence of Tremor	1.36 (1.00 – 1.86)	0.02
Blepharospasm	0.65 (0.55 – 0.77)	<0.001
Cervical dystonia	0.75 (0.62 – 0.91)	0.003
Oromandibular dystonia	0.97 (0.72 – 1.31)	0.52

Predictors of good outcome

A “good outcome” was defined as a self-reported benefit of 70% or more for more than or equal to 3 months. A good outcome was observed in 46(85.2%) of BSP, 77(72%) of CD, 19(63.3%) or OMD, and 26(36.1%) of FHD. Age at onset > 40 years, presence of sensory trick, and absence of tremor were found to be predictors of a good clinical outcome (Table-5) on univariate analysis. Compared to the other two groups, a better outcome was seen in patients with BSP and CD. Gender, positive family history, and earlier initiation of BoNT therapy did not predict a statistically significant good therapeutic outcome.



DISCUSSION

Discussion

This study provides data on the demographic and clinical profile, treatment responses to botulinum toxin injections, and evolution over time in a cohort of patients with focal and segmental dystonia in the real-life setting, outside of a clinical trial. In this study, 242 cases of isolated focal dystonia who underwent botulinum toxin injection at least twice were observed in a single-centre review, and clinical and demographic characteristics were recorded. We believe that the cohort is the true representation of the population with isolated focal and segmental dystonia in the community. Focal dystonia formed a significant portion of the cohort, and among these, CD was the most common type. FHD was found to have an earlier onset age than other focal dystonias. The study reiterates the efficacy and safety of BoNT injection in focal and segmental dystonia. The presence of sensory tricks and absence of tremor were predictors of a good outcome. The study also observed that the first site of onset in isolated focal dystonia is associated with the risk of spread to other body regions later on, with BSP at onset having more risk of spreading than those with cervical, hand, or oromandibular dystonia.

CD was the most common isolated focal dystonia in the study. This finding concurs with studies reported from the west, where the most common type of dystonia was CD(10,11,64). However, recent Indian studies have observed FHD as the commonest isolated focal dystonia(12,13). Regional differences in dystonia prevalence have been reported previously from various countries. In Japan and China, prevalence of BSP exceeded the prevalence of other focal dystonias(14,65).

Many previous studies have shown female predominance in focal dystonia except for focal upper limb dystonia(17,18). However, our study showed an overall male preponderance for isolated focal and segmental dystonia. Compared to western research, the reduced frequency of dystonia in females in our sample could be related to women in rural areas seeking less healthcare and being unaware of the condition. Like in previous studies, the mean age of onset was lesser in males in the current study. The gender-linked genetic susceptibility for dystonia or nongenetic factors such as estrogen and occupational exposure is considered to account for this observation(17).

Although most patients in this study had late adulthood onset dystonia (> 40 years), the age at onset was significantly lesser in focal hand dystonia. Patients who had a positive family

history also and a statistically significant lesser age of onset. Among isolated adult-onset focal dystonia, the age of onset varies in a way, suggesting that with increasing age, the site of onset shifts caudorostrally(16).

In the current study, the disease duration before receiving the first botulinum toxin injection was about five years, indicating a lack of understanding of treatment alternatives and delays in referral to a center that administers botulinum toxin.

Outcome

The mean self-reported benefit was 65.87%. A good therapeutic outcome (defined as >70% improvement lasting for 3 or more months) was present in 62% of the cohort. The patients were followed up for a mean duration of around four years. More than half the patients continue to take BoNT injections at the same center.

The mean benefit and duration of benefit were more in patients with BSP and CD than the other two groups (Table-3). This is in line with previous data showing maximum efficacy in BSP(66). The benefit was lesser in focal hand dystonia compared to other groups. The technical difficulties of the administration of BoNT may be a contributing factor to this difference.

Age at onset > 40 years, presence of sensory trick, and absence of tremor were predictors of a good clinical outcome on univariate analysis (Table-5). Age at onset > 40 was significant probably because the majority of patients with blepharospasm belonged to this category, which may have skewed the results in favour of this age group, as the efficacy of BoNT in BSP was the highest. The pathophysiological background for an association between a sensory trick and treatment outcome remains unclear. A sensory trick response may indicate that dystonic movement patterns are easier to modulate and, therefore, treatment was more effective in these patients. Gender, positive family history, and earlier initiation of BoNT therapy did not predict a statistically significant good therapeutic outcome.

Self-reported benefit has been used to assess outcomes in previous studies(67) with BoNT and has been found to correlate with objective rating scales(68). A previous study on self-reported benefit and weakness after BoNT in isolated focal dystonia showed no differences in the benefit and adverse events in the various focal dystonia. However, the benefit lasted significantly longer in FHD compared to the other groups(67).

The rate of adverse events was low in the current study (Table 3). The most frequent adverse events were muscle weakness, dysphagia, and ptosis.

Cervical Dystonia

CD was the most common isolated focal dystonia in the study. This finding concurs with studies reported from the west, where the most common type of dystonia was CD(10,11,64). However, unlike previous studies(69), the prevalence of CD was more in males in the current study. In the Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD-PROBE) study, an extensive registry of CD patients, the mean age of onset was 49 years, and 74% were females(36). The prevalence of sensory trick(39.2%) in our study was less than previously reported(70). The presence of sensory trick predicted a good outcome in the current study.

Rotacollis was the most common pattern observed, as was the case in previous studies(71). Splenius capitis and sternocleidomastoid were the most commonly injected muscles. The mean benefit with BoNT injection was around 70%. Several previous studies have supported the conclusion that BoNT is a safe and effective CD treatment(41–45). The long-term response rate in open and double-blind studies is between 60% and 80%(46).

Adverse events were seen in 5.9% of the injections. Bilateral injections of sternocleidomastoid muscles and higher doses of BoNT into the anterior neck muscles have been associated with a higher incidence of dysphagia in our study.

Focal hand dystonia

FHD was the second most common focal dystonia in the cohort. Approximately 80.5% of patients with WC were males. Previous studies have shown similar results(17,18). The onset age in FHD was significantly lesser than other focal dystonias ($p < 0.001$). The majority of patients(76.8%) had simple WC, and the most common pattern was extension type. A previous Indian study had shown similar findings(72). Tremor was observed in 23.6% of cases, and 55.5% had mirror dystonia. Mirror dystonia can help identify dystonic muscle activity, distinguish dystonia from compensatory muscle activity, and guide BoNT injection treatment(61). However, no differences in outcome were detected in patients with or without mirror dystonia in the current study. The mean benefit and duration of benefit were significantly lesser in FHD compared to other subgroups. However, it is important to analyze the outcome data for FHD separate from other dystonia, since the BoNT response rates differ.

FHD has a lower overall response rate, with about 50% of patients receiving at least mild benefit compared to 80% for cervical dystonia and over 90% for blepharospasm(73). The minimal benefit in FHD may be contributed by the technical difficulty in administering the toxin specifically to the small forearm muscles. EMG identification of specific muscles for injection does appear to increase the likelihood of therapeutic success.

Blepharospasm

The mean age of onset in the sixth decade and female preponderance was in accordance with previous studies(74,75). The self-reported benefit, duration of benefit, and the mean total number of injections were maximum in BSP. The mean benefit was 76.6%. The risk of spread to other regions was also highest with BSP, and the common areas of spread were oromandibular and cervical regions. Previous data also show similar results(20).

Oromandibular dystonia(OMD)

OMD was the least common isolated focal dystonia in the cohort. The current study results are similar to the data published by others in terms of female preponderance and age of onset in the fifth decade(76). When segmental, OMD was associated with BSP, followed by CD. Jaw opening dystonia(JOD) was the most common subtype seen in 50%. The study by Slaim et al also showed a similar pattern(76); however, a few other studies have previously observed jaw closing dystonia to be the most common OMD(49,52). Lateral pterygoid muscle was the most commonly injected muscle for OMD as JOD was the most common pattern observed in our study. JCD is considered to have a better response to BoNT injection (73). However, there was no statistically significant difference in the outcome of JOD or JCD treated with BoNT in this study.

Evolution of dystonia

Dystonia usually affects only one body region at first. However, it can spread to additional contiguous or distant body regions over time, resulting in higher disability depending on which body region or regions are involved. Our findings show that the first site of onset in isolated focal dystonia is significantly related to the likelihood of spread and the body areas later affected by dystonia. Those with BSP at onset have almost thrice the risk of dissemination than those with CD, FHD, or OMD. We also observed that patients with BSP were more likely to spread to the oromandibular region and neck. In our analysis, the risk of spread in isolated focal dystonia across the different phenotypes did not relate to sex or age of onset.

Previous data also suggest that BSP has a higher rate of spread compared to other forms of focal dystonia(20). Recent data have shown that dystonia more frequently spreads in patients with tremors than those without(77). However, no such association was detected in our study.

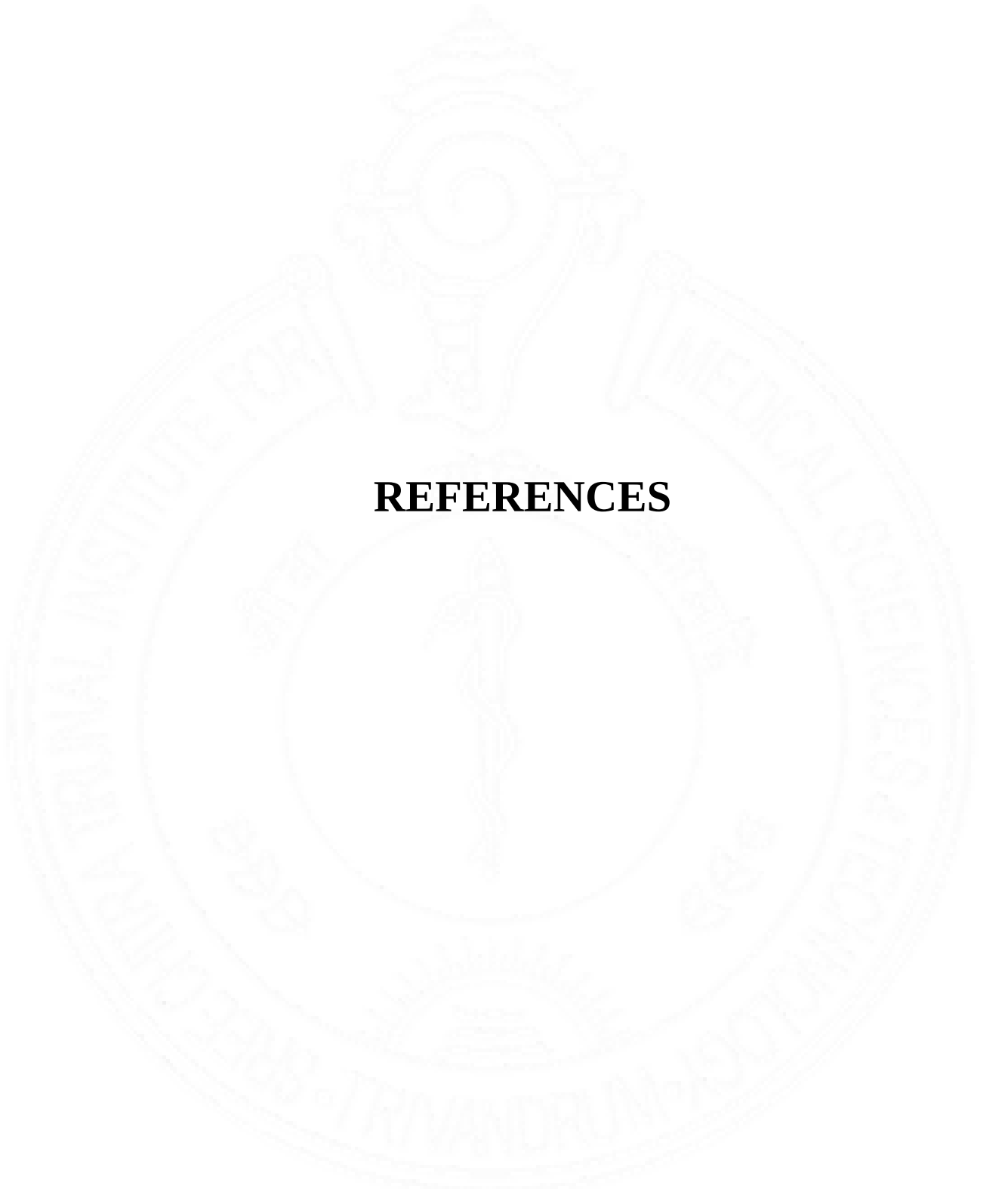
Limitations

The retrospective nature and self-reported benefit were the current study's limitations. Possibly, pain in CD and visual impairment in BSP patients may bias responses in subjective recall-based questionnaires. Finally, due to the exploratory nature of analyses, strict multiple comparisons were not addressed in statistical analyses across groups that may produce additional false-positive statistical errors.

CONCLUSION

Conclusion

The focal dystonia formed a significant portion of the cohort, and among these, cervical dystonia was the most common type. The study confirms the efficacy and safety of BoNT injection in focal and segmental dystonia. In addition, the presence of sensory trick and absence of tremor may predict the outcome after BoNT injection. We also observed that BSP has a higher risk of spreading than other focal dystonia.



REFERENCES

References

1. Albanese A, Bhatia K, Bressman SB, DeLong MR, Fahn S, Fung VSC, et al. Phenomenology and classification of dystonia: A consensus update: Dystonia: Phenomenology and classification. *Mov Disord*. 2013 Jun 15;28(7):863–73.
2. Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, et al. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008 May 6;70(19):1699–706.
3. Camargo CHF, Teive HAG. Use of botulinum toxin for movement disorders. *Drugs Context*. 2019 Jun 18;8:1–14.
4. Choudhury S, Baker MR, Chatterjee S, Kumar H. Botulinum Toxin: An Update on Pharmacology and Newer Products in Development. *Toxins*. 2021 Jan 14;13(1):58.
5. Jankovic J, Adler CH, Charles D, Comella C, Stacy M, Schwartz M, et al. Primary results from the cervical dystonia patient registry for observation of onabotulinumtoxin A efficacy (CD PROBE). *J Neurol Sci*. 2015 Feb 15;349(1–2):84–93.
6. Castelão M, Marques RE, Duarte GS, Rodrigues FB, Ferreira J, Sampaio C, et al. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev*. 2017 Dec 12;12:CD003633.
7. Kruisdijk JJM, Koelman JHTM, Ongerboer de Visser BW, de Haan RJ, Speelman JD. Botulinum toxin for writer's cramp: a randomised, placebo-controlled trial and 1-year follow-up. *J Neurol Neurosurg Psychiatry*. 2007 Mar;78(3):264–70.
8. Dadgardoust PD, Rosales RL, Asuncion RM, Dressler D. Botulinum neurotoxin A therapy efficacy and safety for oromandibular dystonia: a meta-analysis. *J Neural Transm*. 2019 Feb;126(2):141–8.
9. Steeves TD, Day L, Dykeman J, Jette N, Pringsheim T. The prevalence of primary dystonia: a systematic review and meta-analysis. *Mov Disord Off J Mov Disord Soc*. 2012 Dec;27(14):1789–96.
10. Dhaenens C-M, Krystkowiak P, Douay X, Charpentier P, Bele S, Destée A, et al. Clinical and genetic evaluation in a French population presenting with primary focal dystonia. *Mov Disord Off J Mov Disord Soc*. 2005 Jul;20(7):822–5.
11. Maniak S, Sieberer M, Hagenah J, Klein C, Vieregge P. Focal and segmental primary dystonia in north-western Germany--a clinico-genetic study. *Acta Neurol Scand*. 2003 Mar;107(3):228–32.
12. Prasad R, Joshi D, Mishra V, Chaurasia R, Pathak A. Clinical spectrum of focal dystonias: Experience from a tertiary care center. *Ann Mov Disord*. 2020;3(2):99.
13. Rajan R, Srivastava A, Anandapadmanabhan R, Vibha D, Pandit A, Prasad K. Clinical spectrum of dystonia in a tertiary care movement disorders clinic in India. 2018;

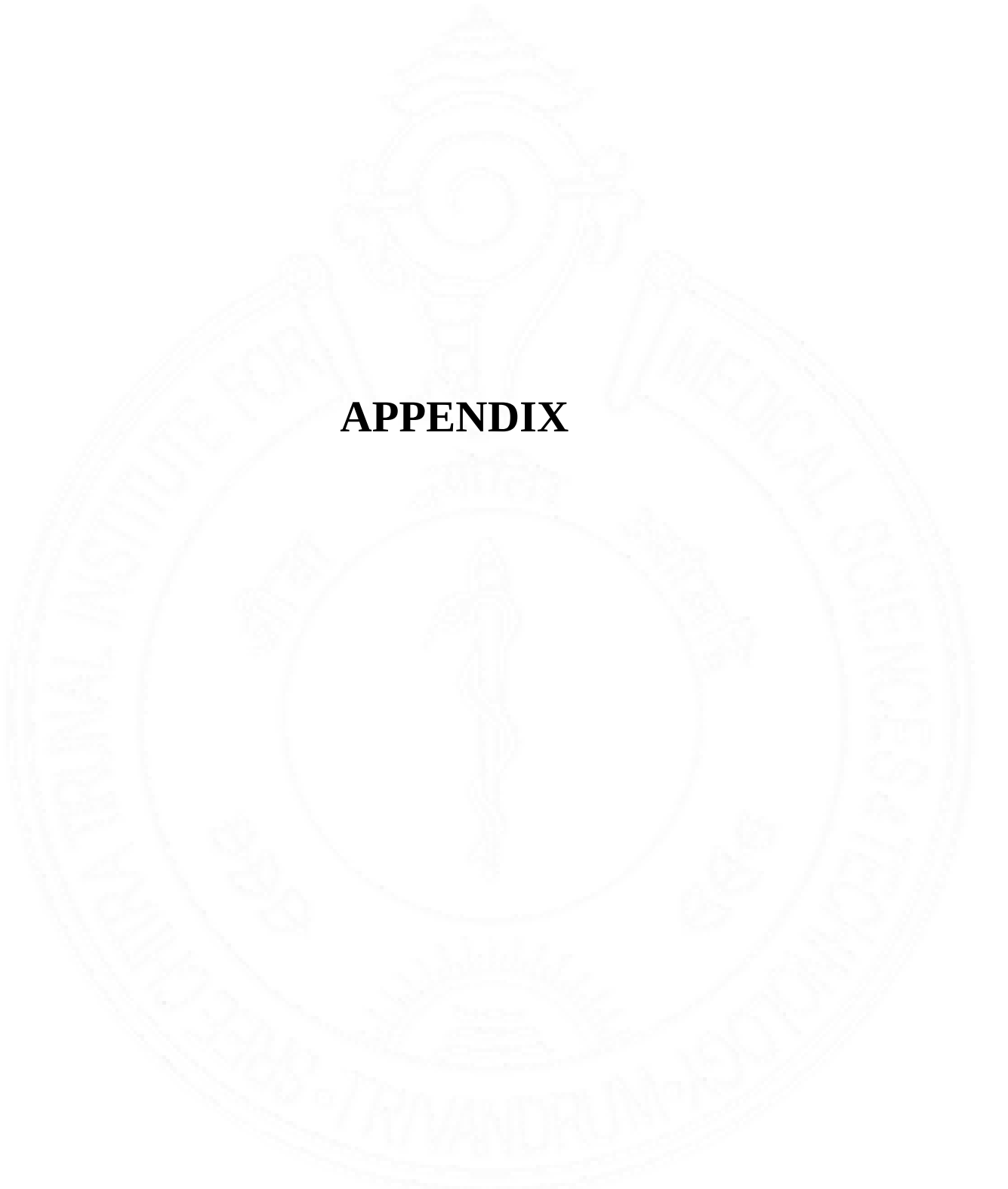
14. Matsumoto S, Nishimura M, Shibasaki H, Kaji R. Epidemiology of primary dystonias in Japan: comparison with Western countries. *Mov Disord Off J Mov Disord Soc.* 2003 Oct;18(10):1196–8.
15. Defazio G, Abbruzzese G, Livrea P, Berardelli A. Epidemiology of primary dystonia. *Lancet Neurol.* 2004 Nov;3(11):673–8.
16. O’Riordan S, Raymond D, Lynch T, Saunders-Pullman R, Bressman SB, Daly L, et al. Age at onset as a factor in determining the phenotype of primary torsion dystonia. *Neurology.* 2004 Oct 26;63(8):1423–6.
17. Sex-related influences on the frequency and age of onset of primary dystonia. Epidemiologic Study of Dystonia in Europe (ESDE) Collaborative Group. *Neurology.* 1999 Nov 10;53(8):1871–3.
18. Pekmezović T, Ivanović N, Svetel M, Nalić D, Smiljković T, Raicević R, et al. Prevalence of primary late-onset focal dystonia in the Belgrade population. *Mov Disord Off J Mov Disord Soc.* 2003 Nov;18(11):1389–92.
19. Filipović SR, Jahanshahi M, Viswanathan R, Heywood P, Rogers D, Bhatia KP. Clinical features of the geste antagoniste in cervical dystonia. *Adv Neurol.* 2004;94:191–201.
20. Berman BD, Groth CL, Sillau SH, Pirio Richardson S, Norris SA, Junker J, et al. Risk of spread in adult-onset isolated focal dystonia: a prospective international cohort study. *J Neurol Neurosurg Psychiatry.* 2020 Mar;91(3):314–20.
21. Defazio G, Berardelli A, Hallett M. Do primary adult-onset focal dystonias share aetiological factors? *Brain.* 2007 Apr 2;130(5):1183–93.
22. Jankovic J, Schwartz K, Donovan DT. Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasm. *J Neurol Neurosurg Psychiatry.* 1990 Aug;53(8):633–9.
23. Jinnah HA, Factor SA. Diagnosis and Treatment of Dystonia. *Neurol Clin.* 2015 Feb;33(1):77–100.
24. Adam OR, Jankovic J. Treatment of dystonia. *Parkinsonism Relat Disord.* 2007;13 Suppl 3:S362–368.
25. Anandan C, Jankovic J. Botulinum Toxin in Movement Disorders: An Update. *Toxins.* 2021 Jan 8;13(1):42.
26. Arndt JW, Jacobson MJ, Abola EE, Forsyth CM, Tepp WH, Marks JD, et al. A structural perspective of the sequence variability within botulinum neurotoxin subtypes A1–A4. *J Mol Biol.* 2006 Sep 29;362(4):733–42.
27. Anandan C, Jankovic J. Botulinum Toxin in Movement Disorders: An Update. *Toxins.* 2021 Jan 8;13(1):42.
28. Safarpour Y, Jabbari B. Botulinum Toxin Treatment of Movement Disorders. *Curr Treat Options Neurol.* 2018 Feb 24;20(2):4.

29. Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve Suppl.* 1997;6:S146-168.
30. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of Botulinum Toxin Type A Action on Pain. *Toxins.* 2019 Aug 5;11(8).
31. Mittal SO, Jabbari B. Botulinum Neurotoxins and Cancer-A Review of the Literature. *Toxins.* 2020 Jan 5;12(1).
32. Albrecht P, Jansen A, Lee J-I, Moll M, Ringelstein M, Rosenthal D, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. *Neurology.* 2019 Jan 1;92(1):e48–54.
33. Bellows S, Jankovic J. Immunogenicity Associated with Botulinum Toxin Treatment. *Toxins.* 2019 Aug 26;11(9).
34. Brin MF, Comella CL, Jankovic J, Lai F, Naumann M, for the CD-017 BoNTA Study Group. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. *Mov Disord.* 2008 Jul 30;23(10):1353–60.
35. Ceballos-Baumann AO. Evidence-based medicine in botulinum toxin therapy for cervical dystonia. *J Neurol.* 2001 Apr;248 Suppl 1:14–20.
36. Jankovic J, Adler CH, Charles D, Comella C, Stacy M, Schwartz M, et al. Primary results from the cervical dystonia patient registry for observation of onabotulinumtoxinA efficacy (CD PROBE). *J Neurol Sci.* 2015 Feb 15;349(1–2):84–93.
37. Reichel G. Cervical dystonia: A new phenomenological classification for botulinum toxin therapy. *Basal Ganglia.* 2011 Mar;1(1):5–12.
38. Charles PD, Adler CH, Stacy M, Comella C, Jankovic J, Manack Adams A, et al. Cervical dystonia and pain: characteristics and treatment patterns from CD PROBE (Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy). *J Neurol.* 2014 Jul;261(7):1309–19.
39. Volkmann J, Mueller J, Deuschl G, Kühn AA, Krauss JK, Poewe W, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. *Lancet Neurol.* 2014 Sep;13(9):875–84.
40. Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2016 May 10;86(19):1818–26.
41. Bledsoe IO, Comella CL. Botulinum Toxin Treatment of Cervical Dystonia. *Semin Neurol.* 2016 Feb;36(1):47–53.
42. Charles D, Brashear A, Hauser RA, Li H-I, Boo L-M, Brin MF, et al. Efficacy, tolerability, and immunogenicity of onabotulinumtoxinA in a randomized, double-blind, placebo-controlled trial for cervical dystonia. *Clin Neuropharmacol.* 2012 Oct;35(5):208–14.
43. Poewe W, Deuschl G, Nebe A, Feifel E, Wissel J, Benecke R, et al. What is the optimal dose of botulinum toxin A in the treatment of cervical dystonia? Results of a double blind, placebo

- controlled, dose ranging study using Dysport. German Dystonia Study Group. *J Neurol Neurosurg Psychiatry*. 1998 Jan;64(1):13–7.
44. Truong D, Comella C, Fernandez HH, Ondo WG, Dysport Benign Essential Blepharospasm Study Group. Efficacy and safety of purified botulinum toxin type A (Dysport) for the treatment of benign essential blepharospasm: a randomized, placebo-controlled, phase II trial. *Parkinsonism Relat Disord*. 2008;14(5):407–14.
 45. Truong D, Brodsky M, Lew M, Brashear A, Jankovic J, Molho E, et al. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. *Parkinsonism Relat Disord*. 2010 Jun;16(5):316–23.
 46. Jost WH. [Clinical use of botulinum toxin]. *Nervenarzt*. 2008 Jun;79 Suppl 1:9–14.
 47. Greene P, Kang U, Fahn S, Brin M, Moskowitz C, Flaster E. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology*. 1990 Aug;40(8):1213–8.
 48. Contarino MF, Van Den Dool J, Balash Y, Bhatia K, Giladi N, Koelman JH, et al. Clinical Practice: Evidence-Based Recommendations for the Treatment of Cervical Dystonia with Botulinum Toxin. *Front Neurol*. 2017;8:35.
 49. Tan EK, Jankovic J. Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up. *Neurology*. 1999 Dec 10;53(9):2102–7.
 50. Singer C, Papapetropoulos S. A comparison of jaw-closing and jaw-opening idiopathic oromandibular dystonia. *Parkinsonism Relat Disord*. 2006 Mar;12(2):115–8.
 51. Møller E, Bakke M, Dalager T, Werdelin LM. Oromandibular dystonia involving the lateral pterygoid muscles: four cases with different complexity. *Mov Disord Off J Mov Disord Soc*. 2007 Apr 30;22(6):785–90.
 52. Sinclair CF, Gurey LE, Blitzer A. Oromandibular dystonia: long-term management with botulinum toxin. *The Laryngoscope*. 2013 Dec;123(12):3078–83.
 53. Yoshida K. Botulinum Neurotoxin Therapy for Lingual Dystonia Using an Individualized Injection Method Based on Clinical Features. *Toxins*. 2019 Jan 17;11(1).
 54. Teive HAG, Klüppel LE, Munhoz RP, Becker N, Müller PR, Werneck LC. Jaw-opening oromandibular dystonia secondary to Wilson's Disease treated with botulinum toxin type A. *Arq Neuropsiquiatr*. 2012 Jun;70(6):407–9.
 55. Tan EK, Jankovic J. Tardive and idiopathic oromandibular dystonia: a clinical comparison. *J Neurol Neurosurg Psychiatry*. 2000 Feb;68(2):186–90.
 56. Hallett M, Daroff RB. Blepharospasm: report of a workshop. *Neurology*. 1996 May;46(5):1213–8.
 57. Jankovic J, Havins WE, Wilkins RB. Blinking and blepharospasm. Mechanism, diagnosis, and management. *JAMA*. 1982 Dec 17;248(23):3160–4.
 58. Peckham EL, Lopez G, Shamim EA, Richardson SP, Sanku S, Malkani R, et al. Clinical features of patients with blepharospasm: a report of 240 patients. *Eur J Neurol*. 2011 Mar;18(3):382–6.

59. Girlanda P, Quartarone A, Sinicropi S, Nicolosi C, Messina C. Unilateral injection of botulinum toxin in blepharospasm: Single fiber electromyography and blink reflex study. *Mov Disord*. 1996 Jan;11(1):27–31.
60. Karp BI, Alter K. Botulinum Toxin Treatment of Blepharospasm, Orofacial/Oromandibular Dystonia, and Hemifacial Spasm. *Semin Neurol*. 2016 Feb;36(1):84–91.
61. Singer C, Papapetropoulos S, Vela L. Use of mirror dystonia as guidance for injection of botulinum toxin in writing dysfunction. *J Neurol Neurosurg Psychiatry*. 2005 Nov;76(11):1608–9.
62. Lungu C, Ahmad OF. Update on the Use of Botulinum Toxin Therapy for Focal and Task-Specific Dystonias. *Semin Neurol*. 2016 Feb;36(1):41–6.
63. Kruisdijk JJM, Koelman JHTM, Ongerboer de Visser BW, de Haan RJ, Speelman JD. Botulinum toxin for writer's cramp: a randomised, placebo-controlled trial and 1-year follow-up. *J Neurol Neurosurg Psychiatry*. 2007 Mar;78(3):264–70.
64. Nutt JG, Muentner MD, Aronson A, Kurland LT, Melton LJ. Epidemiology of focal and generalized dystonia in Rochester, Minnesota. *Mov Disord*. 1988;3(3):188–94.
65. Wang L, Chen Y, Hu B, Hu X. Late-onset primary dystonia in Zhejiang province of China: a service-based epidemiological study. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol*. 2016 Jan;37(1):111–6.
66. Hsiung G-YR, Das SK, Ranawaya R, Lafontaine A-L, Suchowersky O. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. *Mov Disord Off J Mov Disord Soc*. 2002 Nov;17(6):1288–93.
67. Kassavetis P, Lungu C, Ehrlich D, Alter K, Karp BI. Self-reported benefit and weakness after botulinum toxin in dystonia. *Parkinsonism Relat Disord*. 2020 Nov;80:10–1.
68. Tomić A, Vujović B, Svetel M, Misković ND, Petrović I, Pekmezović T, et al. Efficacy of botulinum toxin type A in treatment of different forms of focal dystonias in the Serbian population: experience of the Botulinum Toxin Outpatients Department. *Vojnosanit Pregl*. 2015 Dec;72(12):1069–73.
69. Defazio G, Jankovic J, Giel JL, Papapetropoulos S. Descriptive epidemiology of cervical dystonia. *Tremor Hyperkinetic Mov N Y N*. 2013;3:tre-03-193-4374-2.
70. Martino D, Liuzzi D, Macerollo A, Aniello MS, Livrea P, Defazio G. The phenomenology of the geste antagoniste in primary blepharospasm and cervical dystonia: Geste Antagoniste in Primary Adult-Onset Dystonia. *Mov Disord*. 2010 Mar 15;25(4):407–12.
71. Castelão M, Marques RE, Duarte GS, Rodrigues FB, Ferreira J, Sampaio C, et al. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev*. 2017 Dec 12;12:CD003633.
72. Jhunjhunwala K, Lenka A, Pal PK. A Clinical Profile of 125 Patients with Writer's Cramp. *Eur Neurol*. 2015;73(5–6):316–20.
73. Hallett M, Benecke R, Blitzer A, Comella CL. Treatment of focal dystonias with botulinum neurotoxin. *Toxicon*. 2009 Oct;54(5):628–33.

74. Peckham EL, Lopez G, Shamim EA, Richardson SP, Sanku S, Malkani R, et al. Clinical features of patients with blepharospasm: a report of 240 patients: Clinical features of patients with blepharospasm. *Eur J Neurol*. 2011 Mar;18(3):382–6.
75. Fang X, Xie M, Song Z, Zhong Z, Wang Y, Ou Z, et al. Long-term treatment of blepharospasm with botulinum toxin A: a service-based study over a 16-year follow-up in southern China. *Neurol Sci*. 2020 Mar;41(3):645–52.
76. Slaim L, Cohen M, Klap P, Vidailhet M, Perrin A, Brasnu D, et al. Oromandibular Dystonia: Demographics and Clinical Data from 240 Patients. *J Mov Disord*. 2018 May 25;11(2):78–81.
77. Defazio G, Gigante AF, Abbruzzese G, Bentivoglio AR, Colosimo C, Esposito M, et al. Tremor in primary adult-onset dystonia: prevalence and associated clinical features. *J Neurol Neurosurg Psychiatry*. 2013 Apr;84(4):404–8.



APPENDIX

ABBREVIATIONS

BoNT – Botulinum neurotoxin

BSP – Blepharospasm

CD – Cervical dystonia

FHD – Focal hand dystonia

JOD – Jaw opening dystonia

JCD – Jaw closing dystonia

OMD - Oromandibular dystonia

TPD – Tongue protrusion dystonia

U – Units

TSD – Task specific dystonia

WC – Writer’s cramp

Proforma

Serial No:

Master Chart No:

Age:

Sex : M/F

Name and Address:

Date of Initial Evaluation:

Initial Diagnosis:

Symptoms:

Duration of Symptoms:

Family History:

Pattern of Dystonia at Initial Evaluation:

Site

Duration of symptoms

Disability

Presence of Tremor:

Site

Duration

Disability

Presence Of Pain :

Site Duration

Disability:

Other Symptoms:

Dystonic Movement Patterns :

- A) Oromandibular/ Lingual:
- B) Blepharospasm:
- C) Cervical Dstonia:
- D) Uppia
- E) Lower Limb Dystonia
- F) Truncal Involvement

Muscles Selected for Injection Initially:

Doses For Individual Muscles :

Type Of Botulinum Toxin :

Total Dose :

Benefits (Vas -0 To 100%) :

Duration Of Benefit:

Adverse Effects:

Duration Of Adverse Effects :

Follow-Up Injections:

Date	Muscle Injected	Individual Doses For Muscles	Total Dose	Benefit	Duration Of Benefit	Adverse Effects	Duration Of Adverse Effects

Total duration of follow-up:

Total number of injections received:

Reason for discontinuation of treatment, if applicable:

New dystonic symptoms during follow up:

New non-dystonic neurological symptoms / signs:

Diagnosis at last follow up:

Pattern of dystonia at last follow up:

Non-dystonic neurological features at last follow up:

IEC APPROVAL LETTER

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM Thiruvananthapuram - 695 011, Kerala, India (An Institute of National Importance under Govt. of India) Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in					
Institutional Ethics Committee (IEC Regn No. ECR/189/Inst/KL/2013/RR-16)					
SCT/IEC/1702/AUGUST-2021			31.08.2021		
Dr. Asish Vijayaraghavan Post Doctoral Fellow, Movement Disorder Department of Neurology SCTIMST Thiruvananthapuram					
Dear Dr. Asish Vijayaraghavan,					
The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "CLINICAL PROFILE AND OUTCOME OF ISOLATED FOCAL AND SEGMENTAL DYSTONIA IN ADULTS TREATED WITH BOTULINUM TOXIN INJECTION-A RETROSPECTIVE STUDY FROM A TERTIARY CARE CENTER IN INDIA (IEC/1702)" on 18 th August, 2021.					
The following members of the Ethics Committee were present at the meeting held on 18 th August, 2021 at Residences and Offices of IEC Members via Video Conference					
SL No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sethi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Dr. Achuth Sankar S. Nair	Ph.D (Engineering & Music)	Male	Social Scientist	No
6.	Dr. Rejish Kumar	MBBS,MD ,DNB	Male	Clinician	No
7.	Adv. N Anand	BAL, LLB	Male	Legal Expert	No
8.	Adv. Priya Kamal	LLM, MBL	Female	Legal Expert	No
9.	Dr. Harkristna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
10.	Dr. Manikandan S	MBBS,MD,POCC	Male	Clinician	Yes
11.	Dr. Narayanan Namboodiri K.K	MBBS,MD,DM	Male	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

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The following documents were reviewed:

1. Covering letter addressed to the Chairman, IEC, SCTIMST
2. IEC Application form
3. Project Proposal
4. TAC Approval Letter
5. CV of PI and Co-PIs
6. Declaration Form

IEC Decision

The IEC approved the conduct of the study in the present form.

This approval is in continuation of IEC Regn No. ECR/189/Ins/KL/2013/RR-16, subject to IEC Renewal pending process with CDSCO.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,



G. Srinivas
Member Secretary, IEC

