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Original Research Article

A Cross-Sectional Study to Assess the Impact of Botulinum Toxin on Cervical Dystonia and its Influence on Quality of Life

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Abstract

Aim: To determine the impact of Botulinum Toxin on Cervical Dystonia and its influence on Quality of Life.

Materials and Methods: This study was conducted in the Department of physical medicine and rehabilitation, ESIC Medical College, Bihta, Patna, Bihar, India. Male and female patients aged between 18 and 80 years who fulfilled the diagnostic criteria for primary CD, had good consciousness and comprehension of the HRQoL questionnaires, and could communicate in and understand Thai language were included in the study. All the patients were included and completed the study. To assess the disease-specific HRQoL, this study used the CDIP-58 and CDQ-24. This study employed the SF-36 and the EQ-5D to assess patients' general HRQoL.

Results: Mean duration of symptoms in enrolled patients was 5.0 years (range from 0 to 12 years). There were 16 cases of torticollis, two of laterocollis, one of anterocollis, and one of latrocollis included in the study. The previous mean number of botulinum toxin A injections received per patient was 8.85±5.32 injections, ranging from 1 to 22. After 24 weeks of treatment, the mean (SD) score of all eight domains of CDIP-58 including head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, and psychosocial functioning were significantly improved (P<0.001) (Table 2). The mean (SD) of each of the five categories of CDQ-24 was also significantly improved with P-values of 0.004, 0.001, 0.003, 0.001, and 0.0005 for stigma, emotional well-being, pain, activities of daily living, and social and family life, respectively (Table 2). After 24 weeks of treatment, the mean values of results of all eight domains of SF-36 did not significantly improved. The P-values for PF, RP, RE, VT, mental health, SF, BP, and GH are 0.726, 1.000, 0.505, 0.349, 0.115, 0.171, 0.427, and 0.380 respectively. The mean score of each category of EQ-5D including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression revealed a nonsignificant change (P>0.05).

Conclusion: In conclusion, the quality of life of CD patients improved after multiple botulinum toxin A injections. Each injection of botulinum toxin A seems to have cumulative effects in multiple-injection patients. The direct mechanism behind an improvement in physical health is well understood; however, that behind mental health is less obvious. A relief of dystonia could make a positive difference to patients' relaxation state and stress level, which would account for mental improvement.

Keywords: Botulinum Toxin, Cervical Dystonia, Quality of Life

Introduction

Cervical dystonia, also known as spasmodic torticollis, is a chronic neurological disorder characterized by involuntary muscle contractions in the neck, leading to abnormal postures and movements of the head. It is the most common form of focal dystonia and can significantly impair daily functioning and quality of life. Botulinum toxin (BoNT), particularly types A and B, has emerged as the primary treatment for cervical dystonia, offering significant relief from symptoms and improvements in quality of life for many patients. Cervical dystonia is believed to result from abnormalities in the basal ganglia and associated neural circuits, which are responsible for regulating motor control. The exact etiology remains unclear, but it is thought to involve both genetic and environmental factors. The disorder typically presents in midlife, and its clinical manifestations can vary widely among individuals,

including rotational (torticollis), tilting (laterocollis), flexion (anterocollis), and extension (retrocollis) movements of the head and neck. [1] Botulinum toxin is a neurotoxin produced by the bacterium *Clostridium botulinum*. It exerts its effect by inhibiting the release of acetylcholine at the neuromuscular junction, leading to a temporary reduction in muscle activity. This localized muscle paralysis helps alleviate the abnormal muscle contractions associated with cervical dystonia. The effects of BoNT are temporary, typically lasting three to four months, necessitating repeated injections for ongoing symptom control. [2] Numerous clinical trials and studies have demonstrated the efficacy of botulinum toxin in treating cervical dystonia. A pivotal study by Jankovic et al. (1987) established BoNT-A as an effective treatment, showing significant reductions in the severity of dystonic symptoms and associated pain. [3] Subsequent studies have confirmed these findings, indicating that BoNT injections result in marked improvements in both objective measures of dystonia and subjective assessments of symptom severity and pain. [4] A comparative study by Brin et al. (1999) demonstrated that both BoNT-A and BoNT-B are effective in reducing the symptoms of cervical dystonia, though patients treated with BoNT-A experienced fewer adverse effects and longer durations of symptom relief. [5] Another study by Comella et al. (2011) provided evidence that long-term treatment with BoNT-A is safe and maintains its efficacy over time, with sustained improvements in dystonia severity and pain. [6] Cervical dystonia significantly impairs quality of life due to chronic pain, physical disability, and psychosocial distress. The abnormal postures and movements can be socially stigmatizing, leading to social withdrawal and emotional distress. Botulinum toxin treatment has been shown to substantially improve quality of life in patients with cervical dystonia. A study by Marras et al. (2001) demonstrated that BoNT-A treatment leads to significant improvements in quality of life, as measured by the SF-36 Health Survey and the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). [7] These improvements were attributed to reductions in pain and disability, as well as enhanced physical and social functioning. A long-term study by Dashtipour et al. (2015) corroborated these findings, showing that sustained BoNT-A treatment is associated with persistent improvements in health-related quality of life. Patients reported better overall health, reduced impact of dystonia on daily activities, and greater emotional well-being. [8] Furthermore, a systematic review by Camargo et al. (2018) confirmed that BoNT-A is effective in enhancing quality of life, with significant benefits in physical functioning, mental health, and social interactions. [9] While botulinum toxin is generally well-tolerated, it is not without potential side effects. Common adverse effects include neck weakness, dysphagia, dry mouth, and injection site pain. These side effects are typically mild and transient. Severe complications are rare but can include significant dysphagia and respiratory issues, particularly if the toxin spreads beyond the targeted muscles. [10] The effectiveness of CD treatment by botulinum toxin A injections has not been studied in Thai patients. Many questionnaires are used to assess general and disease-specific HRQoL of CD patients before and after treatment with botulinum toxin A injections. Medical Outcomes' 36-Item Short Form Health Survey (SF-36) and the EuroQoL 5-dimension questionnaire (EQ-5D) are used to assess general HRQoL while the Cervical Dystonia Impact Profile-58 questionnaire (CDIP-58) and the 24-question Craniocervical Dystonia Questionnaire (CDQ-24) are used to assess disease-specific HRQoL. [11-24]

Materials and Methods

This study was conducted in the Department of physical medicine and rehabilitation, ESIC Medical College Bihta, Patna, Bihar, India for 12 months. Male and female patients aged between 18 and 80 years who fulfilled the diagnostic criteria for primary CD, had good consciousness and comprehension of the HRQoL questionnaires, and could communicate in and understand Thai language were included in the study. Patients who were <18 years of age, could not understand Thai language, declined consent to join the study, and were potentially pregnant or lactating were excluded. Patients with other medical conditions that could influence trial assessments, for example, bleeding abnormalities, arthritis, heart disease, and other neurological and psychological disease, were also excluded. Twenty patients with CD were screened and invited to the study. All the patients were included and completed the study.

The disease-specific HRQoL questionnaires

To assess the disease-specific HRQoL, this study used the CDIP-58 and CDQ-24.

CDIP-58 is a validated patient-based scale for health outcomes of patients with CD. It comprises eight health dimensions with proven good reliability testing and has been used to measure health impacts of CD.[18] The eight subscales include head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, and psychosocial functioning. [20,24] The Thai language translation of CDIP-58 has previously been tested at Hospital for its consistency in comparison with the original CDIP-58, resulting in Cronbach's alpha of >0.7.

CDQ-24 is a validated disease-specific questionnaire designed to evaluate HRQoL of CD and blepharospasm patients. It has been shown to be

appropriate for use in both clinical trials and clinical practice with stable internal consistency for all preliminary subscales (α>0.7 each). The 24 items of CDQ-24 comprise five categories, which are stigma (questions 7, 8, 9, 10, 18, 22), emotional well-being (questions 11, 12, 13, 14, 15), pain (questions 4, 5, 21), activities of daily living (ADL) (questions 1, 2, 3, 6, 19, 20), and social and family life (questions 16, 17, 23, 24). [16,24] Thai translation of the original CDQ-24 has previously been tested at Hospital to ensure its conformity to the original CDIP-58, resulting in Cronbach's alpha of >0.7.

The general HRQoL questionnaires

This study employed the SF-36 and the EQ-5D to assess patients' general HRQoL.

SF-36 is a 36-item questionnaire that consists of eight domains: physical functioning (PF), role limitations due to physical health (RP), role limitations due to emotional problems (RE), vitality (VT), mental health, social functioning (SF), bodily pain (BP), and general health (GH). PF, RP, and BP domains comprise the physical health half of the questionnaire while RE, VT, mental health, and SF the mental health. The Thai language version of SF-36 has been validated and tested for its reliability in Thai patients. [21,22,24]

EQ-5D is a short five-item questionnaire to assess the GH outcome after treatments. EQ-5D is a simple survey questionnaire often used in general clinics. It is cognitively simple. It has a short completing time and instructions to respondents included in the questionnaire, which makes it useful for screening. The EQ-5D comprises five dimensions, which are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of potential outcomes: no problems, some problems, and extreme problems. [23,24] The EQ-5D (Thai version) has also been validated and tested for reliability in Thai patients. [25]

This study is a 24-week prospective assessment of the quality of life of CD patients who were treated with botulinum toxin A injections. Patients who met all inclusion criteria and no exclusion criteria were enrolled in the study. They filled the four questionnaires at week 0 before the first injection and at week 24 after the follow-up injection. All patients were trained to self-evaluate intensity scores on a 5-point scale. Botulinum toxin A, which was supplied as a freeze-dried powder, was diluted in normal saline, and used within 2 h of preparation. All enrolled patients received intramuscular injections in the following neck muscles: sternocleidomastoid, trapezius, and splenius capitis muscles at the opposing side. Each patient was assessed agonist/antagonist spasm of the sternocleidomastoid, trapezius and splenius capitis muscles to determine the site of injection. Totally 100 units of botulinum toxin A were resuspended in 3 mL of normal saline, resulting in solution of ~33.33 units of botulinum toxin A per mL. Each patient was injected 5–10 units (0.15–0.30 mL) into each affected site of muscles by using 29G insulin needles. However, if each muscle has several affected sites, then the total botulinum toxin was 50 units per injection. All patients gave written informed consent before the start of the treatment. Two assessments were performed during the course of the study. The first (baseline) assessment was performed at week 0 before the first injection, and the second at week 24 during the follow-up treatment. At each visit, patients underwent physical and neurological examinations and completed four HRQoL questionnaires, CDIP-58, CDQ-24, SF-36, and EQ-5D. The primary endpoints were the mean change from baseline of CDIP-58 and CDQ-24 scores. The secondary endpoints were the change in the mean score of SF-36 and EQ-5D questionnaire results.

Statistical Analysis

Descriptive statistical analysis was used for demographic data. The mean (standard deviation [SD]) scores of CDIP-58, CDQ-24, SF-36, and EQ-5D at week 0 and week 24 were compared by the Wilcoxon signed-rank test. Cytel® Studio® (license no 2060107) software package was used in data analysis. Results with $P<0.05$ are deemed significant. Sample size estimation was not performed because there is no previous study regarding HRQoL in CD patients treated with botulinum toxin A.

Results

Mean duration of symptoms in enrolled patients was 5.0 years (range from 0 to 12 years). There were 16 cases of torticollis, two of laterocollis, one of anterocollis, and one of latrocollis included in the study. The previous mean number of botulinum toxin A injections received per patient was 8.85±5.32 injections, ranging from 1 to 22. Demographic data are shown in Table 1.

Table 1: Demographic and baseline clinical characteristics of patients with cervical dystonia

Demographics	
Number	20
Gender	
Male	7 (35%)

Female	13 (65%)
Mean (SD) age (years)	54.8 (12.5)
Mean (SD) disease duration (years)	5.0 (3.1)
Type of cervical dystonia n (%)	
Torticollis	16 (80)
Laterocollis	2 (10)
Anterocollis	1 (5)
Retrocollis	1 (5)
Mean (SD) BTX injection dosage	50.0 (0.0)
Previous mean (SD) BTX injection time	8.9 (5.3)

Abbreviations: BTX, botulinum toxin; SD, standard deviation.

Table 2: Clinical score before (week 0) and after (week 24) treatment as measured by CDIP-58, CDQ-24, SF-36, and EQ-5D, mean (SD)

Questionnaires	Score at week 0 (baseline) mean (SD)	Score at week 24 mean (SD)	*P*-value
CDIP-58			
Head and neck symptoms (6 items)	16.1 (2.3)	9.5 (2.7)	<0.001
Pain and discomfort (5 items)	18.2 (2.7)	10.4 (2.6)	<0.001
Upper limb activity (9 items)	26.8 (6.2)	15.3 (4.7)	<0.001
Walking (9 items)	26.6 (6.5)	15.4 (5.9)	<0.001
Sleep (4 items)	13.4 (3.4)	7.4 (2.6)	<0.001
Annoyance (8 items)	22.7 (4.3)	13.5 (3.8)	<0.001
Mood (7 items)	15.7 (5.0)	9.4 (2.4)	<0.001
Psychosocial functioning (10 items)	25.0 (6.8)	16.1 (5.5)	<0.001
CDQ-24			
Stigma	15.3 (6.6)	9.3 (3.1)	0.004
Emotional well-being	11.8 (4.7)	6.8 (2.1)	0.001
Pain	7.9 (2.8)	4.6 (2.4)	0.003
Activities of daily living	15.9 (5.8)	9.9 (3.1)	0.001
Social and family life	7.0 (1.7)	4.6 (0.9)	<0.001
SF-36			
Physical functioning	54.7 (38.2)	61.6 (25.3)	0.726
Role limitations due to physical health	57.8 (45.4)	57.8 (36.2)	1.000
Role limitations due to emotional problems	66.7 (43.9)	75.0 (35.5)	0.505
Vitality	58.1 (22.6)	61.3 (14.3)	0.349
Mental health	63.0 (22.1)	71.5 (14.1)	0.115
Social functioning	76.5 (21.0)	83.8 (13.7)	0.171
Bodily pain	58.8 (30.5)	62.5 (25.4)	0.427
General health	47.7 (17.5)	50.6 (12.8)	0.380
EQ-5D			
Mobility	1.500 (0.610)	1.375 (0.500)	0.157
Self-care	1.313 (0.602)	1.563 (0.727)	0.102
Usual activities	1.750 (0.683)	1.750 (0.683)	1.000
Pain/discomfort	1.875 (0.619)	1.875 (0.619)	1.000
Anxiety/depression	1.750 (0.447)	1.625 (0.500)	0.157

Abbreviations: CDIP-58, Cervical Dystonia Impact Profile-58 questionnaire; CDQ-24, Craniocervical Dystonia Questionnaire-24; EQ-5D, EuroQoL 5-dimension questionnaire; SF-36, 36-Item Short Form Health Survey; SD, standard deviation.

After 24 weeks of treatment, the mean (SD) score of all eight domains of CDIP-58 including head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, and psychosocial functioning were significantly improved (P<0.001) (Table 2). The mean (SD) of each of the five categories of CDQ-24 was also significantly improved with P-values of 0.004, 0.001, 0.003, 0.001, and 0.0005 for stigma, emotional well-being, pain, activities of daily living, and social and family life, respectively (Table 2). After 24 weeks of treatment, the mean values of results of all eight domains of SF-36 did not significantly improved. The P-values for PF, RP, RE, VT, mental health, SF, BP, and GH are 0.726, 1.000, 0.505, 0.349, 0.115, 0.171, 0.427, and 0.380 respectively. The mean score of each category of EQ-5D including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression revealed a nonsignificant change (P>0.05) (Table 2).

Discussion

This prospective study employed four questionnaires to compare the HRQoL of CD patients before and after treatment with botulinum toxin A injections. With respect to the primary endpoint, disease-specific HRQoL (CDIP-58 and CDQ-24) scores were significantly improved in all sub-categories (P<0.001), and both the questionnaires showed a good correlation. Similar results have been shown in previous studies with botulinum toxin A treatment. [1–16,18,20-29] The secondary endpoints (SF-36 and EQ-5D) were not statistically significant in improvement in all subscales. CDIP-58 and CDQ-24 are two disease-specific HRQoL questionnaires that have been developed and established to use to assess the quality of life of CD patients worldwide. Both the questionnaires, originally in English, have been well validated. [16,18,20,24] They were translated into Thai language and tested at Hospital. Both have been shown to be consistent with the original questionnaires with Cronbach's alpha >0.7. The results of SF-36 and EQ-5D questionnaires were not significantly improved after treatment with botulinum toxin A. This may be due to the low sensitivity of SF-36 and EQ-5D. The SF-36 and EQ-5D may be suitable for the evaluation of general HRQoL; however, they may not be sensitive enough in detecting an improvement in HRQoL of CD patients compared to disease-specific questionnaires CDIP-58 and CDQ-24. The main limitation of this study was the small sample size. It has been suggested to recruit a larger subject group in future studies. Furthermore, a double-blind randomized placebo-controlled study is proposed to compare the primary outcomes such as the disease-specific QoL among the different commercial brands of Botulinum toxin (Ona-botulinum toxin A, Abo-botulinum toxin A, and Neu-botulinum toxin A). Further investigation with a larger sample size is warranted in order to account for individual differences, which may mask or exaggerate the outcomes of the study. Botulinum toxin A is a zinc endopeptidase that acts on snare proteins in the pre-synaptic nerve terminal. Botulinum toxin A inhibits acetylcholine release by blocking calcium influx into pre-synaptic junction, resulting in focal denervation of neuromuscular junctions and loss of electrical activity in muscle action potential units.29 As shown in the results of this study, a significant improvement of HRQoL in CD patients after two consecutive injections with botulinum toxin A is predominantly due to an improvement in mental health rather than physical health. Botulinum toxin A itself does not affect the role of central neurotransmitter and is used only locally and in a small amount in this study. Therefore, an improvement in mental health is more likely a result of an improvement of physical health rather than a direct neural effect of the agent.

Conclusion

In conclusion, the quality of life of CD patients improved after multiple botulinum toxin A injections. Each injection of botulinum toxin A seems to have cumulative effects in multiple-injection patients. The direct mechanism behind an improvement in physical health is well understood; however, that behind mental health is less obvious. A relief of dystonia could make a positive difference to patients' relaxation state and stress level, which would account for mental improvement. Disease-specific HRQoL questionnaires are better than general HRQoL questionnaires when the sample size is small.

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