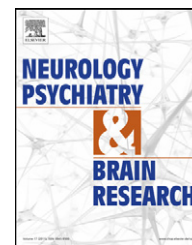


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# Effects of botulinum toxin type a on quality of life assessed with the WHOQOL-BREF in hemifacial spasm and blepharospasm

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## ABSTRACT

**Objective:** The aim of the study was to compare Quality of life (QoL), depression and anxiety in hemifacial spasm (HFS) and essential blepharospasm (BSP) patients and to analyze the effect of Botulinum Toxin Type A (BtxA) therapy. **Materials and methods:** Seventy nine consecutive patients with HFS (N = 53, 76% women, mean age 58 years, mean disease duration 98 months) and BSP (N = 26, 62% women, mean age 63 years, mean disease duration 105 months) were included in this study. Quality of Life was measured by the World Health Organization Quality of Life Measurement Instrument Short Form, Turkish Version (WHOQOL-BREF TR), depression by the Hamilton Depression Rating Scale (HDRS) and anxiety by the Hamilton Anxiety Scale (HAS) before the treatment with BtxA and four weeks after the treatment. **Results:** At baseline, physical health, psychological well-being, and satisfaction with the environment domain scores of WHOQOL-BREF TR, HDRS and HAS scores were not significantly different in two patient groups. Social relationship domain score was found significantly higher in HFS group compared with BSP group. BtxA therapy resulted in a significant improvement of clinical symptom severity, of all domain scores of WHOQOL-BREF TR and of depression and anxiety scores in both HFS and BSP groups. **Conclusions:** This study demonstrates significant benefit of Botulinum toxin therapy on quality of life, depression and anxiety in patients with BSP and HFS.

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## 1. Introduction

Hemifacial spasm (HFS) is characterized by involuntary intermittent tonic and clonic contractions of the muscles innervated by the facial nerve.<sup>1</sup> Blepharospasm (BSP) is characterized by bilateral involuntary contractions of the orbicularis oculi muscles leading to intermittent or sustained

eye closure and is classified as a form of focal dystonia.<sup>2</sup> Medical treatment, Botulinum Toxin Type A (BtxA) injections and surgical interventions are the treatment options for BSP and HFS.<sup>3</sup> Because of unsatisfactory effects of medical treatment options and risk of serious complications of surgical interventions BtxA injections have become the therapy of choice for both disorders.<sup>3</sup> So far, various scales have been used to evaluate the efficacy of the BtxA injections on BSP and

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HFS.<sup>4,5</sup> Quality of life (QoL) scales are of great importance in evaluation of therapeutic interventions.<sup>6</sup> QoL of patients with BSP and HFS may be significantly affected because of difficulty in daily living activities and emotional and social distress related to significant disfigurement.<sup>7</sup> Patients with BSP and HFS were assessed with various QoL scales in the relevant literature. The World Health Organization developed the WHOQOL-100 and an abbreviated form of the WHOQOL, the WHOQOL-BREF scales, to overcome the limitations making comparative studies difficult due to cultural and disease specific differences. The WHOQOL-BREF is a generic, trans-cultural and short instrument that represents good psychometric characteristics in general and clinical settings.<sup>8</sup> To the best of our knowledge, WHOQOL-BREF has not been used in any study to evaluate Btx A treatment effect on the QoL of patients with HFS and BSP. The aim of this study was to compare QoL in patients with HFS and BSP using WHOQOL-BREF questionnaire, and to determine the effects of anxiety and depression on QoL using the Hamilton Depression Rating Scale and Hamilton Anxiety Scale, and to analyze the effect of Botulinum Toxin A therapy on QoL.

## 2. Methods

### 2.1. Subjects

Seventy nine consecutive patients with idiopathic HFS ( $N = 53$ , 67%) and BSP ( $N = 26$ , 33%) recruited from Botulinum Toxin application clinic of Bezmialem Vakıf University, Faculty of Medicine were included in the study. All patients had been diagnosed using standard criteria.<sup>1,2</sup> Patients with other movement disorders such as parkinsonism, chorea or other focal or generalized form of dystonia, cognitive disturbances, known psychiatric disorders and concomitant chronic debilitating diseases such as organ failure or malignancies and patients using antidepressive or antipsychotic medications were excluded. Clinical data including disease duration before treatment, duration of treatment, number of repeated BtxA injections and demographic data including age and gender were obtained from each participant were collected. The severity of HFS and BSP is graded into five levels according to the Jankovic Rating Scale (JRS) from 0 (no hemifacial spasms or no blepharospasm) to 4 (severe incapacitating spasms for HFS and severe, forceful contractions for BSP).<sup>9,10</sup> After the neurological assessment, all patients were referred to the Department of Psychiatry and assessed using World Health Organization Quality of Life Measurement Instrument Short Form, Turkish Version (WHOQOL-BREF TR). The WHOQOL-BREF TR consists 26 items: 24 items tap 4 subscales/domains, including physical health (7 items), psychological well-being (6 items), social relationship (3 items), and satisfaction with the environment (8 items). There are also two items that are examined separately: question 1 asks about an individuals overall perception of quality of life and question 2 asks about an individuals overall perception of their health. Each item is rated on a 5-point Likert scale. After reversing three negatively phrased items (Questions 3,4 and 26) the mean score of items within each domain (raw score) is transformed to domain score using the scale developed by WHO. Domain scores range from

4 to 20, with higher scores representing better QOL. Domains are not scored where 20% of items or more are missing. For the severity of depression and anxiety symptoms Hamilton Depression Rating Scale (HDRS) (21-item version) and Hamilton Anxiety Rating Scale (HAS) were used.<sup>11–13</sup> The HDRS is an inventory of questions or test that is employed to detect and identify the intensity or severity of the signs and symptoms of depression and it comprises 21 questions. HDRS is generally used to measure or examine the decrease in the intensity of depression. Items are scored between 0 and 2 or 4 by the clinician.<sup>11,13</sup> The HAS is a rating scale developed to measure the severity of anxiety symptoms. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe).<sup>12</sup> Both scales are interviewer-rated and their Turkish versions have been validated.<sup>14,15</sup> After the psychiatric assessment, the patients with BSP were treated with BtxA (Botox<sup>®</sup>) injected bilaterally into 3 or 5 sites in the pretarsal regions of the orbicularis oculi muscle, and if needed into the corrugator muscle. The patients with HFS were treated with BtxA (Botox<sup>®</sup>) injected into 3 or 5 sites in the pretarsal regions of the orbicularis oculi muscle and if needed in to the selected muscles of the lower part (zygomaticus major and minor, levator anguli oris, levator labii superioris, rhysorius, depressor anguli oris, mentalis, and platysma) of the face. The dose of BtxA per injection site was 2.5–5 U at the first application. The dose for the subsequent injections was sometimes modified according to the therapeutic response. Each patient was evaluated twice: on the day of first BtxA injection or reinjection at least three months following the previous injection and four weeks after the injection. The therapeutic response was assessed according to the following 0–4 scale: 0 = no effect; 1 = mild effect, no functional improvement; 2 = moderate improvement, no change in functional disability; 3 = moderate improvement in both severity and function; 4 = marked improvement in both severity and function.<sup>16</sup>

The study was approved by the Institutional Ethics Committee, Faculty of Medicine, Bezmialem Vakıf University, and written informed consent was obtained from each participant before study.

### 2.2. Statistical analyses

The Mann–Whitney  $U$  and chi-square tests were used to examine differences between the two groups of patients. Correlations between the WHOQOL-BREF TR scores and selected variables were evaluated using Spearman's Rank Correlations. Statistical significance of the changes was determined by the Wilcoxon matched-pairs test. Statistical significance was defined at  $p < .05$ . All the data analyses were performed using SPSS for Windows (version 16.0).

## 3. Results

Sociodemographic and clinical characteristics of the patients with BSP and HFS are presented in Table 1. There was no statistically significant difference between two patient groups

**Table 1 – Comparison of sociodemographic and clinical characteristics of the patients with hemifacial spasm and blepharospasm.**

	Hemifacial spasm patients (n = 53)	Blepharospasm patients (n = 26)	Between groups analysis
Age (mean ± SD)	58.06 ± 11.971	62.89 ± 11.303	$z = -1.503$ . $p = .133$
Gender (male/female)	13/40	10/16	$\chi^2 = .93$ . $p = .36$
Disease duration before treatment (months, mean ± SD)	97.52 ± 63.573	104.79 ± 71.176	$z = -.314$ . $p = .754$
Duration of BtxA treatment (months, mean ± SD)	36.12 ± 36.486	46.26 ± 32.958	$z = -1.290$ . $p = .197$
Number of injections (mean ± SD)	5.82 ± 4.606	9.84 ± 6.431	$z = -2.359$ . $p = .018^*$
Disease severity (JRS) (mean ± SD)	3.42 ± .50	3.74 ± .45	$z = -2.156$ . $p = .031^*$
BtxA Dosage (unit, mean ± SD)	21.10 ± 6.66	33.68 ± 13.03	$z = -5.085$ . $p < .001^*$

Btx A: Botulinum Toxin Type A; JRS: Jankovic Rating Scale.  
\*  $p < .05$ .

in terms of age, gender, disease duration before treatment and BtxA treatment duration. The mean score of severity of movement disorders, the number of repeated injections and the used BtxA dosage were found significantly higher in BSP group compared with HFS group (Table 1). At baseline no significant difference was found in HDRS, HAS and WHOQOL-BREF TR scores for physical health, psychological well-being, and satisfaction with the environment domains between HFS and BSP groups. Social relationship domain scores were found significantly higher in HFS group compared with BSP group. Perceived overall QoL and overall perception of health scores did not differ between the two patient groups (Table 2).

HDRS scores were significantly correlated with physical health domain (Spearman's  $\rho = -.692$ ,  $p < .001$ ), psychological well-being domain (Spearman's  $\rho = -.528$ ,  $p = .002$ ), social relationship domain (Spearman's  $\rho = -.426$ ;  $p = .013$ ) and satisfaction with the environment domain (Spearman's  $\rho = -.570$ ,  $p < .001$ ) of WHOQOL-BREF TR scale in HFS group. Similarly, HDRS scores were correlated with all domains of WHOQOL-BREF TR scale in BSP group (Spearman's  $\rho = -.505$ ,  $p = .027$ ; Spearman's  $\rho = -.781$ ,  $p < .001$ ; Spearman's  $\rho = -.540$ ,  $p = .017$ ; Spearman's  $\rho = -.796$ ,  $p < .001$  respectively) (Table 3).

HAS scores were significantly correlated with all domain scores of WHOQOL-BREF TR (Spearman's  $\rho = -.715$ ,  $p < .001$ ; Spearman's  $\rho = -.575$ ,  $p < .001$ ; Spearman's  $\rho = -.516$ ,  $p = .002$ ; Spearman's  $\rho = -.642$ ,  $p < .001$ , respectively) in HFS group and with the psychological well-being (Spearman's

$\rho = -.760$ ,  $p < .001$ ), social relationship (Spearman's  $\rho = -.584$ ,  $p = .009$ ), satisfaction with the environment (Spearman's  $\rho = -.755$ ,  $p < .001$ ) domain scores in BSP group except physical well being domain (Spearman's  $\rho = -.438$ ,  $p = .061$ ). Disease severity according to JRS, age, disease duration before treatment and BtxA treatment duration did not correlate with WHOQOL-BREF TR scale scores in both patient groups as shown in Table 3.

Four weeks after the BtxA injection all the WHOQOL-BREF TR domain scores were significantly higher and HDRS and HAS scores were significantly lower in both patient groups. The disease severity of HFS and BSP was also significantly reduced (Table 4, Fig. 1). Therapeutic response was not significantly different between two patient groups ( $3.68 \pm .58$  in BSP patients vs  $3.64 \pm .55$  in HFS patients;  $p = .654$ ). There was no correlation between therapeutic response and baseline WHOQOL-BREF TR domain scores, HDRS scores and HAS scores (Table 5). Disease severity before treatment did not correlate with HDRS, HAS and WHOQOL-BREF TR scale domain score improvements and with therapeutic response as shown in Table 6.

#### 4. Discussion

BtxA, that reduces excessive contractions of muscles by inhibiting the release of acetylcholine at the neuromuscular junction, is a treatment of choice in a variety of neurologic

**Table 2 – Baseline comparison of WHOQOL-BREF TR, HDRS and HAS scores in hemifacial spasm and blepharospasm patient groups.**

	Hemifacial spasm patients (n = 53)	Blepharospasm patients (n = 26)	p
Physical well-being	10.09 ± 2.23	9.21 ± 1.93	.173
Psychological well-being	10.94 ± 2.40	10.42 ± 3.67	.058
Social relationships	12.45 ± 1.39	11.32 ± 2.29	.035*
Satisfaction with the environment	11.79 ± 1.95	11.21 ± 1.75	.414
Perceived overall QoL	2.33 ± .69	2.26 ± .87	.661
Overall perception of health	2.42 ± .66	2.21 ± .63	.342
HDRS	11.91 ± 5.43	14.47 ± 8.56	.282
HAS	10.73 ± 6.61	13.63 ± 8.15	.230

QoL: Quality of life; HDRS: Hamilton Depression Rating Scale; HAS: Hamilton Anxiety Scale.

\*  $p < .05$ .

Table 3 – Correlation between domains of the WHOQOL-BREF and selected variables.

	Perceived overall QoL	Overall perception of health	Physical well-being	Psychological well-being	Social relationships	Satisfaction with the environment
<i>Age</i>						
Total	-.057 <sup>a</sup>	.024	-.082	-.220	-.162	-.108
HFS	.167	.064	-.117	-.204	-.139	-.213
BS	-.320	.085	.089	-.113	.042	.144
<i>Disease duration before treatment</i>						
Total	.146	-.010	-.126	-.178	-.022	-.251
HFS	.129	-.015	-.064	-.169	-.025	-.340
BSP	.217	.096	-.143	-.062	.105	.030
<i>BtxA treatment duration</i>						
Total	.032	.051	-.074	-.022	.055	-.002
HFS	.014	-.097	-.033	.003	-.051	-.169
BSP	.166	.443	.053	.156	.442	.313
<i>Disease severity (JRS)</i>						
Total	.095	-.009	-.195	-.190	-.122	-.055
HFS	-.011	.249	-.036	-.197	-.065	-.043
BSP	.333	-.384	-.335	-.011	.037	.000
<i>HDRS</i>						
Total	-.456 <sup>†</sup>	-.542 <sup>†</sup>	-.629 <sup>†</sup>	-.674 <sup>†</sup>	-.497 <sup>†</sup>	-.678 <sup>†</sup>
HFS	-.478 <sup>†</sup>	-.673 <sup>†</sup>	-.692 <sup>†</sup>	-.528 <sup>†</sup>	-.426 <sup>*</sup>	-.570 <sup>†</sup>
BSP	-.460 <sup>*</sup>	-.323	-.505 <sup>*</sup>	-.781 <sup>†</sup>	-.540 <sup>*</sup>	-.796 <sup>†</sup>
<i>HAS</i>						
Total	-.593 <sup>†</sup>	-.519 <sup>†</sup>	-.618 <sup>†</sup>	-.657 <sup>†</sup>	-.550 <sup>†</sup>	-.671 <sup>†</sup>
HFS	-.583 <sup>†</sup>	-.681 <sup>†</sup>	-.715 <sup>†</sup>	-.575 <sup>†</sup>	-.516 <sup>†</sup>	-.642 <sup>†</sup>
BSP	-.593 <sup>†</sup>	-.314	-.438	-.760 <sup>†</sup>	-.584 <sup>†</sup>	-.755 <sup>†</sup>

HFS: Hemifacial spasm; BSP: Blepharospasm; JRS: Jankovic Rating Scale; HDRS: Hamilton Depression Rating Scale; HAS: Hamilton Anxiety Scale.

<sup>a</sup> Correlation coefficient.

<sup>\*</sup>  $p < .05$ .

<sup>†</sup>  $p < .001$ .

disorders including dystonia, HFS, spasticity and migraine. Previous studies provided evidence for the efficacy and safety of BtxA in the treatment of BSP and HFS.<sup>2,10,17–26</sup> Good to excellent improvement was reported in 76–100% of HFS and BSP patients in a review of the relevant literature.<sup>2</sup> Clinical

effectiveness of BtxA injections has been analyzed in most of the studies based on objective assessments using disease-specific rating scales. Physiologic measures provide information to clinicians but usually these tools do not reflect the impact of the disease on functional, social and psychological

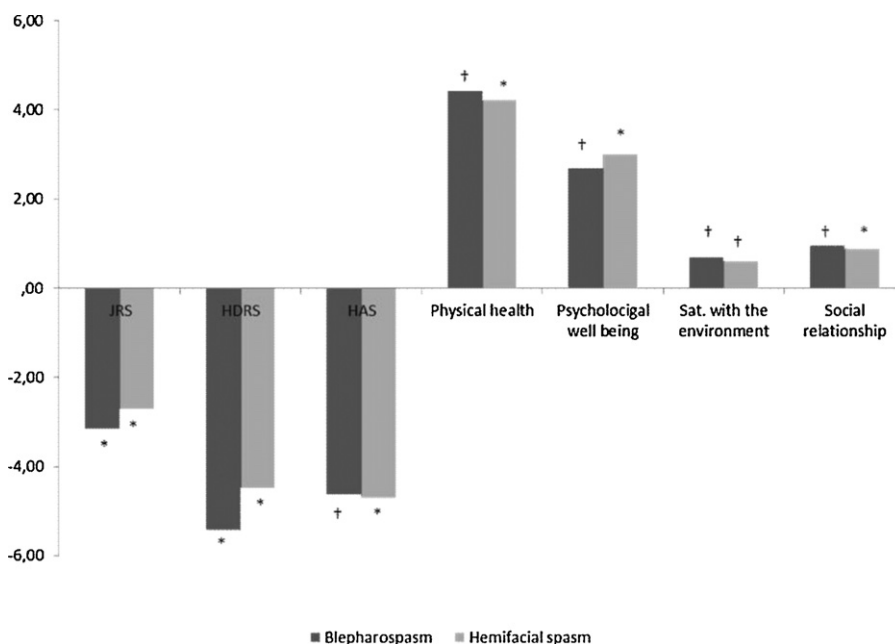
Table 4 – Comparison of WHOQOL-BREF TR, HDRS, HAS and JRS scores before and after Btx A treatment.

		Before treatment (mean ± SD)	After treatment (mean ± SD)	<i>p</i>
Physical well-being	HFS	10.09 ± 2.23	14.30 ± 2.07	<.001 <sup>*</sup>
	BS	9.21 ± 1.93	13.63 ± 2.48	<.001 <sup>*</sup>
Psychological well-being	HFS	10.94 ± 2.40	13.94 ± 2.25	<.001 <sup>†</sup>
	BS	10.42 ± 3.67	13.11 ± 2.51	.003 <sup>†</sup>
Social relationships	HFS	12.45 ± 1.39	13.06 ± 1.73	.027 <sup>†</sup>
	BS	11.32 ± 2.29	12.00 ± 1.76	.048 <sup>†</sup>
Satisfaction with the environment	HFS	11.79 ± 1.95	12.67 ± 1.88	<.001 <sup>*</sup>
	BS	11.21 ± 1.75	12.16 ± 1.80	.004 <sup>†</sup>
Perceived overall QoL	HFS	2.33 ± .69	3.15 ± .83	<.001 <sup>†</sup>
	BS	2.26 ± .87	2.79 ± .79	.032 <sup>†</sup>
Overall perception of health	HFS	2.42 ± .66	3.55 ± .62	<.001 <sup>*</sup>
	BS	2.21 ± .63	3.16 ± .90	.002 <sup>†</sup>
HDRS	HFS	11.91 ± 5.43	7.42 ± 4.99	<.001 <sup>*</sup>
	BS	14.47 ± 8.56	9.05 ± 6.14	.001 <sup>†</sup>
HAS	HFS	10.73 ± 6.61	6.03 ± 4.49	<.001 <sup>†</sup>
	BS	13.63 ± 8.15	9.00 ± 8.12	.006 <sup>†</sup>
Disease severity (JRS)	HFS	3.42 ± .50	.73 ± .52	<.001 <sup>*</sup>
	BS	3.74 ± .45	.58 ± .84	<.001 <sup>†</sup>

JRS: Jankovic Rating Scale; HDRS: Hamilton Depression Rating Scale; HAS: Hamilton Anxiety Scale.

<sup>\*</sup>  $p < .001$ .

<sup>†</sup>  $p < .05$ .



**Fig. 1 – Mean disease severity (JRS), HDRS, HAS and WHOQOL-BREF TR domain score differences between before and after treatment in blepharospasm and hemifacial spasm patients.**

\*  $p < .001$ ; †  $p < .05$ .

domains<sup>27</sup> QoL scales have been considered as important outcome measurement tools in the evaluation of treatment effectiveness especially in patients with chronic diseases.<sup>28</sup> QoL has been defined by World Health Organization (WHO) as individual's perception of their position in life in context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.<sup>8</sup> So far, disease specific QoL measurement tools such as HFS-30, HFS-36, HFS-7, National Eye Inventory Visual Function Questionnaire (NEI-VFQ), and generic Quality of Life measurement tools such as SF 36 have been used to assess QoL of patients with HFS and BSP.<sup>7,28–35</sup> Regarding the results of these studies it is concluded that either BSP or HFS is accompanied by substantial QoL impairment, both globally and disease-specifically.<sup>7,28,31–36</sup> We assessed in this study QoL using the Turkish validated form of WHOQOL-BREF. WHOQOL-BREF measures a broad range of facets, including perception of one's life, personal health, access to health care and social services, spirituality, and personal environment. WHOQOL group suggested that WHOQOL and WHOQOL-Bref assessments will

be of considerable use in clinical trials, in establishing baseline scores in a range of areas, and looking at changes in quality of life over the course of interventions.<sup>8</sup> WHOQOL-BREF is based on a cross-culturally sensitive concept and is available in most of the world's major languages.<sup>37</sup> This instrument has been used widely in clinical trials in patients with various chronic conditions. Our results showed no significant difference among physical health, psychological well-being, and satisfaction with the environment domain scores of WHOQOL-BREF TR questionnaire between HFS and BSP patient groups. In social domain, patients with BSP had significantly lower scores than patients with HFS. This domain assesses the quality of interpersonal relationships other than the family, social support and sexual activity. Social isolation due to the severe disfigurement and functional visual disturbances might have an impact on the social domain in BSP patients. Previous studies demonstrated that patients with BSP and HFS experience a multitude of physical and emotional symptoms.<sup>28,35,38–40</sup> Although Hall et al. reported that patients with BSP were more depressive and anxious than patients with HFS,

**Table 5 – Correlation between therapeutic response and baseline HDRS, HAS and WHOQOL-BREF TR scores.**

	HDRS	HAS	Physical well-being	Psychological well-being	Social relationships	Satisfaction with the environment
	<i>Therapeutic response</i>					
Total	-.138 <sup>a</sup>	.032	.018	.033	.037	-.068
HFS	.136	.143	-.024	.120	-.194	-.012
BSP	.137	-.048	.142	-.038	-.242	-.218

HFS: Hemifacial spasm; BSP: Blepharospasm; HDRS: Hamilton Depression Rating Scale; HAS: Hamilton Anxiety Scale.

<sup>a</sup> Correlation coefficient.

\*  $p < .05$ .

**Table 6 – Correlation between disease severity before treatment and therapeutic response, HDRS, HAS and WHOQOL-BREF TR score improvement.**

	Therapeutic response	HDRS	HAS	Physical well-being	Psychological well-being	Social relationships	Satisfaction with the environment
	<i>Disease severity (JRS)</i>						
Total	-.188 <sup>a</sup>	-.130	.035	.123	.066	.086	-.059
HFS	-.274	-.074	.045	-.039	.062	-.004	-.065
BSP	-.099	-.187	.011	.256	.056	.240	-.035

HFS: Hemifacial spasm; BSP: Blepharospasm; JRS: Jankovic Rating Scale; HDRS: Hamilton Depression Rating Scale; HAS: Hamilton Anxiety Scale.  
<sup>a</sup> Correlation coefficient.  
<sup>\*</sup>  $p < .05$ .

we did not find significant difference among depression and anxiety scores between two patient groups.<sup>32</sup> Several studies have assessed the impact of depression in chronic diseases in terms of the individual's functional ability or QoL. Our results showed that higher HDRS and HAS scores were significantly correlated with the impairment of QoL. Both BSP and HFS can considerably limit activities of daily living because of involuntary tightening and closure of the eyelids. Limitation of daily living activities may lead to depressive and anxiety disorders. Additionally it is suggested that facial expression of emotion may play a causal role in the subjective experience of emotion.<sup>41</sup> Whatever the mechanism involved, these data indicate that the addition of depression and anxiety to facial movement disorders has an impact on QoL. We showed significant improvement in WHOQOL-Bref TR, HDRS and HAS scores in both HFS and BSP patients after treatment with BtxA. There are conflicting results about the effect of BtxA on QoL. Müller et al. reported that clinically effective BtxA therapy completely failed to improve quality of life measured with Short Form 36 in BSP<sup>35</sup> and they concluded that generic quality of life instruments have limitations in evaluating craniocervical dystonia. We showed significant improvement with another generic quality of life instrument. One explanation for this discrepancy could be the low percentage of follow-up patients in the study of Müller et al. (37 of 89 patients with BSP completed follow-up assessment.) In a recent study it is concluded that HFS and BSP affect both the Physical and Mental Components of QOL despite clinical improvement during long-term therapy with BtxA.<sup>31</sup> In other studies, QoL improvement has been described in patients with cervical dystonia, hyperhidrosis, spasmodic dysphonia, oromandibular dystonia, HFS and BSP receiving BtxA therapy.<sup>29,34,36,42,43</sup> Interestingly Finzi and Wasserman<sup>44</sup> reported beneficial effect of Btx A on major depression. To our knowledge, this is the first study compared QoL and evaluated Btx A therapy effect on QoL using WHOQOL-Bref in HFS and BSP patients. In conclusion, the present study provides further evidence for the beneficial effect of BtxA treatment on QoL, depression and anxiety in both of BSP and HFS patients.

### Conflict of interest

There are no financial or other relationships that might lead to conflicts of interest.

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