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Health-related quality of life outcomes from botulinumtoxin treatment in blepharospasm

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ABSTRACT

Objective: Blepharospasm associates with impairment in generic health-related quality of life (HR-QoL). Albeit botulinum toxin is widely used to alleviate the motor symptoms of blepharospasm, its effect on generic health-related quality of life (HR-QoL) is heterogeneous.

Patients and methods: In this open-label clinical observational study, we characterized outcomes on HR-QoL in terms of the EuroQol (EQ-5D-5 L) from botulinum toxin (BoNT) injection in a prospective cohort of patients with blepharospasm (n = 55). Additionally, we characterized motor and non-motor signs of blepharospasm including motor symptom improvement, life satisfaction, depressive symptoms, pain and sleep quality. Patients were assessed at the end of a regular three-month period from last injection (Timepoint1) and four weeks after the re-injection of BoNT (Timepoint2).

Results: There was no improvement of generic HR-QoL on group-level. Individual findings were heterogeneous, dividing patients in three groups of responders (RESP), unchanged outcomes (UNCHN), and worsening (WORSE). We identified, that these subgroups differed at Timepoint 1 with respect to EQ-5D-5 L, EQ-VAS, life satisfaction (health and movement disorders domains), Beck's Depression inventory, and sleep quality (One-way ANOVAs, $P < 0.05$, adjusted for multiple comparisons). In post-hoc Tuckey tests, RESP or WORSE showed distinct differences from UNCHN that might help to separate the subgroups in future. As such, RESP showed higher impairment in EQ-5D-5L, EQ-VAS, and Beck's Depression Inventory compared to UNCHN (unlike WORSE), whereas WORSE showed higher impairment in life satisfaction 'movement disorders' domain (unlike RESP).

Conclusion: Our study suggests, that several dependent non-motor, life satisfaction and generic HR-QoL measures associate to individual patient outcomes. The variables identified in this study may be validated in future studies to predict HR-QoL outcomes in patients with blepharospasm.

1. Introduction

Health-related quality of life (HR-QoL) is impaired in blepharospasm when compared to the healthy population [1–5]. Although botulinum toxin (BoNT) injection effectively ameliorates motor symptoms of blepharospasm and disease-related disability in daily life functioning [6–8], an effect on generic HR-QoL could not be demonstrated [3,9]. According to a Cochrane Review in 2009 [10], a closer characterization of HR-QoL outcomes in patients with blepharospasm treated with BoNT was encouraged.

For comparison, in cervical dystonia, rather multifold non-motor variables modify HR-QoL outcome of BoNT treatment. As such, anxiety and pain were – amongst others - strong predictors on HR-QoL costs in cervical dystonia patients [11]. This is an important aspect, given that pain is a predominant feature in up to 75% of the patients with cervical dystonia [12]. Moreover, good BoNT responders yielded lower depression scores and lower dystonia motor severity [1]. The effect of BoNT on HR-QoL in blepharospasm is less characterized and strongly

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Table 1
Patient characteristics.

	Blepharospasm
Number of patients	55
Age (mean ± STD)	66.5 ± 12.9
Male : female	18 : 37
Age at onset	59.5 ± 13.7
Disease duration	7.1 ± 5.7
Repeated injections	53
First time injection	2
BoNT preparations (in units)	173.2 ± 70.8
Dysport	42.4 ± 14.9
Botox	66.6 ± 27.2
Xeomin	–
Neurobloc	

Error indicators are given as standard deviation.

warrants additional observational clinical studies, given that HR-QoL outcomes have become a mainstay for therapy referral across wide fields of movement disorders [9,13–19].

In this open-label clinical 'real world' observational study, we address this need by characterizing outcomes on generic HR-QoL from repetitive BoNT injection in a prospective cohort of patients with blepharospasm. We corroborated these HR-QoL assessments by an in-depth evaluation of related motor and non-motor outcomes. The latter included assessments on life satisfaction, depressive symptoms, dystonia severity, pain, and sleep quality. We characterized these outcome variables at the end of a regular three-month washout period from last injection and four weeks after the re-injection of BoNT.

2. Patients and methods

We assessed 55 consecutive patients with blepharospasm treated with BoNT in an observational clinical study. Detailed patient characteristics are given as Table 1. Most patients (n = 53) received repeated injections along regular three-month reinjection intervals, whereas only two patients received first time injection (Table 1). We recorded the scores first at the end of a three-month interval from the last BoNT injection (prior to first injection in first-time recipients) (Timepoint1). This is in keeping with previous considerations, suggesting that the effects of BoNT on HR-QoL will reverse within twelve weeks from injection [2,16,17]. As second recording, patients reported the scores again at four weeks after injection reflecting the time point of expected optimal BoNT efficacy (Timepoint 2). To this end, patients were provided with the question forms that were filled out by themselves in their home environment and sent back by mail. Accordingly, all outcome measures at Timepoint 2 were subjective according to the patients' self-perception. No clinical visit or examination was conducted at Timepoint 2. The EQ-5D-5 L (used for HR-QoL assessments in this study) was suggested to reflect the subject's situation at the time of completion [20] and makes no attempt to recall the health status over the preceding days or weeks.

Patients were included at the following neurological centres and practices: Centre for Neurology, Department for Neurodegenerative Diseases, Tübingen University; Centre for Neurology Stuttgart Bürgerhospital; Centre of Neurology Sindelfingen, Neurology Practice 'Dr. Appy & Molt' Stuttgart; Neurology Practice 'am Seelberg' Stuttgart. All neurologists had at least five years of experience in BoNT treatment.

In order to reflect the 'real-word' therapeutic environment, we kept inclusion and exclusion criteria wide in order to prevent selection (as opposed to randomized controlled trials that generally consider stringent eligibility criteria). Inclusion criteria were age > 18 years and written informed consent. We excluded patients treated with concomitant medications potentially interacting with BoNT treatment, such as oral anticoagulants (e.g. phenprocoumon) or aminoglycoside antibiotics. The local Ethics committee of Tübingen University and of the Landesärztekammer Baden-Württemberg approved the study, and patients participated after written informed consent.

First, we analysed outcomes on HR-QoL based on the EuroQol (EQ) self-rating scale at Timepoint 1 compared to Timepoint 2. The EQ-5D-5 L comprises five questions on subjectively perceived mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Patients reported on a five-point scale whether they have no problems (1), slight problems (2), moderate problems (3), severe problems (4), or extreme problems (5). The second part EQ VAS is a vertical 20 cm visual analogue scale from 0 to 100 with steps of one in order to assess the self-rated momentary health state (0 indicating worst possible state, 100 indicating best possible state). Further, we ensured that EQ-5D-5 L characteristics were similar at Timepoint1 across centres (one-way ANOVA: $F = 0.975$; $P = 0.431$). Moreover, we found that the treatment outcomes across centres on the EQ-5D-5L (difference of Timepoint2 – Timepoint1) were similar across centres (one-way ANOVA: $F = 0.955$; $P = 0.442$).

We recorded the questionnaire on life satisfaction validated in German language (i.e. 'Fragen zur Lebenszufriedenheit' (FLZ)) including the modules on: 'general life satisfaction' (FLZ-A), satisfaction with health (FLZ-G), satisfaction with movement disorder (FLZ-BS). Further, Beck's depression inventory (BDI), subjective rating of perceived severity in both dystonia (1–10), average and maximal pain during the last seven days assessed as visual analogue scale, and Pittsburgh sleep quality index (PSQI) were assessed. All scores were obtained in native German language. We performed the study and all statistical analyses with exploratory intent and, therefore, no sample size estimation was considered in the planning phase of this observational study.

We conducted non-parametric Wilcoxon tests with two-sided significance level of $P < 0.05$ (SPSS, Version 23) comparing the scores at Timepoint1 vs. Timepoint2. We corrected for false positives in terms of the false discovery rate [21].

Moreover, we conducted a subanalysis on three subgroups on EQ-5D-5 L outcomes on Timepoint 2 compared to Timepoint 1, i.e. responders (RESP), unchanged response (UNCHN), and worsening (WORSE). We tested with one-way ANOVAs whether these subgroups differed in dependent variables at a significance level of $P < 0.05$. Again, we used FDR correction to correct for multiplicity when repeated one-way ANOVAs were conducted. In terms that the homogeneity assumption was violated (Levene's test), the robust Welch test was used to verify significance of the one-way ANOVAs. Post-hoc comparison between subgroups were conducted with Tuckey tests ($P < 0.05$).

3. Results

Patients with blepharospasm showed no improvement in EQ-5D-5 L and EQ-VAS on group-level (Table 2). However, clinical motor symptoms of dystonia improved, as expected. There was no difference in life satisfaction domains, depressive symptoms, pain, or sleep quality (Table 2) between Timepoint1 and Timepoint2 on group-level.

To further analyse the heterogeneous individual outcomes of generic HR-QoL on BoNT treatment, we conducted subanalyses on individual treatment responses. As subgroups, we defined patients with improvement (RESP), unchanged outcomes (UNCHN), and worsening (WORSE) of EQ-5D-5 L from BoNT. 19 out of 30 female patients (63.3%) but only 6 out of 16 male patients (37.5%) changed their outcomes between Timepoint 1 and Timepoint 2. Fifteen patients (RESP) reported subjective improvement (EQ-5D-5 L before 6.07 ± 4.98, after 3.20 ± 3.76), 21 patients (UNCHN) reported HR-QoL unchanged (EQ-5D-5 L before and after: 1.24 ± 2.02), and n = 10 patients (WORSE) reported worsening of HR-QoL four weeks after re-injection (EQ-5D-5 L before 4.50 ± 4.09, after 6.9 ± 3.98).

We analysed as one-way ANOVAs whether the three independent groups differed in their dependent variable characteristics at Timepoint