Health related quality of life is improved by botulinum neurotoxin type A in long term treated patients with focal dystonia

R Hilker, M Schischniaschvili, M Ghaemi, A Jacobs, J Rudolf

Abstract

Objectives—The advent of botulinum neurotoxin type A (BoNT/A) gave rise to substantial progress in the treatment of focal dystonias. In the light of the high costs of the toxin and the necessity to establish valid outcome indices for this treatment apart from sheer reduction of dystonic muscle tone and posture, the impact of focal dystonia and its treatment with BoNT/A on patients' health related quality of life (HRQL) was determined.

Methods—Fifty patients with cranial and cervical dystonia treated long term with BoNT/A were enrolled in a prospective, open labelled cohort study. The HRQL was assessed using the EuroQol (EQ-5D) and the short form 36 health survey questionnaire (SF-36) at baseline before BoNT/A injections and at two follow up visits after 6 and 12 weeks covering one BoNT/A treatment period with maximum effect size at the first follow up.

Results—Compared with a general population sample, a considerable negative impact of focal dystonia on HRQL was found in patients under investigation. In both disease types, BoNT/A treatment led to a significant improvement in several HRQL dimensions, in particular providing moderate to marked effect sizes in the fields of mental health and pain. The impairment of HRQL due to pain as well as the BoNT/A induced improvement within this SF-36 subscore were significantly higher in patients with cervical dystonia. Under BoNT/A therapy, no correlation was found between changes of clinical outcome scores and HRQL measures.

Conclusions—The data confirm that BoNT/A is able to induce a significant, but temporary amelioration of several aspects of HRQL in both types of focal dystonia. This may substantially contribute to the patients' subjective benefit from the therapy. Moreover, the data provide further arguments to accept high costs of the BoNT/A treatment in these severely handicapped patients, as a consequence of its considerable benefit on quality of life.

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Keywords: focal dystonia; botulinum neurotoxin type A; health related quality of life

The focal dystonias represent a distinct disease entity among the movement disorders, where treatment options have significantly improved after the introduction of botulinum toxin type A (BoNT/A) as a neuromuscular paralytic agent. In placebo controlled studies, BoNT/A provided efficient reduction of the increased muscle tone in dystonia¹ and is now considered as the first line treatment in cranial and cervical dystonia.² Jankovic *et al* also showed long term clinical efficacy of BoNT/A injections over at least five treatment sessions in patients with blepharospasm and cervical dystonia.³ However, besides the clinical problems with increased painful muscle tone leading to involuntary abnormal postures and repetitive movements, the dystonic patients present with a wide range of social disabilities and impairments of health related quality of life (HRQL)—for example, low self esteem, depression, and poor social interaction.⁴ In view of the requirement of regular BoNT/A injections about every 3 months to maintain its clinical effect and the high costs of the drug, therapy feasibility and patient compliance will be increased if several aspects of the diminished HRQL were also considerably improved by the BoNT/A treatment.

In our study, we focused on patients with cranial and cervical dystonia as the two most common forms of focal dystonia and the most common indications for a regular BoNT/A treatment.⁵ We sought to determine the impact of the diseases on HRQL and the effectiveness of BoNT/A to provide a subjective relief to patients treated long term that cannot be measured with neurological examination and clinical severity scales alone. For this purpose, the use of generic health status measures is feasible, because they allow the comparison of HRQL and treatment outcome between different groups of patients and the general population.⁶ We applied two measures of health status to the study population: The EuroQol questionnaire (EQ-5D) provides an overall assessment of HRQL (EQ-5D utility index and visual analogue scale).⁷ The medical outcomes study short form 36 (SF-36) is a self report questionnaire which measures eight multi-item variables and which has been widely used to determine the functional health status in outpatient populations.⁸

Patients and methods

This open prospective study was intended to be performed in patients with adult onset idiopathic cranial and cervical dystonia and

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Table 1 Clinical data of the study subgroups

	Age (y)	Sex	Disease duration (y)	BoNT/A duration (y)	Baseline		First follow up		Second follow up	
					Tsui scale	BIM scale	Tsui scale	BIM scale	Tsui scale	BIM scale
Cranial dystonia (n=25):										
Blepharospasm (n=20)	68.7 (11.4)*	4 M / 16 F	6.8 (5.1)	3.6 (2.0)	—	7.4 (2.6)**	—	4.7 (1.9)**†	—	6.1 (2.6)**
Meige syndrome (n=5)	61.4 (10.8)	2 M / 3 F	10.6 (8.8)	3.9 (1.9)	—	12.6 (2.1)**	—	9.4 (2.1)**††	—	10.8 (2.3)**
Cervical dystonia (n=25)	51.2 (14.0)*	9 M / 16 F	8.5 (7.4)	3.7 (2.1)	7.9 (2.1)†	—	5.3 (1.3)†	—	7.3 (1.9)	—

Results (excepting sex) are means (SD). * $p < 0.05$ for difference blepharospasm versus cervical dystonia (ANOVA). ** $p < 0.01$ for difference blepharospasm versus Meige syndrome (unpaired t test). † $p < 0.05$; †† $p < 0.01$ for difference of first follow up assessment compared with baseline (paired t test).

continuous BoNT/A treatment for at least 6 months before the beginning of the study. Consecutive patients fulfilling these criteria and treated in our outpatient movement disorder department were asked to participate. Their diagnoses had been established in accordance with common diagnostic criteria.⁹ As clinical experience had shown that patients just starting on BoNT/A often report an initial dramatic treatment effect compared with follow up injections, only patients with long term BoNT/A treatment were selected to avoid possible confounding of our results. After obtaining written informed consent, 50 patients (15 men, 35 women) aged 26–84 years (mean (SD) 59.2 (15.0) years) were included in chronological order and assigned to the cranial dystonia (20 patients with blepharospasm and five patients with Meige syndrome) and the cervical dystonia subgroup (n=25).

Dosages and injection sites of BoNT/A were individualised according to the distribution and degree of dystonic muscle activity. Botox® (Allergan Inc, Irvine, CA, USA) was applied in 20 patients with cervical (139 (31) IU (mean (SD))) and 24 patients with cranial dystonia (16 (9) IU). Five patients of the cervical dystonia group received Dysport® (Speywood Biopharm Ltd, Wrexham, UK; dosage 610 (151) IU, (mean (SD))), whereas only one woman with blepharospasm was treated with this BoNT/A preparation (80 IU).

In each patient, the SF-36 and EQ-5D questionnaires were obtained at three time points covering one BoNT/A treatment period (duration 12.1 (1.9) weeks (mean (SD))): first at the baseline assessment before the BoNT/A injection and at two follow up visits reflecting the presumed time of the maximal BoNT/A effect in the first (interval from baseline to first follow up visit 5.9 (1.0) weeks (mean (SD))) and the end of the BoNT/A treatment period in the second visit (interval from first to second follow up visit 6.2 (1.3) weeks (mean (SD))). At each visit, the disease severity was assessed by the modified Tsui scale¹⁰ in cervical dystonia and the blepharospasm involuntary movement (BIM) scale¹¹ in cranial dystonia (table 1). As additional sociodemographic data, after age and sex, the individual marital (unmarried, married, divorced) and employment status (employed, unemployed/ retired) were surveyed at the baseline examination.

The EQ-5D measure¹² used in this study consisted of two parts: In the first section, individually rated health state profiles defined by five HRQL dimensions (mobility, self care, usual activities, pain and discomfort, and anxiety and depression) with three answering options (no problems, some problems, extreme problems) are corresponded to EQ-5D utility values (utility index, UI) that reflect the relative weighting of this health state profile by a sample of the general population. In the second part, the respondents rated their own health on a visual analogue scale (VAS) ranging from 0 (worst possible health state) to 100 (best possible health state).

In the SF-36 generic measure,¹³ scores are generated ranging from 0 (worst health) to 100

(best health) for each of eight dimensions, namely physical functioning, physical limitations of role, pain, general health, vitality, social functioning, emotional limitations of role, and mental health.

The statistical analysis of ordinal data was performed with unpaired *t* test statistics (for the comparing of two groups) and with one way analysis of variance (ANOVA) with Bonferroni's correction for multiple testing (for comparison of more than two groups and determination of specific intergroup differences), and χ^2 tests were applied to compare categorical variables. The impact of the BoNT/A treatment on each HRQL variable was expressed in effect sizes, calculated as the difference between the variable's mean baseline and first follow up score divided by the SD of the baseline score. An effect size less than 0.2 was considered small, whereas effect sizes of 0.2–0.5 and greater than 0.5 were regarded as moderate and large, respectively.¹⁴ Changes of the HRQL measures within the BoNT/A treatment period were calculated using paired *t* test statistics. Bivariate correlations between the baseline SF-36 and EQ-5D subscores were performed with Spearman's rank correlation. To evaluate the influence of sociodemographic data, a multivariate ANOVA with sex, marriage, and employment status as cofactors and age as a covariate was undertaken twice: first including the baseline HRQL variables and second the BoNT/A effect sizes as dependent variables. Finally, we calculated a univariate ANOVA to adjust the BoNT/A effect size within the SF-36 pain subscore for employment status and disease type as cofactors. Statistical significance was accepted at the level of $p < 0.05$. All analyses were performed with the superior performance software SPSS version 10.0 for Windows (SPSS Inc, UK Ltd, Surrey, England).

Results

The clinical data of the study subgroups are summarised in table 1. Patients with blepharospasm had a significantly higher mean age than those with Meige syndrome and those with cervical dystonia (68.7 (SD 11.4) *v* 61.4 (SD 10.8) and 51.2 (SD 14.0) years, $p < 0.01$; ANOVA), whereas there were no intergroup differences for disease duration and duration of BoNT/A treatment before the study. In the cranial dystonia group, the disease severity assessed with the blepharospasm involuntary movement scale was significantly higher in

patients with Meige syndrome ($p < 0.01$, unpaired *t* test). BoNT/A treatment led to a significant improvement of clinical severity scales assessed at the first follow up visit in both groups, whereas no differences between the baseline and the second follow up assessment could be found (table 1, paired *t* test). The cervical dystonia group had a significantly higher number of employed than unemployed or retired subjects than the cranial dystonia cohort (14/25 *v* 6/25, $p < 0.05$, χ^2 test). However, no differences were found for sex and marital status.

All study participants provided correctly completed HRQL questionnaires. The baseline assessment of the SF-36 disclosed remarkable lower values in the HRQL dimensions in patients with focal dystonia compared with a general German population sample (table 2).¹⁵ In particular, physical and emotional limitations of role as well as a decreased mental health were obvious in patients with both disease types. Furthermore, restrictions of physical and social functioning predominantly affected patients with cranial dystonia, whereas pain values were mostly lowered in cervical dystonia. The sociodemographic factors at baseline showed a significant decrease of the SF-36 physical functioning subscore with age ($p < 0.05$, multivariate ANOVA), whereas the marital status significantly interfered with the emotional limitations of role (means: married 74.4, unmarried 77.7, divorced 28.4; $p < 0.01$).

At baseline, each SF-36 subscore was positively correlated with the EQ-5D utility index, whereas the EQ-5D VAS scores showed only significant positive correlations with the physical functioning, emotional limitation of role, vitality, and pain dimensions of the SF-36 (Spearman's rank correlation, ρ =correlation coefficient, table 3). With the exception of general health, which only showed significant correlations with the vitality ($\rho = 0.56$, $p < 0.001$), emotional limitation of role ($\rho = 0.30$, $p < 0.05$) and mental health ($\rho = 0.28$, $p < 0.05$) subscores, each dimension of the SF-36 correlated with every other dimension and all correlations reached significance.

Under effective BoNT/A treatment, changes in the overall health rating of the study population as a whole were reflected by increased EQ-5D scores assessed at the first follow up visit. This phenomenon was confirmed by the distribution of individual EQ-5D UI and VAS scores shifting to the right on the graph's x axis in figure 1 A and B. At the first follow up

Table 2 SF-36 measurement of health related quality of life in 50 patients with focal dystonia compared with a German general population sample¹⁵

SF-36 dimensions	Cranial dystonia mean (SD)	Cervical dystonia mean (SD)	General population mean (SD)	Patients below age matched mean-2 SD (%)	
				Cranial dystonia	Cervical dystonia
Physical functioning	63.6 (26.0)	73.8 (22.7)	83.8 (23.6)	16	8
Social functioning	67.8 (27.5)	74.4 (20.6)	87.7 (19.5)	16	8
Physical limitation of role	53.0 (34.1)	52.0 (31.2)	81.2 (33.8)	16	12
Emotional limitation of role	61.1 (41.6)	75.9 (39.2)	88.2 (28.3)	24	16
Mental health	62.1 (16.9)	62.7 (19.0)	72.8 (17.3)	8	8
Vitality	54.8 (22.0)	55.6 (22.4)	61.8 (19.2)	0	8
Pain	60.5 (24.3)	55.6 (25.0)	77.2 (28.5)	0	8
General health	47.7 (18.1)	53.2 (19.6)	66.2 (21.0)	0	0

Table 3 Spearman's rank correlation coefficients of the SF-36 health dimensions and the EQ-5D measures at baseline assessment

	Social functioning	Role-physical	Role-emotional	Mental health	Vitality	Pain	General health	EQ-5D: utility index	EQ-5D: VAS
Physical functioning	0.29*	0.46**	0.39**	0.29*	0.47**	0.58	0.27 NS	0.49	0.45**
Social functioning	●	0.51	0.55	0.54	0.50	0.51	0.26 NS	0.50	0.14 NS
Role-physical		●	0.39**	0.49	0.49	0.62	0.22 NS	0.54	0.17 NS
Role-emotional			●	0.38**	0.54	0.45**	0.30*	0.39**	0.30*
Mental health				●	0.53	0.45**	0.28*	0.42**	0.19 NS
Vitality					●	0.65	0.56	0.59	0.41**
Pain						●	0.26 NS	0.65	0.42**
General health							●	0.46**	0.25 NS
EQ-5D: utility index								●	0.47

p<0.001 except where indicated as follows: *p<0.05; **p<0.01; NS=not significant.

assessment, some SF-36 HRQL values showed a significant increase in both types of dystonia (table 4): social functioning, mental health ($p<0.01$) and physical limitation of role and EQ-5D VAS scores ($p<0.05$, paired t test). Vitality scores were also improved in both groups and reached $p<0.01$ in the cervical versus $p<0.05$ level in patients with cranial dystonia. Physical functioning and emotional limitations of role ameliorated in the cranial dystonia group solely ($p<0.05$), whereas improvements in pain and EQ-5D utility index were only found in the patients with cervical dystonia ($p<0.01$). Significant changes of general health were not seen in either group and patients with

cervical dystonia even showed lower follow up scores compared with the baseline assessment in this point.

The extent of improvement in each HRQL dimension (expressed as the effect size of the BoNT/A treatment) is given in table 4. In cranial dystonia, a moderate effect size was seen in the mental health dimension (0.5) and smaller ones in social and physical functioning (0.4 and 0.3, respectively), in emotional and physical limitations of role (0.4 and 0.3, respectively) and in vitality (0.4). In patients with cervical dystonia, we found large effect sizes within the mental health (0.7) and, particularly, in the pain dimensions (0.8), whereas significant improvement in the pain dimension was absent in the cranial dystonia group. Furthermore, the cervical dystonia group presented with smaller effect sizes in the vitality (0.4), physical limitation of role (0.4), and social functioning (0.4) dimensions, whereas improvements were absent in the physical functioning, emotional limitation of role, and general health area. For the overall EQ-5D scores, the effect sizes tended to be higher in the cervical dystonia group. Among the sociodemographic factors, the employment status significantly interfered with the BoNT/A effect size of the SF-36 vitality (means: employed 0.6, unemployed or retired 0.3; $p<0.01$) and the SF-36 pain score (means: employed 0.7, unemployed or retired 0.3; $p<0.05$, multivariate ANOVA). Comparing both types of dystonia, only the BoNT/A effect size within the SF-36 pain dimension differed significantly, reaching higher values in cervical dystonia (means: 0.8 *v* 0.2, $p<0.01$, unpaired t test). The univariate ANOVA adjusting this effect size for disease type and employment status also disclosed a significant effect of the first ($p<0.05$), but not of the employment status or the interaction of both.

No correlation was found between the improvement in any HRQL dimension and the disease duration as well as the dosage and the overall duration of the BoNT/A treatment. Neither the modified Tsui nor the blepharospasm involuntary movement scale values correlated with any of the HRQL dimensions at the baseline and the follow up assessments. After BoNT/A application, no significant relation was found between changes of the clinical severity scales and the HRQL measures. This is illustrated in figure 2 showing individual changes of the examiner rated disease severity paired with changes of the self reported EQ-5D VAS scores after BoNT/A injections.

Figure 1 Distribution of the EQ-5D utility index (A) and the EQ-5D visual analogue scale (B) in 50 patients with cranial and cervical dystonia at baseline (pre-BoNT/A) and at the first follow up assessment after BoNT/A injection. Improvement in self reported overall health status under treatment is reflected by a shift of individual scores towards higher values.

Table 4 SF-36 and EQ-5D measures over time and effect sizes of BoNT/A treatment within the HRQL dimensions assessed in 50 patients with focal dystonia

	Cranial dystonia				Cervical dystonia			
	Baseline	First follow up	Second follow up	BoNT/A effect size	Baseline	First follow up	Second follow up	BoNT/A effect size
SF-36:								
PF	63.6 (26.0)	70.8 (27.9)*	59.6 (29.6)	0.3 (0.6)	73.8 (22.7)	74.6 (27.5)	74.2 (23.1)	0.03 (0.9)
SF	67.9 (27.5)	77.4 (25.3)**	68.4 (29.1)	0.4 (0.7)	74.4 (20.6)	83.0 (19.6)**	70.9 (24.1)	0.4 (0.6)
RP	53.0 (34.1)	63.0 (37.6)*	49.0 (37.8)	0.3 (0.6)	52.0 (31.4)	64.0 (35.4)*	46.0 (29.5)	0.4 (0.7)
RE	61.2 (41.6)	75.8 (34.1)**	59.8 (40.8)	0.4 (0.8)	75.9 (39.2)	78.5 (33.3)	73.2 (37.3)	0.1 (0.4)
MH	62.2 (16.9)	70.9 (21.0)**	66.4 (18.9)	0.5 (0.7)	62.7 (19.0)	74.6 (14.4)**	59.0 (21.6)	0.7 (1.0)
VIT	54.8 (22.0)	63.2 (24.6)*	53.6 (24.3)	0.4 (0.7)	55.6 (22.4)	64.8 (23.0)**	55.0 (23.8)	0.4 (0.7)
BP	60.5 (24.3)	64.2 (27.8)	60.8 (27.6)	0.2 (0.6)†	55.7 (25.0)	74.2 (20.5)**	57.5 (26.5)	0.8 (0.9)†
GH	47.8 (18.1)	51.3 (19.6)	48.3 (19.8)	0.2 (0.7)	53.2 (19.6)	52.3 (18.1)	49.0 (18.5)	-0.1 (0.7)
EQ-5D:								
UI	0.59 (0.26)	0.66 (0.29)	0.63 (0.27)	0.3 (0.9)	0.60 (0.24)	0.76 (0.21)**	0.66 (0.21)	0.6 (0.9)
VAS	59.6 (19.9)	67.4 (21.4)*	62.2 (20.3)	0.4 (0.9)	57.0 (21.2)	69.2 (18.0)*	58.8 (15.9)	0.6 (1.1)

*p<0.05; **p<0.01 for difference of first follow up assessment compared with baseline (paired *t* test); no significant differences between second follow up and baseline assessments; †p<0.01 for difference in BoNT/A effect size between cranial and cervical dystonia (unpaired *t* test); BoNT/A effect size=(first follow up score–baseline score)/1 SD of baseline scores; PF=physical functioning; SF=social functioning; RP=role-physical; RE=role-emotional; MH=mental health; VIT=vitality; BP=bodily pain; GH=general health; UI=utility index; VAS=visual analogue scale.

Figure 2 Spearman's rank correlation of individual changes within clinical scores and the EQ-5D visual analogue scale (VAS) after BoNT/A application in 50 patients with focal dystonia. The modified Tsui scale was used in cervical dystonia ($p=0.05$, $p=0.81$) and the blepharospasm involuntary movement scale in cranial dystonia ($p=0.27$, $p=0.20$).

Discussion

In this open labelled prospective study, we assessed changes of self rated HRQL scores in two cohorts of patients with either cranial or cervical dystonia over a 12 week BoNT/A treatment cycle. Our data demonstrate a remarkable negative impact of cervical and cranial dystonia on patients' HRQL and a significant temporary improvement in several HRQL dimensions in both types of focal dystonia after BoNT/A treatment.

At baseline, the patients under investigation scored below the mean of an age matched German control population in all SF-36 HRQL dimensions. In keeping with the results of a British study that evaluated HRQL in patients with focal and non-focal dystonia,¹⁶ our data demonstrate a remarkable negative impact of cervical and cranial dystonia on patients' HRQL. They are also in line with previous findings showing significant levels of depression and negative body image in patients with torticollis.^{17,18} In both of our study groups, limitations of role due to emotional and physical reasons were evident. Moreover, considerable impairment of physical and social functioning as well as a lowered perception of general health was found in patients with cranial dystonia. In general, this cohort seemed

to experience a higher degree of disability related to an impaired quality of life than patients with cervical dystonia, which was expressed by lower mean baseline scores in most of the HRQL dimensions. However, the higher mean age of patients with cranial dystonia has to be kept in mind while interpreting these results. Moreover, patients with severe blepharospasm experience an extraordinary strong restriction of their functional capabilities due to the disease related limitation of sight. Statistically significant intergroup differences were seen in the SF-36 pain dimension, indicating a considerably higher disability due to pain in the cervical dystonia group. Indeed, it is well known that cervical dystonia is accompanied by pain in up to 75% of the patients,¹⁹ which has been ascribed to the big muscle mass involved or to the higher density of pain receptors in the neck muscles.²⁰

Both the SF-36 and the EQ-5D measure distinguished the HRQL status of our patients with focal dystonia from a general population sample. With the exception of the general health dimension, the baseline SF-36 subscores correlated well with each other providing evidence for construct validity of the instrument. The EQ-5D utility index correlated significantly with all SF-36 dimensions, whereas the VAS score did not. This finding suggests a superiority of the EQ-5D utility index in capturing a more comprehensive range of disability associated with impaired HRQL in patients with focal dystonia.

In both study groups, most of the SF-36 subscores improved under BoNT/A therapy. The profile of improved functional health dimensions seemed to be more balanced but with smaller effect sizes in cranial dystonia, whereas patients with cervical dystonia showed marked effect sizes in some and no improvements in other SF-36 areas. To date, there are just a few studies published which measured HRQL in patients with focal dystonia treated with BoNT/A. Brans *et al* evaluated the long term effect of BoNT/A application in cervical dystonia and found improvements in the handicap and general health perception subscales of the medical outcome study scale

(MOS-20).²¹ Significant BoNT/A induced improvements of single HRQL aspects measured by the SF-36 were also demonstrated by Gudex *et al* in British patients with non-focal and focal dystonia.¹⁶

With regard to the effect size of BoNT/A treatment, the alleviation of pain was the only significant difference between patients with cranial dystonia and those with cervical dystonia. This corroborates the results of previous studies, which emphasised the impact of pain on disability in patients with cervical dystonia. Furthermore, our data confirm findings by Greene *et al* who demonstrated a substantial relief of pain by BoNT/A injections.²² At the baseline assessment, the EQ-5D measures correlated most strongly with the SF-36 bodily pain dimension, indicating a considerable influence of pain on these scores. Thus, we propose that the higher effect sizes of BoNT/A in the EQ-5D subscores found in the cervical dystonia group are most probably based on the effective pain reduction in these patients. In the same way, BoNT/A may reduce limitations of role performance more from physical than from emotional reasons in patients with cervical dystonia.

BoNT/A also induced significant amelioration of mental health in both types of focal dystonia, which is in line with previous findings in torticollis²³ and emphasises the remarkable influence of regular BoNT/A injections on psychological wellbeing, apart from the sheer relief of the increased muscle tone. Both combined may presumably lead to a higher degree of social functioning and vitality, which was seen in the cranial as well as the cervical dystonia cohort. Unexpectedly, a significantly better physical functioning under effective BoNT/A therapy was found in patients with cranial dystonia. However, this group had lower baseline scores in this dimension, most likely due to a higher degree of disability related to age and concomitant diseases. Thus, it may be presumed that the ability of BoNT/A to reduce an additional source of disability is more obvious in these patients compared with the younger patients with cervical dystonia.

Despite the availability of BoNT/A as an effective treatment option, it is important to note that patients with focal dystonia do not seem to experience “normal health” even at the time of maximal BoNT/A effect. This is reflected by lower mean values in the SF-36 subscores assessed at the first follow up visit compared with those of an age matched German control sample, with the exception of vitality (cranial and cervical dystonia) and mental health (cervical dystonia). Furthermore, the temporary character of the BoNT/A effect becomes evident in the absence of significant differences between the HRQL scores at baseline and at the follow up assessment immediately before the next BoNT/A injection. Thus, we found no evidence for a long lasting, cumulative effect of BoNT/A on quality of life.

We are aware of some methodological shortcomings of an open study, such as the small sample sizes and the lack of randomisation and

blinding. Due to these limitations, a placebo effect of the injection procedure cannot be ruled out with certainty and might contribute to our favourable results. However, given the valid data on clinical efficacy of BoNT/A in focal dystonia,¹ a randomised placebo controlled study was considered unethical. Moreover, a further possible bias is to include only patients with long term BoNT/A treatment, which may be a preselection of those with a good treatment response, as patients with focal dystonia without benefit from BoNT/A might have stopped the treatment before reaching 6 months of continuous therapy. However, in our own experience, the drop out rate in the BoNT/A treatment of focal dystonia is very low. Thus, we think that the last bias effect does not remarkably interfere with our results. On the other hand, our study design including long term treated patients may have underestimated the usefulness of BoNT/A at the 6 week follow up, because some residual effect of the foregoing treatment session at the baseline examination cannot be ruled out in a 12 week treatment cycle.

In clinical routine, the therapeutic efficacy of BoNT/A is usually evaluated with validated clinical outcome measures alone. However, it is important to know whether changes of these scores represent real improvements of the disease related disability, which are relevant from the patient's point of view. We found no correlation between BoNT/A induced changes in the clinical outcome scores and the HRQL measures. Previous studies evaluating this relation in patients with cervical dystonia reported comparable results. For instance, Pirtosek *et al* found no correlation between changes in the Tsui score and a torticollis disability scale.²⁴ Tarsy *et al* reported low to moderate correlations between changes in clinical impairment, disability, and pain in cervical dystonia.²⁵ In another study, the degree of impaired HRQL measured with the Nottingham health profile did not correlate with the Tsui score, but significantly with the Fahn disability rating scale also covering data on pain.²⁶ Lindeboom *et al* compared the effect size of repeated BoNT/A injections on clinical impairment and functional health status outcome measures in 54 patients with cervical dystonia, who decided to continue on BoNT/A treatment, as well as in 10 patients who dropped out of the therapy due to the subjective impression of ineffectiveness.²⁷ They confirmed significantly lower effect sizes of BoNT/A on the functional health measures in drop out patients, whereas there were no significant differences between both groups for the clinical impairment scales. These findings as well as our own results indicate that the subjective therapeutic efficacy of BoNT/A is far better reflected by functional health status assessments than by clinical outcome scores.

In conclusion, our study confirmed a remarkable negative impact of cranial and cervical dystonia on the patients' HRQL. Long term treatment with BoNT/A induces a significant, but temporary amelioration of several HRQL dimensions in both types of focal dystonia. This effect may contribute substantially to the

subjective benefit from the therapy, which is also apparent from patient's regularity and reliability in attendance for BoNT/A injections over a long period of time. The results of our study may contribute to the general acceptance of relatively high costs of the BoNT/A treatment in patients with focal dystonia. Moreover, our findings emphasise the significance of functional health measures in the evaluation of the BoNT/A treatment outcome. We propose that some of these HRQL measures should be used in clinical routine and may also be considered as adequate endpoints in future clinical trials.

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